Alteration patterns of peripheral concentrations of cytokines and associated inflammatory proteins in acute and chronic stages of schizophrenia: a systematic review and network meta-analysis

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Introduction

The past three decades have witnessed a burgeoning research interest in the involvement of the immune system in the pathophysiology of schizophrenia, a severe multisystem disorder with an elusive aetiology.[1] An array of genetic, epidemiological, and interventional evidence supports the role of immunological processes.[2–4] This evidence for immune system involvement also includes aberrant concentrations of cytokines, which are hypothesised to mediate the effect of stressors on the development of psychosis in those with a genetic predisposition to psychosis.[5]

Cytokines are a diverse group of small circulating proteins that act as chemical messengers within the innate and adaptive immune systems.[6] Produced by both immune and non-immune cells, cytokines elicit their effects through binding to specific cell surface receptors.[7] Receptor binding typically involves cascades, in which certain cytokines stimulate the production and release of subsequent cytokines.[8] In addition to cell surface receptors, there can also be soluble forms of cytokine receptors that can either increase or decrease the biological activity of the cytokine.[8] Functions of individual cytokines are varied, with generally either a pro-inflammatory or anti-inflammatory effect.[8] As they are unable to cross the majority of the blood–brain barrier in normal physiological conditions, it is postulated that peripheral cytokines communicate with the central nervous system (CNS) through a variety of mechanisms, including inducing secondary messengers, carrier-mediated transport of cytokines, and passive transport at sites lacking a blood–brain barrier.[9] The blood–brain sbarrier is thought to be more frequently disrupted in schizophrenia, but whether this is a cause or consequence of neurological dysfunction remains unclear.[10] Cytokines can also be produced locally in the CNS by glial cells.[11,12]

Research in context

Evidence before this study

Aberrant concentrations of peripheral inflammatory proteins have been broadly identified in people with schizophrenia-spectrum disorders compared with healthy controls, as part of the ever-growing support for hypothesised immune involvement. However, inconsistencies in the literature remain regarding which inflammatory proteins are altered, and how these alterations differ between acute and chronic stages of psychotic illness. Furthermore, there is limited evidence on lesser studied cytokines, such as interleukin (IL)-4, IL-12, and IL-17, compared with the more routinely studied cytokines: IL-1β, IL-6, and tumour necrosis factor (TNF)-α. We performed a systematic search in PubMed, PsycINFO, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials, from inception to March 31, 2022, to identify studies published in any language containing data on peripheral cytokine concentrations in people with schizophrenia-spectrum disorders, compared with healthy controls. Key search terms included those relating to the various diagnoses grouped under schizophrenia-spectrum disorder (eg, "schizophrenia", "schizoaffective disorder", "psychosis not otherwise specified"), and those relating to inflammatory proteins, such as the names of cytokine families (eg, "interleukin") and appropriate synonyms (eg, "inflammatory biomarker"). From the collated data, we performed extensive pairwise and network-meta-analyses to determine if there were significant alterations of inflammatory protein concentrations in schizophrenia-spectrum disorders.

Added value of this study

By use of a network meta-analysis and utilisation of a large sample, we were able to provide clarification on the alteration patterns of inflammatory proteins associated with schizophrenia-spectrum disorders and compare the indirect relations in inflammatory protein concentrations between acute and chronic schizophrenia-spectrum disorders. Our analyses identified a group of markers (IