TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Inflammation and the immune system

Introduction

Inflammation is caused by the immune system's response to pathogens or tissue damage. The immune system is the body's first line of defense and predominantly uses proteins called cytokines that are secreted by immune cells and act to allow cell-to-cell communication. Cytokines have influence over many cell types, including T helper lymphocytes (Th cells, or white blood cells). There are two types of Th cells, Th1 and Th2, which have different functions in the body's defense against infection. Cytokines act to regulate immunological and inflammatory responses to pathogens and are understood to function as intermediaries between the immune system and the central nervous system (CNS). C-reactive protein (CRP) is released by the body during inflammation. Increased CRP blood levels are not only suggestive of infection, but also chronic inflammatory conditions, including cardiovascular disease, diabetes, and metabolic dysfunction.

Cytokines include interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), transforming growth factors (TGF), and chemokines. These molecules are synthesised and secreted by a variety of cell types, including not only immune cells such as lymphocytes, natural killer (NK) cells, dendritic cells, polymorphonuclear leukocytes, monocytes, macrophages, and microglia, as well as non-immune cells, such as fibroblasts, endothelial cells, adipocytes, and neurons. Alterations of these immune-system mediators could have widespread effects for immune system functioning.

Immunological changes in schizophrenia have investigated an immune system imbalance. The evidence investigating these systems is largely inconsistent however alterations in the cytokine balance could impact on both the immune and CNS actions of the cytokines involved, contributing to the wide symptom profile of the disease.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane Library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% if items checked are excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 22 systematic reviews that met our inclusion criteria[3-24].

Cytokines – in blood

Chronic patients vs. controls

- Moderate to high quality evidence finds a large increase in IL-1β, medium-sized increases in MCP-1, eotaxin-1, and IL-8, and small increases in MIP-1β, IL-6, TNF-α, and sIL-2r in stable patients. There was a large decrease in IFN-γ, and no differences in IL-2, IL-4, IL-10, MIP-1α, fractalkine or IP-10.

Patients with acute symptoms vs. controls

- Moderate to high quality evidence finds medium-sized increases in IL-6, IL-8, TGF-β, IL-1ra, and sIL-2r, and small increases in IFN-γ, IL-1β, and TNF-α in patients with acute symptoms. There were small to medium-sized decreases in IL-10 and IL-4, and no differences in IL-2.

First-episode psychosis patients vs. controls

- Moderate to high quality evidence finds large increases in IL-1β, IL-6, and sIL-2r, medium-sized increases in TGF-β and MCP-1, and small increases in TNF-α, IL-1ra, IL-12, IFN-γ, and IL-10 in first-episode patients. There was a medium-sized decrease in IL-4, and no differences in IL-2, IL-8, IL-17, or IL-18.

Antipsychotic-naïve patients vs. controls

Moderate to high quality evidence finds medium-sized increases in IFN-γ, IL-17, IL-6, sIL-2r, TGF-β, and TNF-α in drug-naïve first-episode psychosis patients. The significant findings for IL-6, IL-17, and IFN-γ, but not TNF-a, remained in studies that matched for age, gender, BMI, and smoking. There were no differences in IL-10, IL-1β, IL-2, IL-4, or IL-8.

Post-treatment changes

- In chronic and first-episode samples combined, moderate to high quality evidence found significant medium-sized reductions post-treatment in IL-1β and IFN-γ, and trend reductions in IL-6, TNF-α and IL-4. sTNF-r2 and sIL-2r were increased post-treatment. There were no differences post-treatment in sIL-6r, IL-8, IL-12, sTNF-r1, IL-2, IL-17, IL1-ra, TGF-β, IL-10 or IL-23.
- In first-episode psychosis samples (drug free but not necessarily drug-naïve), moderate to high quality evidence finds reductions post-treatment in IL-1β, IL-6 and IL-4.
- In drug-naïve first episode samples, moderate to low quality evidence finds medium-sized reductions post-treatment in IL-2 and IL-6. There may also be reductions in IL-1β, IFN-γ, and IL-17 (one-study removed or trend effects).
- In people with an acute exacerbation of schizophrenia, moderate to high quality evidence finds reductions post-treatment in IL-1β, IL-6, sIL-6r, TNF-α and IFN-γ. There was a small, significant increase post-treatment in sIL-2r. There were no significant differences in IL-12, IL-2, IL-17, TGF-β, IL-10, or IL-4.
- In people with treatment-resistant schizophrenia, moderate to high quality evidence finds increases post-treatment in IL-6 and sIL-2r.

People at high-risk of psychosis vs. controls

Moderate to high quality evidence finds a small effect of increased IL-6 blood levels in people at high risk of psychosis. Moderate quality evidence showed a medium-sized

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

effect of lower blood IL-1β levels in people at high risk of psychosis. There may also be higher IL-4 levels and lower IL-10 levels. There were no differences in other cytokines or c-reactive proteins. There was a non-significant trend for higher IL-12 levels in converters vs non-converters.

Cytokines – in CSF

All patients vs. controls

- Moderate to high quality evidence finds medium to large increases in IL-6 and IL-8, a large decrease in sIL-2r (from moderate to low quality evidence), and no differences in IL-1β, IL-1α, IL-2, IL-6R, MIP-1α, MCP-2, sTNFR2, TGF-β1 or TGF-β2.

C-reactive proteins – in blood

All patients vs. controls

- Moderate to high quality evidence finds a medium-sized increase in C-reactive protein levels in people with schizophrenia. The effect was larger in people who were drug-naïve or drug-free than in patients on antipsychotics. There was a larger effect with first than second generation antipsychotics. Increased severity of positive symptoms was related to increased effect size.
- High quality evidence suggests a small association between increased C-reactive protein levels and decreased performance on verbal memory, visual memory, working memory, processing speed, planning/problem solving, executive functioning speed, and attention tasks.

Post-treatment changes

- Moderate to high quality evidence finds no differences in C-reactive protein levels from before to after treatment with antipsychotics.

Autoantibodies – in blood

All patients vs. controls

- High quality evidence finds a medium-sized increase in cardiolipin IgM in people with a schizophrenia spectrum disorder compared to controls. Moderate to high quality evidence also finds a small increase in cardiolipin IgG.
- Moderate quality evidence finds increases in nerve growth factor, antinuclear antibodies, DNA, dopamine receptor, gliadin IgA, heat shock protein 60, lupus anticoagulant, rheumatoid factor, smith, thyroglobulin, thyroid microsomal, and tissue transglutaminase. Moderate to low quality evidence finds increases in cold agglutinin, histone/anti-histone IgG, nucleoprotein, phospholipid, and serotonin.
- Moderate quality evidence finds an increase in N-methyl-D-aspartate antibody seropositivity in people with schizophrenia using a high-specificity (1.320 dilution) threshold, but not a low-specificity threshold (1.10 dilution).
- Moderate quality evidence suggests increases in anti-gliadin IgG and IgA (medium-sized effects), anti-TTG2 IgA (large effects) and other wheat protein antibodies (small effects for anti-gluten, anti-wheat and non-specified anti-gliadin) in people with schizophrenia compared to controls.

First-episode psychosis patients vs. controls

- Moderate quality evidence finds increases in cardiolipin IgG and N-methyl-D-aspartate in first-episode psychosis patients compared to controls.

Autoantibodies – in CSF

All patients vs. controls

- Moderate to low quality evidence finds medium-sized increases in CSF IgG ratio in people with schizophrenia. There was a medium-sized decrease in IgG/albumin ratio, and no differences in CSF IgG or IgG index.

Leukocytes – in blood

All patients vs. controls

- Moderate to high quality evidence finds medium-sized effects of increased total white blood cell count, monocytes, and neutrophils in people with schizophrenia or first-episode psychosis compared to controls. There were no significant

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

differences in lymphocytes, eosinophils, or basophils.

- Moderate to high quality evidence suggests a medium-sized decrease in T-lymphocytes (CD3 percentage) in stable medicated patients compared to controls.
- Moderate to high quality evidence finds medium-sized effects of increased neutrophil-to-lymphocyte and monocyte-lymphocyte ratios in people with schizophrenia or first-episode psychosis compared to controls. There was also a trend effect for increased platelet-lymphocyte ratio in patients.

Antipsychotic-naïve patients vs. controls

- Moderate to high quality evidence suggests a medium-sized effect of decreased T-lymphocytes (CD3 percentage) in drug naïve first-episode psychosis patients compared to controls. Moderate quality evidence also suggests medium to large effects of increased T-lymphocytes (CD3), a large effect of increased T-helper lymphocytes (CD4), and a medium effect of increased T-helper/suppressor lymphocyte ratio (CD4/CD8) in patients.

Patients with acute symptoms vs. controls

- Moderate to high quality evidence finds medium-sized decreases in T-lymphocytes (CD3 percentage), increases in total white blood cell count, T-helper lymphocytes (CD4 percentage), natural killer cells (CD56 absolute), and an increase in T-helper / suppressor lymphocyte ratio (CD4/CD8) in acute patients compared to controls. Moderate to low quality evidence also suggests a large increase in natural killer cells (CD56 percentage). There were no significant differences in total lymphocyte count.

Post-treatment changes

- Moderate to high quality evidence finds a medium-sized increase in T-suppressor/cytotoxic lymphocytes (CD8 percentage), natural killer cells (CD56 absolute), and T-lymphocytes (CD3 percentage), a small to medium effect of increased T-suppressor/cytotoxic lymphocytes (CD8 absolute), and a small effect of decreased T-helper/suppressor lymphocyte ratio (CD4/CD8).

Tryptophan catabolites - CSF

All patients vs. controls

- Moderate to high quality evidence finds a medium-sized increase in kynurenic acid in people with schizophrenia. This effect was most pronounced in studies of CSF, brain tissue, older patients, medicated patients, and male patients. Moderate quality evidence also finds increases in kynurenine in the CSF of people with schizophrenia.

Post-mortem samples vs. controls

- Moderate to high quality evidence finds a medium-sized increase in cell microglia and a small to medium-sized increase in pro-inflammatory molecular components in people with schizophrenia compared to controls. No differences were found in cell macroglia or lymphocyte levels or in anti-inflammatory molecular components.

Translocator protein

All patients vs. controls

- Moderate quality evidence suggests a small to medium-sized increase in translocator protein in people with schizophrenia when measured using binding potential, but not when measured using volume of distribution.

Homocysteine

First-episode patients vs. controls

- Moderate quality evidence finds a large effect of increased homocysteine in first-episode patients.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Bora E

Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: A meta-analysis

Psychological Medicine 2019; 49: 1971-9

View review abstract online

Comparison	**Association between CPR levels and cognition in people with schizophrenia.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small association between increased CPR levels and decreased performance on verbal memory, visual memory, working memory, processing speed, planning/problem solving, executive functioning speed, and attention tasks.**

CPR levels

A small significant effect found increased CPR levels were related to decreased cognitive functioning;

10 studies, N = 1,602, r = -0.13, 95%CI -0.08 to -0.18, $p < 0.05$, I^2 = 0%

Subgroup analysis showed similar associations with verbal memory, visual memory, working memory, processing speed, planning/problem solving, executive functioning speed, and attention. There was no association with verbal fluency.

There were no moderating effects of age, sex, and quality score, or stable vs. non-stable patients.

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Capuzzi E, Bartoli F, Crocamo C, Clerici M, Carra G

Acute variations of cytokine levels after antipsychotic treatment in drug-naive subjects with a first-episode psychosis: A meta-analysis

Neuroscience & Biobehavioral Reviews 2017; 77: 122-8

View review abstract online

Comparison	**Blood cytokine levels before and after four weeks of antipsychotic treatment in drug-naive people with first-episode psychosis.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, mostly inconsistent, mostly precise, direct) finds medium-sized reductions in IL-2 and IL-6 post-treatment in previously antipsychotic naïve patients. There may also be reductions in IL-1β (one study removed analysis), IFN-γ and IL-17 (trend effects). There was no post treatment difference TNF-α.**
Blood cytokine levels	
There were significant medium-sized reductions post-treatment in patients in; IL-2: 2 studies, N = 69, SMD = -0.47, 95%CI -0.87 to -0.07, p = 0.023, I^2 = 24% IL-6: 4 studies, N = 253, SMD = -0.51, 95%CI -0.92 to -0.11, p = 0.012, I^2 = 81% IL-1β - with one study removed: 3 studies, N = 156, SMD = -0.46, 95%CI -0.69 to -0.24, p < 0.001, I^2 = 0% *There were trend-effect reductions in;* IFN-γ: 2 studies, N = 157, SMD = -0.42, 95%CI -0.87 to 0.03, p = 0.068, I^2 = 75% IL-17: 2 studies, N = 157, SMD = -0.57, 95%CI -1.22 to 0.09, p = 0.088, I^2 = 88% *There were no significant differences in;* IL-1β - all studies: 4 studies, N = 212, SMD = -0.19, 95%CI -0.66 to 0.28, p = 0.437, I^2 = 81% TNF-α: 4 studies, N = 214, SMD = 0.03, 95%CI -0.16 to 0.22, p = 0.745, I^2 = 0%	
Consistency	Consistent for IL-2 and TNF-α only
Precision	Precise, apart from IL-17
Directness	Direct

Ezeoke A, Mellor A, Buckley P, Miller B

A systematic, quantitative review of blood autoantibodies in schizophrenia

Schizophrenia Research 2013; 150: 245-251

View review abstract online

Comparison	**Comparison of blood autoantibodies in people with schizophrenia vs. controls.**

Inflammation and the immune system

Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a medium-sized effect of increased levels of cardiolipin IgM in people with a schizophrenia spectrum disorder compared to controls.** **Moderate to high quality evidence (inconsistent) suggests a small effect of increased levels of cardiolipin IgG in people with a schizophrenia spectrum disorder.** **Moderate quality evidence (smaller samples, inconsistent) suggests nerve growth factor may also be increased in people with a schizophrenia spectrum disorder.** **Moderate quality evidence (unable to assess precision or consistency, medium to large samples) also suggests increases in antinuclear antibodies, DNA, dopamine receptor, gliadin IgA, heat shock protein 60, lupus anticoagulant, N-methyl-D-aspartate, rheumatoid factor, smith, thyroglobulin, thyroid microsomal, and tissue transglutaminase.** **Moderate to low quality evidence (smaller samples) suggests increases in cold agglutinin, histone/anti-histone IgG, nucleoprotein, phospholipid, and serotonin.** **The only increases observed in first-episode psychosis patients were for cardiolipin IgG (positive titers only) and N-methyl-D-aspartate gained from moderate quality evidence.**

Blood autoantibodies

Antinuclear antibodies

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

18 studies, N = 2,794, schizophrenia: 22.2% vs. 6.7% in controls, $p < 0.01$

No differences between people with first episode psychosis and controls;

3 studies, N = 243, schizophrenia: 7.2% vs. 5.6% in controls, $p = 0.79$

Note: no differences in analysis of pre vs. post treatment

Cardiolipin IgM

Significant effect of greater prevalence of positive titers, and a significant, medium size effect of more absolute titers in people with a schizophrenia spectrum disorder compared to controls;

Positive titers: 10 studies, N = 1,076, schizophrenia: 16.1% vs. 3.8% in controls, $p < 0.01$

Absolute titers: 2 studies, N = 327, $g = 0.46$, 95%CI 0.26 to 0.66, $p < 0.01$, $X^2 = 1.41$, $p = 0.49$

No differences between people with first episode psychosis and controls;

2 studies, N = 157, schizophrenia: 5.8% vs. 1.9% in controls, $p = 0.33$

Cardiolipin IgG

Significant effect of greater prevalence of positive titers, and a significant, small effect of more absolute titers in people with a schizophrenia spectrum disorder compared to controls;

Positive titers: 9 studies, N = 858, schizophrenia: 11.4% vs. 1.9% in controls, $p < 0.01$

Absolute titers: 3 studies, N = 404, $g = 0.21$, 95%CI 0.03 to 0.40, $p = 0.02$, $X^2 = 97.20$, $p < 0.01$

Significant effect of greater prevalence of positive titers and a medium effect of fewer absolute titers in people with first episode psychosis compared to controls;

Positive titers: 2 studies, N = 157, schizophrenia: 21.2% vs. 3.8% in controls, $p < 0.01$

Absolute titers: 2 studies, N = 140, $g = -0.67$, 95%CI -1.11 to -0.22, $p < 0.01$, $X^2 = 27.52$, $p < 0.01$

Note: no differences in analysis of pre vs. post treatment

Cold agglutinin

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

2 studies, N = 168, schizophrenia: 44.1% vs. 14.0% in controls, $p < 0.01$

DNA

Significant effect of greater prevalence of positive titers in with a schizophrenia spectrum disorder compared to controls;

DNA (ds): 8 studies, N = 1,034, schizophrenia: 12.3% vs. 4.4% in controls, $p < 0.01$

DNA (ss): 2 studies, N = 406, schizophrenia: 33.3% vs. 8.6% in controls, $p < 0.01$

Dopamine receptor

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

4 studies, N = 330, schizophrenia: 4.6% vs. 0% in controls, $p < 0.01$

Histone and anti-histone IgG

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

Histone: 2 studies, N = 208, schizophrenia: 13.5% vs. 4.5% in controls, $p = 0.03$

No differences between people with first episode psychosis and controls;

Anti-histone: 2 studies, N = 98, schizophrenia: 5.0% vs. 6.4% in controls, $p = 0.80$

Gliadin IgA

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

4 studies, N = 3,207, schizophrenia: 23.2% vs. 9.3% in controls, $p < 0.01$

Heat shock protein 60

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

3 studies, N = 284, schizophrenia: 19.0% vs. 2.9% in controls, $p < 0.01$

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Lupus anticoagulant

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

4 studies, N = 373, schizophrenia: 25.2% vs. 0% in controls, $p < 0.01$

N-methyl-D-aspartate

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

6 studies, N = 628, schizophrenia: 5.4% vs. 0.4% in controls, $p < 0.01$

Significant effect of greater prevalence of positive titers in people with first episode psychosis compared to controls;

3 studies, N = 443, schizophrenia: 4.6% vs. 0.4% in controls, $p < 0.01$

Nucleoprotein

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

2 studies, N = 151, schizophrenia: 26.5% vs. 0% in controls, $p = 0.02$

Phospholipid

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

2 studies, N = 173, schizophrenia: 12.1% vs. 0% in controls, $p = 0.01$

Rheumatoid factor

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

9 studies, N = 1,904, schizophrenia: 15.1% vs. 6.3% in controls, $p < 0.01$

Serotonin

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

2 studies, N = 142, schizophrenia: 24.6% vs. 4.9% in controls, $p < 0.01$

Smith

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

2 studies, N = 397, schizophrenia: 12.5% vs. 5.0% in controls, $p < 0.01$

Thyroglobulin

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;

5 studies, N = 947, schizophrenia: 8.1% vs. 4.4% in controls, $p = 0.03$

Thyroid microsomal

Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

disorder compared to controls; 3 studies, N = 827, schizophrenia: 13.0% vs. 7.6% in controls, $p = 0.02$ Tissue Transglutaminase *Significant effect of greater prevalence of positive titers in people with a schizophrenia spectrum disorder compared to controls;* 2 studies, N = 2,412, schizophrenia: 5.2% vs. 0.7% in controls, $p < 0.01$ Nerve growth factor *Significant, large effect of more absolute titers in people with a schizophrenia spectrum disorder compared to controls;* 2 studies, N = 229, $g = 1.21$, 95%CI 0.96 to 1.46, $p < 0.01$, $X^2 = 9.75$, $p = 0.02$ *No significant differences between patients and controls were reported for:* Extractable nuclear antigens, endothelial, glutamic acid decarboxylase, glutamic acid decarboxylase 65, ganglioside, gastric parietal cell, keratin, mitochondria, sarcolemma, smooth muscle, thyroid, thyroid peroxidase, and hippocampus IgG	
Consistency	Consistent for cardiolipin IgM, inconsistent for cardiolipin IgG and nerve growth factor, consistency measures are not reported for prevalence rates.
Precision	Precise for cardiolipin IgM, cardiolipin IgG and nerve growth factor, confidence intervals are not reported for all others.
Directness	Direct

Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, Nardin P, Goncalves CA, Berk M

C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications

Molecular Psychiatry 2016; 21: 554-64

View review abstract online

Comparison 1	**C-reactive protein levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a medium-sized increase in C-reactive protein levels in people with schizophrenia. The effect was larger in people who were drug-naïve or drug-free than in patients on antipsychotics. There was a larger effect with first**

	than second generation antipsychotics. Increased severity of positive symptoms was related to increased effect size.
Blood C-reactive protein	
A significant, medium-sized effect of increased C-reactive protein levels in patients; 24 studies, N = 82,962, *g* = 0.66, 95%CI 0.43 to 0.88, *p* < 0.001, I^2 = 91%, *p* = 0.001 Subgroup analyses found a larger effect in people who were drug-naïve or drug-free (*g* = 0.87) than in patients on antipsychotics (*g* = 0.58). In those on antipsychotics, there was a larger effect with first-generation antipsychotics (*g* = 0.87) than second-generation antipsychotics (*g* = 0.53). There was a larger effect in chronic patients (*g* = 0.76) than in those in the early stages of the disorder (*g* = 0.63). There was a larger effect in clinical samples (*g* = 0.77) than in population samples (*g* = 0.18). Meta-regressions found severity of positive symptoms was related to increased effect size, with no relationship with negative symptoms. Older age in drug-naïve or drug-free patients was related to smaller effect sizes. Higher BMI was related to higher C-reactive protein levels.	
Consistency	Inconsistent
Precision	Precise
Directness	Direct
Comparison 2	**Pre-post treatment levels of C-reactive protein levels in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds no differences in C-reactive protein levels post-treatment with antipsychotics.**
Blood C-reactive protein	
There were no differences in C-reactive protein levels post-treatment; 8 studies, N = 713, *g* = 0.01, 95%CI -0.20 to 0.22, *p* = 0.803, I^2 = 74%, *p* = 0.001 Subgroup and regression analyses found no moderating effects of antipsychotic type, age, or BMI.	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C

Oxidative stress and inflammation in first-episode psychosis: A

Systematic Review and Meta-analysis

Schizophrenia Bulletin 2019; 45(4): 742-51

View review abstract online

Comparison	**Immunological changes in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, inconsistent, precise, direct) finds a large effect of increased homocysteine in first-episode patients, with no differences in c-reactive proteins or cytokines. Note that this review used corrected p-values (Bonferroni-Holm method).**
C-reactive protein, homocysteine, and cytokines	
A large, significant effect of increased homocysteine in first-episode patients; 4 studies, N = 278, *d* = 0.864, 95%CI 0.372 to 1.356, *p* = 0.015, I^2 = 71%, *p* = 0.016 There were no significant differences in c-reactive proteins or cytokines.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Frydecka D, Krzystek-Korpacka M, Lubeiro A, Stramecki F, Stanczykiewicz B, Beszlej JA, Piotrowski P, Kotowicz K, Szewczuk-Boguslawska M, Pawlak-Adamska E, Misiak B

Profiling inflammatory signatures of schizophrenia: A cross-sectional and meta-analysis study

Brain, Behaviour, and Immunity 2018; 71: 28-36

View review abstract online

Comparison 1	**Blood chemokine cytokine levels people with first-episode or multi-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency, precise, direct) finds medium-sized increases in MCP-1, IL-8 and eotaxin-1, and a small increase in MIP-1β in people with schizophrenia. There were no differences in MIP-1α,**

	fractalkine and IP-10.
Blood chemokine cytokine levels	
There were significant, medium-sized increases in people with schizophrenia in; MCP-1 (CCL2): 11 studies, N = 1,423, g = 0.53, 95%CI 0.28 to 0.78, p < 0.001, I^2 = 78%, p < 0.001 IL-8 (CXCL8): 15 studies, N = 1,603, g = 0.46, 95%CI 0.18 to 0.75, p < 0.001, I^2 = 85%, p < 0.001 Eotaxin-1 (CCL11): 4 studies, N = 495, g = 0.43, 95%CI 0.20 to 0.65, p < 0.001, I^2 = 28%, p = 0.243 *There was a significant, small increase in people with schizophrenia in;* MIP-1β (CCL4): 3 studies, N = 368, g = 0.27, 95%CI 0.06 to 0.48, p = 0.012, I^2 = 0%, p = 0.373 *There were no significant differences in;* MIP-1α (CCL3): 4 studies, N = 518, g = 0.40, 95%CI -0.08 to 0.87, p = 0.103, I^2 = 18%, p < 0.001 Fractalkine (CXCL1): 3 studies, N = 367, g = -0.09, 95%CI -0.30 to 0.11, p = 0.374, I^2 = 0%, p = 0.884 IP-10 (CXCL10): 4 studies, N = 540, g = -0.18, 95%CI -0.41 to 0.04, p = 0.104, I^2 = 29%, p = 0.237 The effect for MIP-1β (CCL4) was insignificant after removing either of 2 studies, but the effect remained for MCP-1 (CCL2), eotaxin-1 (CCL11) and IL-8 (CXCL8). There were no moderating effects of type of biological material (serum or plasma), method of assessment (ELISA or CBA), and study quality on MCP-1 (CCL2) and IL-8 (CXCL8).	
Consistency	Consistent, apart from MCP-1, IL-8 and MIP-1α.
Precision	Precise
Directness	Direct
Comparison 2	**Blood chemokine cytokine levels people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, inconsistent, precise, direct) finds a medium-sized increase in MCP-1 in people with first-episode psychosis, with no differences in IL-8.**
Blood chemokine cytokine levels	
There was a significant, medium-sized increase in people with first-episode psychosis in; MCP-1 (CCL2): 6 studies, N = 477, g = 0.40, 95%CI 0.05 to 0.75, p = 0.025, I^2 = 59%, p = 0.034 *There were no significant differences in;* IL-8 (CXCL8): 3 studies, N = 179, g = 0.79, 95%CI -0.22 to 1.80, p = 0.125, I^2 = 94.7% p < 0.001	
Consistency	Inconsistent

Precision	Precise for MCP-1 only.
Directness	Direct
Comparison 3	**Blood chemokine cytokine levels people with multi-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, mostly precise, direct) finds medium-sized increases in MCP-1, eotaxin-1, and IL-8, and a small increase in MIP-1β in people with multi-episode schizophrenia. There were no differences in MIP-1α, fractalkine or IP-10.**
Blood chemokine cytokine levels	
There were significant, medium-sized increases in people with multi-episode schizophrenia in; MCP-1 (CCL2): 5 studies, N = 946, *g* = 0.66, 95%CI 0.26 to 1.07, *p* = 0.001, I^2 = 88%, *p* < 0.001 eotaxin-1 (CCL11): 3 studies, N = 421, *g* = 0.43, 95%CI 0.12 to 0.74, *p* = 0.006, I^2 = 52%, *p* = 0.127 IL-8 (CXCL8): 12 studies, N = 1,424, *g* = 0.40, 95%CI 0.16 to 0.63, *p* = 0.001, I^2 = 76%, *p* <0.001 *There was a significant, small increase in people with multi-episode schizophrenia in;* MIP-1β (CCL4): 2 studies, N = 313, *g* = 0.28, 95%CI -0.01 to 0.57, *p* = 0.055, I^2 = 23%, *p* = 0.255 *There were no differences in;* MIP-1α (CCL3): 3 studies, N = 463, *g* = 0.53, 95%CI -0.05 to 1.11, *p* = 0.079, I^2 = 87%, *p* <0.001 Fractalkine (CX3CL1): 2 studies, N = 293, *g* = -0.09, 95%CI -0.31 to 0.14, *p* = 0.460, I^2 = 0%, *p* = 0.658 IP-10 (CXCL10): 3 studies, N = 485, *g* = -0.20, 95%CI -0.49 to 0.09, *p* = 0.167, I^2 = 53% *p* = 0.121	
Consistency	Consistent, apart from MCP-1, IL-8 and MIP-1α.
Precision	Precise, apart from MIP-1α.
Directness	Direct

Gallego JA, Blanco EA, Husain-Krautter S, Madeline Fagen E, Moreno-Merino P, del Ojo-Jimenez JA, Ahmed A, Rothstein T L, Lencz T, Malhotra AK

Cytokines in cerebrospinal fluid of patients with schizophrenia spectrum disorders: New data and an updated meta-analysis

Schizophrenia Research 2018; 202: 64-71

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

View review abstract online	
Comparison	**CSF cytokine levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, some imprecision, direct) finds medium to large increases in CSF IL-6 and IL-8 in people with schizophrenia, with no differences in CSF IL-1β or IL-2.**
CSF cytokine levels	
There were significant, medium to large increases in patients in; IL-6: 9 studies, N = 514, SMD = 0.53, 95%CI 0.28 to 0.78, $p < 0.001$, $I^2 = 34\%$, $p = 0.145$ Subgroup analyses showed similar effect sizes in studies of patients treated or not treated with antipsychotics (SMD = 0.55 vs. SMD = 0.45). The effect was greater in early psychosis samples than in chronic samples (SMD = 0.72 vs. SMD = 0.52). IL-8: 4 studies, N = 201, SMD = 1.12, 95%CI 0.16 to 2.09, $p = 0.02$, $I^2 = 88\%$, $p < 0.001$ Removing one outlier reduced SMD to 0.44 ($p = 0.003$). *There were no significant differences in;* IL-1β: 4 studies, N = 131, SMD = -0.11, 95%CI -1.97 to -1.75, $p = 0.91$, $I^2 = 93\%$, $p < 0.001$ IL-2: 4 studies, N = 173, SMD = 0.08, 95%CI -0.43 to 0.60, $p = 0.75$, $I^2 = 50\%$, $p = 0.112$	
Consistency	Consistent for IL-6 and IL-2 only.
Precision	Precise for IL-6 and IL-2 only.
Directness	Direct

Goldsmith DR, Rapaport MH, Miller BJ

A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression

Molecular Psychiatry 2016; 21: 1696-709

View review abstract online

Comparison 1	**Blood cytokine levels in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (mostly large samples, mostly inconsistent, precise, direct) finds significant, large increases in first-episode patients in IL-1β, IL-6, and sIL-2r, a medium-sized**

	increase in TGF-β, and small increases in TNF-α, IL-1ra, IL-12, IFN-γ, and IL-10. There was a medium-sized decrease in IL-4, and no differences in IL-2, IL-17 or IL-18.
Blood cytokine levels	
There were significant, large increases in first-episode patients in; IL-1β: 6 studies, N = 631, *g* = 1.25, 95%CI 1.07 to 1.42, *p* < 0.01, I^2 = 94%, *p* < 0.01 IL-6: 11 studies, N = 1,083, *g* = 1.16, 95%CI 1.03 to 1.30, *p* < 0.01, I^2 = 93%, *p* < 0.01 sIL-2r: 3 studies, N = 127, *g* = 1.04, 95%CI 0.55 to 1.52, *p* < 0.01, I^2 = 80%, *p* < 0.01 IL-8: 2 studies, N = 98, *g* = 1.75, 95%CI 1.27 to 2.24, *p* < 0.01, I^2 = 92%, *p* < 0.01 Note: the finding for IL-8 has been updated in Frydecka, 2018, which found no significant effect. *There was a significant, medium-sized increase in first-episode patients in;* TGF-β: 3 studies, N = 467, *g* = 0.58, 95%CI 0.36 to 0.80, *p* < 0.01, I^2 = 83%, *p* < 0.01 *There were significant, small increases in first-episode patients in;* TNF-α: 9 studies, N = 1,429, *g* = 0.31, 95%CI 0.22 to 0.39, *p* < 0.01, I^2 = 97%, *p* < 0.01 IL-1ra: 2 studies, N = 570, *g* = 0.29, 95%CI 0.10 to 0.48, *p* < 0.01, I^2 = 20%, *p* = 0.26 IL-12: 3 studies, N = 720, *g* = 0.26, 95%CI 0.05 to 0.47, *p* = 0.02, I^2 = 97%, *p* < 0.01 IFN-γ: 7 studies, N = 1,199, *g* = 0.23, 95%CI 0.09 to 0.37, *p* < 0.01, I^2 = 84%, *p* < 0.01 IL-10: 4 studies, N = 818, *g* = 0.18, 95%CI 0.04 to 0.31, *p* = 0.01 I^2 = 92%, *p* < 0.01 *There was a significant medium-sized decrease in first-episode patients in;* IL-4: 4 studies, N = 515, *g* = -0.63, 95%CI -0.84 to -0.42, *p* < 0.01, I^2 = 96%, *p* < 0.01 *There were no significant differences in;* IL-2: 5 studies, N = 440, *g* = 0.08, 95%CI -0.14 to 0.29, *p* = 0.48, I^2 = 86%, *p* < 0.01 IL-17: 2 studies, N = 253, *g* = 0.00, 95%CI -0.26 to 0.26, *p* = 0.99, I^2 = 87%, *p* < 0.01 IL-18: 3 studies, N = 738, *g* = 0.08, 95%CI -0.07 to 0.23, *p* = 0.28, I^2 = 0%, *p* = 0.65 Sensitivity analyses showed heterogeneity was no longer significant, but the effect remained significant, after removing one study for IFN-γ,31, sIL-2R37 and TGF-β.47. For IL-12, the effect was no longer significant after removing one study. Between-study heterogeneity remained significant in sensitivity analyses for IL-1β, IL-4, IL-6 and TNF-α. Sensitivity analysis was not possible for IL-8. Meta-regression found no effects of age, sex, illness duration, smoking and BMI on IL-6 and TNF-α analyses.	
Consistency	Inconsistent, apart from IL-1ra and IL-18.
Precision	Precise
Directness	Direct

Inflammation and the immune system

Comparison 2	**Blood cytokine levels in people with an acute exacerbation of chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds significant, medium-sized increases in acute, chronic patients in IL-6, IL-8, TGF-β, IL-1ra, and sIL-2r, and small increases in IFN-γ, IL-1β, and TNF-α. There were small to medium-sized decreases in IL-10 and IL-4, and no differences in IL-2.**
Blood cytokine levels	
There were significant, medium-sized increases in acute, chronic patients in; IL-6: 9 studies, N = 746, *g* = 0.73, 95%CI 0.56 to 0.90, *p* < 0.01, I^2 = 94%, *p* < 0.01 IL-8: 2 studies, N = 98, *g* = 0.59, 95%CI 0.19 to 1.00, *p* < 0.01, I^2 = 51%, *p* = 0.15 TGF-β: 6 studies, N = 625, *g* = 0.50, 95%CI 0.32 to 0.68, *p* < 0.01, I^2 = 65%, *p* = 0.01 IL-1ra: 2 studies, N = 126, *g* = 0.49, 95%CI 0.07 to 0.90, *p* = 0.02 I^2 = 88%, *p* < 0.01 sIL-2r: 3 studies, N = 178, *g* = 0.47, 95%CI 0.14 to 0.80, *p* = 0.01, I^2 = 55%, *p* = 0.11 *There were significant, small increases in acute, chronic patients in;* IFN-γ: 4 studies, N = 428, *g* = 0.35, 95%CI 0.13 to 0.57, *p* < 0.01, I^2 = 44%, *p* = 0.15 IL-1β: 3 studies, N = 282, *g* = 0.28, 95%CI 0.04 to 0.52, *p* = 0.02 I^2 = 73%, *p* = 0.02 TNF-α: 7 studies, N = 718, *g* = 0.22, 95%CI 0.05 to 0.39, *p* = 0.01, I^2 = 96%, *p* < 0.01 *There were significant small to medium-sized decreases in patients in;* IL-10: 2 studies, N = 98, *g* = -0.57, 95%CI -0.98 to -0.17, *p* < 0.01, I^2 = 71%, *p* = 0.07 IL-4: 5 studies, N = 519, *g* = -0.36, 95%CI -0.56 to -0.16, *p* < 0.01, I^2 = 92%, *p* < 0.01 *There were no significant differences in;* IL-2: 2 studies, N = 242, *g* = -0.27, 95%CI -0.61 to 0.07, *p* = 0.12, I^2 = 93%, *p* < 0.01 In sensitivity analyses, the heterogeneity was no longer significant, but the effect remained significant, after removing one study for IL-1β and IL-6. The heterogeneity remained significant in a sensitivity analysis for IL-4, TGF-β, and TNF-α. Sensitivity analyses were not possible for IL-1ra, IL-8 and IL-10. In meta-regression, sex and BMI showed a trend-level association, with a higher proportion of females and higher BMI associated with larger effect sizes for TNF-α. Age, sex, illness duration and BMI were not related to IL-6; age, illness duration and smoking were not related to TNF-α.	
Consistency	Consistent, apart from IFN-γ, IL-8, IL-1β and sIL-2R.
Precision	Precise
Directness	Direct

Comparison 3	**Post-treatment blood cytokine changes in people with an acute exacerbation of chronic schizophrenia.** **Note: this comparison has been updated in Romeo, 2018.**
Summary of evidence	**Moderate to high quality evidence (mostly medium to large samples, mostly consistent, precise, direct) finds reductions post-treatment in IL-1β and IL-4 and increases post-treatment in IL-12 and sIL-2r in people with an acute exacerbation of schizophrenia. There were no changes in IFN-γ, IL-2, TGF-β, TNF-α, and IL-17.**
Blood cytokine levels	
There were significant, small decreases post-treatment in; IL-1β: 4 studies, N = 378, *g* = -0.29, 95%CI -0.49 to -0.09, *p* < 0.01, I^2 = 39%, *p* = 0.18 IL-4: 2 studies, N = 372, *g* = -0.29, 95%CI -0.50 to -0.09, *p* = 0.01, I^2 = 0%, *p* = 0.83 IL-6: 11 studies, N = 1,021, *g* = -0.13, 95%CI -0.25 to -0.01, *p* = 0.04, I^2 = 47%, *p* = 0.04 *There were significant, small increases post-treatment in;* IL-12: 3 studies, N = 208, *g* = 0.33, 95%CI 0.06 to 0.60, *p* = 0.02, I^2 = 47%, *p* = 0.15 sIL-2r: 3 studies, N = 180, *g* = 0.30, 95%CI 0.01 to 0.60, *p* = 0.04, I^2 = 9%, *p* = 0.34 *There were no significant changes in;* IFN-γ: 4 studies, N = 30, *g* = -0.12, 95%CI -0.29 to 0.05, *p* = 0.16, I^2 = 0%, *p* = 0.81 IL-2: 4 studies, N = 264, *g* = -0.03, 95%CI -0.27 to 0.22, *p* = 0.84, I^2 = 64%, *p* = 0.04 TGF-β: 4 studies, N = 572, *g* = -0.04, 95%CI -0.21 to 0.12, *p* = 0.61, I^2 = 82%, *p* < 0.01 TNF-α: 6 studies, N = 620, *g* = 0.02, 95%CI -0.14 to 0.18, *p* = 0.84, I^2 = 68%, *p* = 0.01 IL-17: 2 studies, N = 386, *g* = 0.13, 95%CI -0.07 to 0.33, *p* = 0.22, I^2 = 0%, *p* = 0.78	
Consistency	Consistent, apart from IL-6, IL-2, TGF-β, and TNF-α.
Precision	Precise
Directness	Direct
Comparison 4	**Blood cytokine levels in people with stable, chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds a large increase in IL-1β and small increases in IL-6, TNF-α, and sIL-2r in stable, chronic patients. There was a large decrease in IFN-γ, and no differences in IL-2, IL-4 and IL-10.**

Blood cytokine levels	
There was a significant, large increase in people with stable, chronic schizophrenia in; IL-1β: 4 studies, N = 633, *g* = 0.89, 95%CI 0.73 to 1.05, *p* < 0.01, I^2 = 96%, *p* < 0.01 *There were significant, small increases in people with stable, chronic schizophrenia in;* IL-6: 12 studies, N = 1,385, *g* = 0.27, 95%CI 0.17 to 0.38, *p* < 0.01, I^2 = 88%, *p* < 0.01 TNF-α: 9 studies, N = 1,017, *g* = 0.30, 95%CI 0.18 to 0.43, *p* < 0.01, I^2 = 81%, *p* < 0.01 sIL-2r: 3 studies, N = 251, *g* = 0.32, 95%CI 0.40 to 0.86, *p* < 0.01, I^2 = 0%, *p* = 0.70 *There was a significant, large decrease in stable, chronic patients in;* IFN-γ: 4 studies, N = 330, *g* = -1.07, 95%CI -1.35 to -0.80, *p* < 0.01, I^2 = 98%, *p* < 0.01 *There were no significant differences in;* IL-2: 6 studies, N = 364, *g* = -0.04, 95%CI -0.24 to 0.16, *p* = 0.68, I^2 = 91%, *p* < 0.01 IL-4: 2 studies, N = 119, *g* = -0.04, 95%CI -0.42 to 0.34, *p* = 0.83, I^2 = 0%, *p* = 0.35 IL-10: 4 studies, N = 244, *g* = -0.03, 95%CI -0.24 to 0.18, *p* = 0.81, I^2 = 1.4%, *p* = 0.40 Between study heterogeneity remained significant in sensitivity analyses for IFN-γ, IL-1β, IL-6 and TNF-α. There were no moderating effects of age, sex, illness duration, smoking and BMI on the effect size for IL-6.	
Consistency	Inconsistent, apart from sIL-2r, IL-4, and IL-10.
Precision	Precise
Directness	Direct

Grain R, Lally J, Stubbs B, Malik S, LeMince A, Nicholson TR, Murray RM, Gaughran F

Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: A systematic review, meta-analysis, and case series

Psychiatry and Clinical Neurosciences 2017; 71: 678-89

View review abstract online

Comparison	**Glutamic acid decarboxylase (GAD) autoantibody levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, consistent, imprecise, direct) finds no differences in GAD65 autoantibody**

	levels.
GAD65 autoantibodies	
There was no significant difference between groups; 6 studies, N = unclear, OR = 1.49, 95%CI 0.76 to 2.92, $p = 0.24$, $I^2 = 0\%$	
Consistency	Consistent
Precision	Imprecise
Directness	Direct

Jackson AJ, Miller BJ

Meta-analysis of total and differential white blood cell counts in schizophrenia

Acta Psychiatrica Scandinavica; 142(1): 18-26

View review abstract online

Comparison	**White blood cell counts in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds medium-sized effects of increased total white blood cell count, monocytes, and neutrophils in people with schizophrenia or first-episode psychosis. There were no differences in lymphocytes, eosinophils, or basophils.**
White blood cell count, neutrophils, and monocytes	
Medium-sized effects of increased total white blood cell count, monocytes, and neutrophils in people with schizophrenia; 24 studies, N = 3,133 Total white blood cell count: SMD = 0.39, 95%CI 0.24 to 0.55, $p < 0.01$, $I^2 = 63\%$ Neutrophils: SMD = 0.53, 95%CI 0.36 to 0.70, $p < 0.01$, $I^2 = 61\%$ Monocytes: SMD = 0.41, 95%CI 0.25 to 0.58, $p < 0.01$, $I^2 = 59\%$ Subgroup analysis of first-episode psychosis patients showed similar effect sizes. There were no moderating effects of age, sex, geography, BMI, smoking, publication year, and quality score on total white blood cell count. There were no differences in levels of lymphocytes, eosinophils, or basophils.	

Consistency	Inconsistent
Precision	Precise
Directness	Direct

Karageorgiou V, Milas GP, Michopoulos I

Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2019; 206: 4-12

View review abstract online

Comparison	**Neutrophil-to-lymphocyte ratio in people with schizophrenia or first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a medium-sized effect of increased neutrophil-to-lymphocyte ratio in people with schizophrenia or first-episode psychosis.**

Neutrophil-to-lymphocyte ratio

A medium-sized effect showed the neutrophil-to-lymphocyte ratio was increased in people with schizophrenia;

10 studies, N = 1,474, SMD = 0.65, 95%CI 0.54 to 0.86, $p < 0.0001$, $I^2 = 62\%$

Subgroup analysis showed a similar effect in both acutely relapsed and first-episode patients.

There were no moderating effects of study quality, age, sample size, duration of illness, gender, smoking status, platelet, monocyte count, or symptom severity, but increased polymorphonuclear count and increased antipsychotic use increased the effect size.

Consistency	Inconsistent
Precision	Precise
Directness	Direct

Lachance L, McKenzie K

Biomarkers of gluten sensitivity in patients with non-affective psychosis:

A meta-analysis

Schizophrenia Research 2014; 152: 521-527

View review abstract online

Comparison	**Comparison of biomarkers of gluten sensitivity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests increases in anti-gliadin IgG and IgA (medium effects), anti-TTG2 IgA (large effects) and other wheat protein antibodies (small effects for anti-gluten, anti-wheat and non-specified anti-gliadin) in people with schizophrenia.**

Blood biomarkers of gluten sensitivity

Anti-gliadin IgG

Significant, medium effect of increased of anti-gliadin IgG in people with a non-affective psychosis compared to controls;

6 studies, N = 5,858, OR 2.51, 95%CI 1.16 to 4.58, $p = 0.02$, $I^2 = 91\%$, $p < 0.00001$

Anti-gliadin IgA

Significant, medium effect of increased anti-gliadin IgA in people with a non-affective psychosis compared to controls;

6 studies, N = 4,023, OR 2.57, 95%CI 1.13 to 5.82, $p = 0.02$, $I^2 = 91\%$, $p < 0.00001$

Anti-TTG2 IgA

Significant, large effect of increased of anti-TTG2 IgA in people with a non-affective psychosis compared to controls;

5 studies, N = 3,962, OR 5.86, 95%CI 2.88 to 11.95, $p < 0.00001$, $I^2 = 0\%$, $p = 0.52$

Anti-gluten, anti-wheat, anti-gliadin unspecified

Significant, small effect of increased anti-gluten, anti-wheat, anti-gliadin (unspecified) in people with a non-affective psychosis compared to controls;

8 studies, N = 405, OR 1.93, 95%CI 1.21 to 3.08, $p > 0.05$, I^2 not reported

No significant differences between patients and controls were reported for;

Extractable nuclear antigens, endothelial, glutamic acid decarboxylase, glutamic acid decarboxylase 65, ganglioside, gastric parietal cell, keratin, mitochondria, sarcolemma, smooth muscle, thyroid, thyroid peroxidase, and hippocampus IgG

Consistency	Inconsistent
Precision	Imprecise
Directness	Direct

Marques TR, Ashok AH, Pillinger T, Veronese M, Turkheimer FE, Dazzan P, Sommer IE, Howes OD

Neuroinflammation in schizophrenia: Meta-analysis of in vivo microglial imaging studies

Psychological Medicine 2019; 49: 2186-96

View review abstract online

Comparison	**Translocator protein (measured by PET) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small samples, some inconsistency, precise, direct) suggests a small to medium-sized increase in translocator protein in people with schizophrenia when measured using binding potential, but not volume of distribution.**

Translocator protein

A small to medium-sized, significant elevation in tracer binding in schizophrenia when binding potential was used as an outcome measure;

6 studies, N = 191, g = 0.31, 95%CI 0.02 to 0.60, p = 0.03, I^2 = 58%

The results were not significant after correcting for potential publication bias (g = 0.13).

There was no significant difference when volume of distribution was used as the outcome measure;

6 studies, N = 226, g = -0.22, 95%CI -0.64 to 0.19, p = 0.30, I^2 = 53%

Authors report that five out of the six studies included in the binding potential meta-analysis used the first-generation tracer [11C]-PK11195, and the volume of distribution studies used second-generation tracers. Therefore, the difference between the findings could reflect tracer differences.

Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

Mazza MG, Lucchi S, Rossetti A, Clerici M

Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and

systematic review	
World Journal of Biological Psychiatry 2019; 21(5): 326-338 View review abstract online	
Comparison	**Neutrophil-to-lymphocyte, monocyte-lymphocyte, and platelet-lymphocyte ratios in people with schizophrenia or first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds medium-sized effects of increased neutrophil-to-lymphocyte and monocyte-lymphocyte ratios in people with schizophrenia or first-episode psychosis. There was also a trend effect for increased platelet-lymphocyte ratio.**
Neutrophil-to-lymphocyte ratio, monocyte-lymphocyte ratio, and platelet-lymphocyte ratio	
Medium-sized effects showed people with schizophrenia had increased; Neutrophil-to-lymphocyte ratio: 8 studies, N = 1,234, SMD = 0.715, 95%CI 0.525 to 0.905, $p < 0.001$, $I^2 = 58\%$ Monocyte-lymphocyte ratio: 5 studies, N = 769, SMD = 0.417, 95%CI 0.147 to 0.686, $p = 0.002$, $I^2 = 66\%$ There were no moderating effects of diagnosis, sex, and country of origin. *There was a trend effect for increased platelet-lymphocyte ratio;* 3 studies, N = 545, SMD = 0.399, 95%CI -0.012 to 0.810, $p = 0.057$, $I^2 = 78\%$	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Miller BJ, Gassama B, Sebastian D, Buckley P, Mellor A

Meta-Analysis of Lymphocytes in Schizophrenia: Clinical Status and Antipsychotic Effects

Biological Psychiatry 2013; 73: 993-999 View review abstract online	
Comparison 1	**Comparison of lymphocyte levels in people with an acute exacerbation of psychosis vs. controls.**

Inflammation and the immune system

Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) suggests a medium size effect of decreased T-lymphocytes (CD3 percentage), increased total white blood cell count, T-helper lymphocytes (CD4 percentage), natural killer cells (CD56 absolute), and a small effect of increased T-helper / suppressor lymphocyte ratio (CD4/CD8) in people with an acute exacerbation of psychosis. Moderate to low quality evidence (inconsistent) also suggests a large effect of increased natural killer cells (CD56 percentage) in patients.**

Blood immune cell parameters

Total white blood cell count

Significant, medium effect of increased total white blood cell count in people with an acute exacerbation of psychosis compared to controls;

2 studies, N = 84, g = 0.54, 95%CI 0.08 to 1.00, p = 0.02, I^2 = 0%, p = 0.43

T-lymphocytes; CD3 percentage

Significant, medium effect of decreased CD3% in people with an acute exacerbation of psychosis compared to controls;

4 studies, N = 213, g = -0.49, 95%CI -0.77 to -0.21, p < 0.01, I^2 not reported, p > 0.05

T-helper lymphocytes; CD4 percentage

Significant, small effect of increased CD4% in people with an acute exacerbation of psychosis compared to controls;

5 studies, N = 277, g = 0.26, 95%CI 0.02 to 0.50, p = 0.04, I^2 = 58.4%, p = 0.05

In sensitivity analyses removing one study, the heterogeneity was no longer significant, and the effect size increased slightly;

4 studies, N = 245, g = 0.35, 95%CI 0.10 to 0.61, p < 0.01, I^2 not reported, p > 0.05

T-helper/suppressor lymphocyte ratio; CD4/CD8

Significant, small effect of increased CD4/CD8 in people with an acute exacerbation of psychosis compared to controls;

5 studies, N = 295, g = 0.31, 95%CI 0.08 to 0.54 p < 0.01, I^2 not reported, p > 0.05

Natural killer cells; CD56 percentage and CD56 absolute

Significant, large effect of increased CD56% and a medium effect of increased CD56 in people with an acute exacerbation of psychosis compared to controls;

CD56%: 2 studies, N = 96, g = 0.83, 95%CI 0.41 to 1.25, p < 0.01, I^2 = 79.7%, p = 0.03

CD56: 2 studies, N = 120, g = 0.63, 95%CI 0.26 to 0.99, p < 0.01, I^2 not reported, p > 0.05

No significant differences between patients and controls were reported for;

Total lymphocyte count, T-lymphocytes (CD3), T-helper lymphocytes (CD4, although there was a trend increase in the sensitivity analysis), T-suppressor/cytotoxic lymphocytes (CD8 & CD8%), B-

lymphocytes (CD19 & CD19%), and activated T-lymphocytes (CD25%).	
Consistency	Consistent for total white blood cell count, T-lymphocytes (CD3%), T-helper lymphocytes, sensitivity analysis only (CD4%), T-helper / suppressor lymphocyte ratio (CD4/CD8), and natural killer cells (CD56 absolute). Inconsistent for natural killer cells (CD56%).
Precision	Precise
Directness	Direct
Comparison 2	**Comparison of lymphocyte levels in drug naïve first-episode psychosis patients vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) suggests a medium effect of decreased T-lymphocytes (CD3 percentage) in drug naïve first-episode psychosis patients.** **Moderate quality evidence (imprecise) also suggests medium to large effects of increased T-lymphocytes (CD3), a large effect of increased T-helper lymphocytes (CD4), and a medium effect of increased T-helper/suppressor lymphocyte ratio (CD4/CD8) in patients.**
T-lymphocytes; CD3 percentage and CD3 absolute *Significant, medium effect of decreased CD3%, and medium to large effect of increased CD3 in drug naïve first-episode psychosis patients compared to controls;* CD3%: 2 studies, N = 182, g = -0.31, 95%CI -0.63 to 0.00, p = 0.05, I^2 = 59.3%, p = 0.09 CD3: 2 studies, N = 81, g = 0.72, 95%CI 0.20 to 1.24, p < 0.01, I^2 = 0%, p = 0.82 T-helper lymphocytes; CD4 absolute *Significant, large effect of increased CD4 in drug naïve first-episode psychosis patients compared to controls;* 2 studies, N = 91, g = 0.86, 95%CI 0.33 to 1.38, p < 0.01, I^2 = 0%, p = 0.32 T-helper/suppressor lymphocyte ratio; CD4/CD8 *Significant, medium effect of increased CD4/CD8 in drug naïve first-episode psychosis patients compared to controls;* 2 studies, N = 62, g = 0.56, 95%CI 0.04 to 1.07, p = 0.03, I^2 = 0%, p = 0.99 *No significant differences between patients and controls were reported for:* T-helper lymphocytes (CD4%), T-suppressor/cytotoxic lymphocytes (CD8 & CD8%), and B-lymphocytes (CD19) Total lymphocyte count *Significant, medium to large effect of increased total lymphocyte count in drug naïve first-episode*	

psychosis patients compared to controls; 2 studies, N = 81, *g* = 0.77, 95%CI 0.25 to 1.29, *p* < 0.01, I^2 = 0%, *p* = 0.42 Note that this finding has been updated in Pillinger, 2018, where no significant effect was found.	
Consistency	Consistent
Precision	Precise for CD3% only.
Directness	Direct
Comparison 3	**Comparison of lymphocyte levels in stable medicated patients vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium sized sample, consistent, precise, direct) suggests a medium-sized effect of decreased T-lymphocytes (CD3 percentage) in stable medicated patients.**
<u>T-lymphocytes; CD3 percentage</u> *Significant, medium effect of decreased CD3% in stable medicated patients compared to controls;* 2 studies, N = 129, *g* = -0.41, 95%CI -0.79 to -0.03, *p* = 0.04, I^2 not reported, *p* > 0.05	
Consistency	Consistent
Precision	Precise
Directness	Direct
Comparison 4	**Pre-post treatment comparison of lymphocyte levels following an average of 9 weeks of antipsychotic treatment for acute exacerbation of psychosis.**
Summary of evidence	**Moderate to high quality evidence (small to medium sized samples, consistent, precise, direct) suggest a medium effect of increased T-suppressor/cytotoxic lymphocytes (CD8 percentage), natural killer cells (CD56 absolute), and T-lymphocytes (CD3 percentage), a small to medium effect of increased T-suppressor/cytotoxic lymphocytes (CD8 absolute), and a small effect of decreased T-helper/suppressor lymphocyte ratio (CD4/CD8) following antipsychotic treatment for acute psychosis.**
Lymphocyte levels	
<u>T-suppressor/cytotoxic lymphocytes; CD8 percentage and CD8 absolute</u> *Significant, medium effect of increased CD8%, and a small to medium sized effect of increased CD8 after an average of 9 weeks of antipsychotic treatment;* CD8%: 4 studies, N = 165, *g* = 0.53, 95%CI 0.21 to 0.85, *p* < 0.01, = I^2 0%, *p* = 0.61	

CD8: 4 studies, N = 186, *g* = 0.34, 95%CI 0.04 to 0.64, *p* = 0.03, I^2 = 13.3%, *p* = 0.33

T-helper/suppressor lymphocyte ratio; CD4/CD8

Significant, small effect of decreased CD4/CD8 after an average of 8 weeks of antipsychotic treatment;

6 studies, N = 258, *g* = -0.26, 95%CI -0.51 to -0.01, *p* = 0.05, I^2 = 19.5%, *p* = 0.29

Natural killer cells; CD56 absolute

Significant, medium effect of increased natural killer cells CD56 absolute after an average of 9 weeks of antipsychotic treatment;

3 studies, N = 109, *g* = 0.58, 95%CI 0.18 to 0.98, *p* < 0.01, I^2 = 39.4%, *p* = 0.22

T-lymphocytes; CD3 percentage

Significant, medium effect of increased CD3% after an average of 11weeks of antipsychotic treatment;

2 studies, N = 196, *g* = 0.46, 95%CI 0.14 to 0.78, *p* < 0.01, I^2 not reported, *p* > 0.05

No significant differences between patients and controls were reported for;

Total white blood cell count, total lymphocytes, T-lymphocytes (CD3), T-helper lymphocytes (CD4% & CD4, although there was a trend increase in CD4 in the sensitivity analysis), B-lymphocytes (CD19 & CD19%), activated T-lymphocytes (CD25%), and natural killer cells (CD56%).

Consistency	Consistent
Precision	Precise
Directness	Direct

Orlovska-Waast S, Kohler-Forsberg O, Brix SW, Nordentoft M, Kondziella D, Krogh J, Benros ME

Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis

Molecular Psychiatry 2018; 24: 869-87

View review abstract online

Comparison	**CSF markers of inflammation and infection in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, some inconsistency and imprecision, direct) finds medium-sized increases in CSF total protein, albumin ratio, IgG ratio, IL-6 and IL-8 in people with schizophrenia. There was a**

	medium-sized decrease in IgG/albumin ratio, and no differences in CSF cell count, albumin, IgG, IgG index, IL-1α, IL-1β, IL-2, IL-6R, neopterin, MIP-1α, C3, MCP-2, TNFR2, TGFB1 or TGFB2.
CSF markers of inflammation and infection	
There were medium-sized increases in; Total protein: 3 studies, N = 239, SMD = 0.41, 95%CI 0.15 to 0.67, p = 0.002, I^2 = 0% Albumin ratio: 1 study, N = 114, SMD = 0.71, 95%CI 0.33 to 1.09, p = 0.0002 IgG ratio: 1 study, N = 114, SMD = 0.68, 95%CI 0.30 to 1.06, p = 0.0004 IL-6: 7 studies, N = 418, SMD = 0.55, 95%CI 0.35 to 0.76, p < 0.00001, I^2 = 1% IL-8: 3 studies, N = 197, SMD = 0.46, 95%CI 0.17 to 0.75, p = 0.002, I^2 = 0% *There was a medium-sized decrease in;* IgG/albumin ratio: 1 study, N = 63, SMD = -0.62, 95%CI -1.13 to -0.12, p = 0.02 *There were no significant differences in;* Cell count: 1 study, N = 63, SMD = 0.19, 95%CI -0.31 to 0.68, p = 0.46 Albumin: 2 studies, N = 177, SMD = 0.21, 95%CI -0.29 to 0.70, p = 0.41, I^2 = 62% IgG: 2 studies, N = 177, SMD = -0.12, 95%CI -0.93 to 0.69, p = 0.77, I^2 = 85% IgG index: 2 studies, N = 180, SMD = 0.25, 95%CI -0.07 to 0.56, p = 0.13, I^2 = 7% IL-1α: 3 studies, N = 105, SMD = -0.16, 95%CI -0.91 to 0.60, p = 0.68, I^2 = 43% IL-1β: 2 studies, N = 79, SMD = -0.13, 95%CI -4.96 to 4.71, p = 0.96, I^2 = 98% IL-2: 3 studies, N = 139, SMD = 0.18, 95%CI -0.49 to 0.85, p = 0.60, I^2 = 64% IL-6R: 1 study, N = 81, SMD = -0.24, 95%CI -0.68 to 0.20, p = 0.28 Neopterin: 1 study, N = 21, SMD = -0.05, 95%CI -0.91 to 0.81, p = 0.91 MIP-1α: 1 study, N = 16, SMD = -0.70, 95%CI -1.72 to 0.32, p = 0.18 C3: 1 study, N = 81, SMD = 0.00, 95%CI -0.44 to 0.44, p = 1.00 MCP-2: 1 study, N = 81, SMD = 0.26, 95%CI -0.18 to 0.71, p = 0.24 TNFR2: 1 study, N = 81, SMD = 0.06, 95%CI -0.38 to 0.50, p = 0.78 TGFB1: 1 study, N = 63, SMD = 0.29, 95%CI -0.25 to 0.83, p = 0.29 TGFB2: 1 study, N = 63, SMD = -0.14, 95%CI -0.68 to 0.40, p = 0.61	
Consistency	Consistent for IL-6, IL-8, total protein and IgG index
Precision	Precise, apart from IgG/Albumin ratio, IgG, IL-1α, IL-1β, IL-2, neopterin, MIP-1α, TGFB1, and TGFB2.
Directness	Direct

Park S, Miller BJ

Meta-analysis of cytokine and C-reactive protein levels in high-risk psychosis

Schizophrenia Research 2019; Apr: doi: 10.1016/j.schres.2019.03.012

View review abstract online

Comparison	**Cytokine and C-reactive proteins in people at clinical or genetic high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) finds a small effect of increased IL-6 blood levels in people at high risk of psychosis. Moderate quality evidence (small sample, consistent, imprecise, direct) showed a medium-sized effect of lower blood IL-1β levels in people at high risk of psychosis. There may also be higher IL-4 levels and lower IL-10 levels. There were no differences in other cytokines or c-reactive proteins.** **There was a non-significant trend for higher IL-12 levels in converters vs non-converters.**
Cytokine and C-reactive proteins	
A small effect showed blood IL-6 levels were significantly higher in people at high risk; 5 studies, N = 229, SMD = 0.31, 95%CI 0.02 to 0.59, p = 0.04, I^2 = 0% There were no moderating effects of age, sex, body mass index, or year of publication. *There was a non-significant trend for higher IL-4 levels;* 2 studies, N = 102, SMD = 1.10, 95%CI -0.14 to 2.35, p = 0.08, I^2 = 85% *A medium-sized effect showed blood IL-1ß levels were significantly lower in people at high risk;* 2 studies, N = 74, SMD = -0.66, 95%CI -1.27 to -0.05, p = 0.05, I^2 = 0% *There was a non-significant trend for lower IL-10 levels;* 2 studies, N = 77, SMD = -0.59, 95% CI -1.20 to 0.02, p = 0.06, I^2 = 0% There were no significant differences in IL-5, IL-8, IL-12, IFN-γ, TNF-α, TNF-β, or CRP. *There was a non-significant trend for higher IL-12 levels in converters vs non-converters;* 3 studies, N = 146, SMD = 0.86, 95%CI -0.06 to 1.79, p = 0.07, I^2 = 77%	
Consistency	Consistent, apart from IL-4 and IL-12 levels.
Precision	Precise for IL-6 only.

Directness	Direct

Pearlman DM, Najjar S

Meta-analysis of the association between N-methyl-D-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder

Schizophrenia Research 2014; 157: 249-258

View review abstract online

Comparison	**Comparison of N-methyl-D-aspartate receptor antibodies in patients with schizophrenia vs. controls.** **Note: samples were predominately people with schizophrenia, but also included people with bipolar and major depressive disorders.**
Summary of evidence	**Moderate quality evidence (large sample size, imprecise, inconsistent, direct) suggests a medium-sized, increased odds of NMDAR antibody seropositivity in patients vs. controls using a high-specificity threshold, but not a low-specificity threshold.**

Blood N-methyl-D-aspartate receptor (NMDAR) antibodies

Significant, medium sized increased odds of NMDAR antibody seropositivity among patients vs. controls using a high-specificity threshold, but not a low-specificity threshold;

High-specificity threshold: 5 studies, N = 3,387, OR = 3.10, 95%CI 1.04 to 9.27, $p = 0.043$, $I^2 = 68\%$, $p = .025$

Low-specificity threshold: 4 studies, N = 3,194, OR = 2.31, 95%CI 0.55 to 9.73, $p = 0.25$, $I^2 = 90\%$, $p < 0.001$

All study participants were 4.5 times more likely to test seropositive for NMDAR antibodies based on a high-specificity threshold (1.320 dilution) than on a low-specificity threshold (1.10 dilution).

No significant differences were reported between people with first episode vs. chronic schizophrenia or schizoaffective disorder.

Consistency	Inconsistent
Precision	Imprecise
Directness	Direct

Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD

A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis

Schizophrenia Bulletin 2019; 45: 1120-33

View review abstract online

Comparison	**Blood cytokine, C-reactive proteins and lymphocyte levels in drug-naive people with first-episode psychosis vs. controls.** **Note: some samples included people with first-episode affective psychosis.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, mostly precise, direct) finds medium to large increases in IFN-y, IL-17, IL-6, sIL-2r, TGF-β, TNF-α and C-reactive proteins (trend effect) in drug-naïve first-episode psychosis patients compared to controls. There were no significant differences in IL-10, IL-1β, IL-2, IL-4, IL-8, or total lymphocyte count.** **The significant findings for IL-6, IL-17, and IFN-γ remained in studies that matched for age, gender, BMI, and smoking, apart from TNF-a which became non-significant suggesting a confounded effect.**

Blood cytokine levels

There were significant, medium to large increases in patients in;

IFN-y: 9 studies, N = 643, g = 0.32, 95%CI 0.11 to 0.53, p = 0.003, I^2 = 37%

IL-17: 7 studies, N = 670, g = 0.48, 95%CI 0.06 to 0.89, p = 0.03, I^2 = 85%

IL-6: 15 studies, N = 1,297, g = 0.62, 95%CI 0.32 to 0.92, p < 0.0001, I^2 = 84%

TGF-β: 3 studies, N = 234, g = 0.53, 95% CI = 0.18 to 0.88, p = 0.003, I^2 = 36%

TNF-α: 11 studies, N = 929, g = 0.56, 95% CI = 0.22 to 0.90, p = 0.001, I^2 = 82%

sIL-2r: 4 studies, N = 156, g = 2.66, 95% CI -0.03 to 5.34, p = 0.05, I^2 = 97%

There were no significant differences between groups for:

IL-10: 9 studies, N = 731, g = 0.24, 95% CI = -0.13 to 0.62, p = 0.20, I^2 = 82%

IL-1β: 7 studies, N = 576, g = 0.49, 95% CI = -0.13 to 1.11, p = 0.12, I^2 = 92%

IL-2: 9 studies, N = 483, g = -0.07, 95% CI = -0.53 to 0.39, p = 0.77, I^2 = 82%

IL-4: 7 studies, N = 560, g = 0.23, 95% CI = -0.05 to 0.51, p = 0.10, I^2 = 57%

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

IL-8: 5 studies, N = 241, *g* = 0.04, 95% CI = -0.62 to 0.70, *p* = 0.90, I^2 = 82% Subgroup analysis containing only studies that matched for age, gender, BMI, and smoking showed elevated IL-6, IL-17, and IFN-γ in patients, with no significant differences in TNF-α, IL-10, or IL-1β. These findings are consistent with the primary meta-analyses, apart from TNF-α suggesting it could be influenced by confounding. There were insufficient data in matched studies to analyse IL-2, sIL-2r, IL-4, IL-8, or TGF-β. Authors report there was no increased heterogeneity within studies of patients compared to within studies of controls (apart from TGF-β), suggesting evidence against the existence of an immune subgroup of psychosis.
Blood lymphocyte levels
There was no significant difference in total lymphocyte count; 3 studies, N = 236, *g* = 0.31, 95%CI -0.13 to 0.76, *p* = 0.17, I^2 = 64%
Blood C-reactive protein
There was a trend effect of increased C-reactive protein levels in patients; 5 studies, N = 579, *g* = 0.66, 95%CI -0.03 to 1.34, *p* = 0.06, I^2 = 92%

Consistency	Inconsistent, apart from IFN-y and TGF-β.
Precision	Precise, apart from IL-1β, sIL-2r and C-reactive protein.
Directness	Direct

Plitman E, Iwata Y, Caravaggio F, Nakajima S, Chung JK, Gerretsen P, Kim J, Takeuchi H, Chakravarty MM, Remington G, Graff-Guerrero A

Kynurenic Acid in Schizophrenia: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 43: 2017 764-77

View review abstract online

Comparison	**Kynurenic acid levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a medium-sized increase in kynurenic acid in people with schizophrenia. This effect was most pronounced in studies of cerebrospinal fluid, brain tissue, in older patients, in medicated patients, and in male patients.**

Kynurenic acid	
There were significant, medium-sized increases in patients; 13 studies, N = 961, SMD = 0.66, 95%CI 0.25 to 1.06, p = 0.001, I^2 = 90% Subgroup analysis found similar effect sizes in cerebrospinal fluid (SMD = 0.66, p < 0.00001), brain tissue (SMD = 0.55, p < 0.0001), and plasma/serum (SMD = 0.51), although the analysis for plasma/serum was not significant (p = 0.23) Meta-regression showed that studies with older patients age (slope = 0.022, p = 0.012), more medicated patients (slope = 0.008, p < 0.001) or more males (slope = 0.012, p = 0.002) reported higher effect sizes.	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Romeo B, Brunet-Lecomte M, Martelli C, Benyamina A

Kinetics of cytokine levels during antipsychotic treatment in schizophrenia: A meta-analysis

International Journal of Neuropsychopharmacology 2018; 21: 828-36

View review abstract online

Comparison 1	**Blood cytokine levels after antipsychotic treatment in drug-free people with schizophrenia (first-episode and chronic patients combined).** **Treatment duration was 3-12 weeks.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, mostly precise, direct) finds significant medium-sized reductions post-treatment in IL-1β and IFN-γ, and trend reductions in IL-6, TNF-α and IL-4. sTNF-r2 and sIL-2r were increased post-treatment. There were no differences in sIL-6r, IL-8, IL-12, sTNF-r1, IL-2, IL-17, IL1-ra, TGF-β, IL-10 or IL-23.**
Blood cytokine levels	
There were significant medium-sized reductions post-treatment in; IL-1β: 7 studies, N = 482, SMD = -0.40, 95%CI -0.58 to -0.22, p < 0.0001, I^2 = 0%, p = 0.61 IFN-γ: 8 studies, N = 760, SMD = -0.38, 95%CI -0.67 to -0.09, p = 0.01, I^2 = 70%, p = 0.002	

There were trend-effect reductions in;
IL-6: 21 studies, N = 1,547, SMD = -0.22, 95%CI: -0.47 to 0.03, p = 0.08, I^2 = 81% p < 0.0001
TNF-α: 19 studies, N = 1,162, SMD = -0.32, 95%CI -0.65 to 0.02, p = 0.07, I^2 = 86%, p < .0001
IL-4: 7 studies, N = 798, SMD = -0.47, 95%CI -0.99 to 0.06, p = 0.08, I^2 = 92%, p < .0001
There were medium to large significant increases post-treatment in;
sTNF-r2: 3 studies, N = 98, SMD = 0.94, 95%CI 0.52 to 1.36, p < 0.0001, I^2 = 0%, p = 0.78
sIL-2r: 11 studies, N = 526, SMD = 0.26, 95%CI, 0.03 to 0.49, p = 0.03, I^2 = 38%, p = 0.10
There were no significant differences in;
sIL-6r: 4 studies, N = 168, SMD = -0.17, 95%CI -0.71 to 0.37, p = 0.53, I^2 = 64%, p = 0.04
IL-8: 4 studies, N = 288, SMD = -0.17, 95%CI -0.41 to 0.06, p = 0.14, I^2 = 0%, p = 0.99
IL-12: 4 studies, N = 242, SMD = 0.13, 95%CI -0.34 to 0.60, p = 0.58, I^2 = 67%, p = 0.03
sTNF-r1: 5 studies, N = 182, SMD = 0.35, 95%CI -0.16 to 0.86, p = 0.18, I^2 = 64%, p = 0.02
IL-2: 10 studies, N = 622, SMD = 0.31, 95%CI -0.03 to 0.40, p = 0.39, I^2 = 94%, p < 0.01
IL-17: 3 studies, N = 496, SMD = 0.02, 95%CI -0.29 to 0.34, p = 0.88, I^2 = 66%, p = 0.05
IL1-ra: 6 studies, N = 262, SMD = -0.03, 95%CI -0.48 to 0.42, p = 0.89, I^2 = 69%, p = 0.006
TGF-β: 5 studies, N = 606, SMD = -0.20, 95%CI -0.61 to 0.21, p = 0.35, I^2 = 82%, p = 0.0002
IL-10: 8 studies, N = 420, SMD = 0.09, 95%CI -0.40 to 0.57, p = 0.72, I^2 = 82%, p < 0.01
IL-23: 2 studies, N = 136, SMD = -0.01, 95%CI -0.35 to 0.32, p = 0.94, I^2 = 0%, p = 0.65
Meta-regression showed a significant, large association between increased effect size for IL-6 and increased positive symptom score pre-post treatment (r = 0.81, p = 0.001), and a statistical trend for IL-10 and positive symptoms (r = 0.76, p = 0.08).
Subgroup analyses of specific antipsychotics showed risperidone decreased IL-1β, IL-6, IL-2, IL-10, and IL-4, and increased IL-12. Olanzapine decreased IL-2 and IFN-γ. Aripiprazole increased IL-10 and a trend decrease in IL-4. Clozapine increased sTNF-R1, sTNF-R2, and sIL-2r, and showed a trend increase in IL-6. Haloperidol decreased IL-2. Quetiapine resulted in no changes in cytokine levels.

Consistency	Inconsistent, apart from IL-1β, sTNF-r2, sIL-2r, IL-8, and IL-23.
Precision	Precise, apart from IL-4, sIL-6r, and sTNF-r1.
Directness	Direct
Comparison 2	**Blood cytokine levels after antipsychotic treatment in people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) finds reductions post-treatment in IL-1β, IL-6 and IL-4 in first-episode patients.**

Blood cytokine levels	
There were significant medium-sized reductions post-treatment in; IL-1β: 4 studies, N = 359, SMD = -0.36, 95%CI -0.63 to -0.10, p = 0.007, I^2 = 27%, p = 0.25 IL-6: 5 studies, N = 452, SMD = -0.36, 95%CI -0.57 to -0.16, p = 0.0004, I^2 = 13%, p = 0.33 IL-4, 3 studies N = 34, SMD = -0.45, 95%CI -0.75 to -0.15, p = 0.003, I^2 = 41%, p = 0.18 There were no significant differences in IFN-γ, IL-10, IL-17, IL-2, TNF-α or IL-8.	
Consistency	Consistent
Precision	Precise
Directness	Direct
Comparison 3	**Post-treatment blood cytokine changes in people with an acute exacerbation of chronic schizophrenia.** **Note: this comparison is an update of comparison 3 in Goldsmith 2016.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds reductions post-treatment in IL-1β, IL-6, sIL-6r, TNF-α and IFN-γ in people with an acute exacerbation of schizophrenia.**
Blood cytokine levels	
There were significant medium-sized reductions post-treatment in; IL-1β: 6 studies, N = 447, SMD = -0.41, 95%CI -0.59 to -0.22, p < 0.0001, I^2 = 0%, p = 0.47 IL-6: 14 studies, N = 1,265, SMD = -0.44, 95%CI -0.74 to -0.15, p = 0.003, I^2 = 83%, p < 0.00001 sIL-6r: 2 studies, N = 106, SMD = -0.51, 95%CI -0.90 to -0.12, p = 0.01, I^2 = 0%, p = 0.35 TNF-α: 12 studies, N = 908, SMD = -0.46, 95%CI -0.89 to -0.03, p = 0.04, I^2 = 89%, p < 0.00001 IFN-γ: 7 studies, N = 726, SMD = -0.41, 95%CI -0.73 to -0.09, p = 0.01, I^2 = 73%, p < 0.0001 *There was a small, significant increase post-treatment in;* sIL-2r: 11 studies, N = 526, SMD = 0.26, 95%CI 0.03 to 0.39, p = 0.03, I^2 = 38%, p = 0.10 *There were no significant differences in;* IL-12: 2 studies, N = 242, SMD = 0.13, 95%CI -0.34 to 0.60, p = 0.58, I^2 = 67%, p = 0.03 IL-2: 10 studies, N = 622, SMD = -0.31, 95%CI -0.03 to 0.40, p = 0.39, I^2 = 94%, p < 0.01 IL-17: 3 studies, N = 496, SMD = 0.02, 95%CI -0.29 to 0.34, p = 0.88, I^2 = 6%, p = 0.05 TGF-β: 5 studies, N = 606, SMD = -0.20, 95%CI -0.61 to 0.21, p = 0.35, I^2 = 82%, p = 0.0002 IL-10: 8 studies, N = 420, SMD = -0.09, 95%CI -0.40 to 0.57, p = 0.72, I^2 = 82%, p < 0.01	

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

IL-4: 7 studies, N = 798, SMD = -0.47, 95%CI -0.99 to 0.06, p = 0.08, I^2 = 92%, p < 0.01	
Consistency	Inconsistent, apart from IL-1β, sIL-2r and sIL-6r.
Precision	Precise
Directness	Direct
Comparison 4	**Blood cytokine levels after antipsychotic treatment in people with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (small samples, consistent, precise, direct) finds reductions post-treatment in IL-6 and sIL-2r in people with treatment-resistant schizophrenia.**
Blood cytokine levels	
There were significant medium-sized increases post-treatment in; IL-6: 3 studies, N = 116, SMD = 0.57, 95%CI 0.20 to 0.95, p = 0.003, I^2 = 0%, p = 0.52 sIL-2r: 2 studies, N = 78, SMD = 0.85, 95%CI 0.39 to 1.32, p = 0.0003, I^2 = 0%, p = 0.83 There were no significant differences in sIL-6 R, TNF-α or IL-1 RA.	
Consistency	Consistent
Precision	Precise
Directness	Direct

van Kesteren CFMG, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG, Kahn RS, Sommer IEC

Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies

Translational Psychiatry 2017; 7: e1075

View review abstract online

Comparison	**Post-mortem evaluation of cell and molecular immunological changes in people with schizophrenia vs. controls**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, inconsistent, precise, direct) suggests a medium-sized increase in cell microglia and a small to medium-sized increase in pro-inflammatory molecular components in people with schizophrenia. No differences were found in cell macroglia or**

	lymphocyte levels or in anti-inflammatory molecular components.
Immune cell density	
A significant, medium-sized effect of increased microglia in people with schizophrenia; 11 studies, N = 340, SMD = 0.69, 95%CI 0.24 to 1.14, $p = 0.0028$, $I^2 = 68.6\%$ Subgroup analysis on brain regions demonstrated this increase was most consistently observed in the temporal cortex and in studies assessing ramified or activated microglia. There were no effects of age at death, suicide as cause of death, pH-value, duration of illness, or gender. *No differences between groups were found for macroglia or lymphocyte levels;* Macroglia: 18 studies, N = 561, SMD = -0.10, 95%CI -0.45 to 0.25, $p = 0.57$ Lymphocyte CD3+: 1 study, N = 52, SMD = 0.61, 95%CI -0.17 to 1.38, $p > 0.05$ Lymphocyte CD20+: 1 study, N = 52, SMD = 0.67, 95%CI -0.11 to 1.44, $p > 0.05$ These results remained, irrespective of brain area or cell type.	
Molecular components	
A significant, small to medium-sized effect of increased pro-inflammatory molecular components in people with schizophrenia; 14 studies, N = 653, SMD = 0.37, 95%CI 0.11 to 0.62, $p = 0.0052$, $I^2 = 83.2\%$ There were no differences between groups in sub-analyses on RNA vs. protein expression. *No differences between groups were found for anti-inflammatory levels;* 3 studies, N = 188, SMD = -0.52, 95%CI 0.09 to -1.12, $p = 0.10$	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Wang AK, Miller BJ

Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons between Schizophrenia, Bipolar Disorder, and Depression

Schizophrenia Bulletin 2018; 44: 75-83

Inflammation and the immune system

View review abstract online	
Comparison	**CSF cytokine and kynurenine levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, mostly consistent and precise, direct) suggests medium to large increases in IL-6, IL8, kynurenine, and kynurenic acid. Moderate to low quality evidence (small sample) also finds a large decrease in sIL-2r in the CSF of people with schizophrenia. No differences were found in IL-1α, IL-2 or sTNF-R2.**
CSF cytokine and kynurenine levels	
There were significant, medium to large increases in patients in; IL-6: 7 studies, N = 420, SMD = 0.40, 95%CI 0.20 to 0.60, $p < 0.001$, $I^2 = 0\%$, $p = 0.53$ IL-8: 3 studies, N = 213, SMD = 0.35, 95%CI 0.07 to 0.63, $p = 0.013$, $I^2 = 0\%$, $p = 0.60$ IL-1β: 3 studies, N = 102, SMD = 0.75, 95%CI 0.29 to 1.21, $p = 0.001$, $I^2 = 95\%$, $p < 0.01$ Note: the IL-1β comparison was not significant in the update in Gallego, 2018. Kynurenine: 3 studies, N = 152, SMD = 1.22, 95%CI 0.86 to 1.58, $p < 0.001$, $I^2 = 86\%$, $p < 0.01$ Kynurenic acid: 4 studies, N = 289, SMD = 0.59, 95%CI 0.34 to 0.83, $p < 0.001$, $I^2 = 0\%$, $p = 0.41$ *There was a significant, large decrease in patients in;* sIL-2r: 2 studies, N = 38, SMD = -0.84, 95%CI -1.50 to -0.18, $p = 0.013$, $I^2 = 0\%$, $p = 0.42$ *There were no significant differences in;* IL-1α: 2 studies, N = 101, SMD = -0.33, 95%CI -0.77 to 0.11, $p = 0.143$, $I^2 = 71\%$, $p = 0.06$ IL-2: 4 studies, N = 166, SMD = -0.01, 95%CI -0.35 to 0.33, $p = 0.954$, $I^2 = 51\%$, $p = 0.11$ sTNF-R2: 2 studies, N = 101, SMD = -0.09, 95%CI -0.49 to 0.30, $p = 0.646$, $I^2 = 61\%$, $p = 0.11$	
Consistency	Consistent, apart from kynurenine and IL-1β.
Precision	Precise, apart from sIL-2r.
Directness	Direct

Inflammation and the immune system

Explanation of acronyms

CBA = cytometric bead array, CI = confidence interval, CRP = C-reactive protein, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, ELISA = enzyme-linked immunosorbent assay, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IFN = interferon, IgG = immunoglobulin G, IL = interleukin, IP-10 = interferon-γ induced protein-10, MCP-1 = monocyte chemoattractant protein-1, MIP-1α = macrophage inflammatory protein-1α, N = number of participants, NMDAR = N-methyl-D-aspartate receptor, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, sIL = soluble interleukin, SMD = standardised mean difference, TGF = transforming growth factor, TNF = tumour necrosis factor, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[25].

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[26]. ORs and RRs are similar when the outcome is rare. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed [27].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Ezeoke A, Mellor A, Buckley P, Miller B (2013): A systematic, quantitative review of blood autoantibodies in schizophrenia. *Schizophrenia Research* 150: 245-51.
4. Lachance LR, McKenzie K (2014): Biomarkers of gluten sensitivity in patients with non-affective psychosis: A meta-analysis. *Schizophrenia Research* 152: 521-7.
5. Miller BJ, Gassama B, Sebastian D, Buckley P, Mellor A (2013): Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. *Biological Psychiatry* 73: 993-9.
6. Pearlman DM, Najjar S (2014): Meta-analysis of the association between N-methyl-d-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder. *Schizophrenia Research* 157: 249-58.
7. van Kesteren CFMG, Gremmels H, de Witte LD, Hol EM, Van Gool AR, Falkai PG*, et al.* (2017): Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. *Translational Psychiatry* 7: e1075.
8. Capuzzi E, Bartoli F, Crocamo C, Clerici M, Carra G (2017): Acute variations of cytokine levels after antipsychotic treatment in drug-naive subjects with a first-episode psychosis: A meta-analysis. *Neuroscience & Biobehavioral Reviews* 77: 122-8.
9. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM*, et al.* (2016): C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Molecular Psychiatry* 21: 554-64.
10. Frydecka D, Krzystek-Korpacka M, Lubeiro A, Stramecki F, Stanczykiewicz B, Beszlej JA*, et al.* (2018): Profiling inflammatory signatures of schizophrenia: A cross-sectional and meta-analysis study. *Brain, Behavior, and Immunity* 71: 28-36.
11. Gallego JA, Blanco EA, Husain-Krautter S, Madeline Fagen E, Moreno-Merino P, del Ojo-Jimenez JA*, et al.* (2018): Cytokines in cerebrospinal fluid of patients with schizophrenia spectrum disorders: New data and an updated meta-analysis. *Schizophrenia Research* 202: 64-71.
12. Goldsmith DR, Rapaport MH, Miller BJ (2016): A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Molecular Psychiatry* 21: 1696-709.
13. Grain R, Lally J, Stubbs B, Malik S, LeMince A, Nicholson TR*, et al.* (2017): Autoantibodies against voltage-gated potassium channel and glutamic acid decarboxylase in psychosis: A systematic review, meta-analysis, and case series. *Psychiatry and Clinical Neurosciences* 71: 678-89.
14. Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD (2019): A Meta-analysis of Immune Parameters, Variability, and Assessment of Modal Distribution in Psychosis and Test of the Immune Subgroup Hypothesis. *Schizophrenia Bulletin* 45: 1120-33.
15. Romeo B, Brunet-Lecomte M, Martelli C, Benyamina A (2018): Kinetics of cytokine levels during antipsychotic treatment in schizophrenia: A meta-Analysis. *International Journal of Neuropsychopharmacology* 21: 828-36.
16. Wang AK, Miller BJ (2018): Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons between Schizophrenia, Bipolar Disorder, and Depression. *Schizophrenia Bulletin* 44: 75-83.
17. Plitman E, Iwata Y, Caravaggio F, Nakajima S, Chung JK, Gerretsen P*, et al.* (2017): Kynurenic Acid in Schizophrenia: A Systematic Review and Meta-analysis. *Schizophrenia Bulletin* 43: 764-77.
18. Marques TR, Ashok AH, Pillinger T, Veronese M, Turkheimer FE, Dazzan P*, et al.* (2019): Neuroinflammation in schizophrenia: Meta-analysis of in vivo microglial imaging studies. *Psychological Medicine* 49: 2186-96.

19. Bora E (2019): Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: A meta-analysis. *Psychological Medicine* 49: 1971-9.
20. Jackson AJ, Miller BJ (2019): Meta-analysis of total and differential white blood cell counts in schizophrenia. *Acta Psychiatrica Scandinavica* 142: 18-26.
21. Karageorgiou V, Milas GP, Michopoulos I (2019): Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research* 206: 4-12.
22. Mazza MG, Lucchi S, Rossetti A, Clerici M (2019): Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and systematic review. *World Journal of Biological Psychiatry* 21: 326-38.
23. Orlovska-Waast S, Kohler-Forsberg O, Brix SW, Nordentoft M, Kondziella D, Krogh J*, et al.* (2019): Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. *Molecular Psychiatry* 24: 869-87.
24. Park S, Miller BJ (2019): Meta-analysis of cytokine and C-reactive protein levels in high-risk psychosis. *Schizophrenia Research* Apr: doi: 10.1016/j.schres.2019.03.012.
25. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
26. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
27. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*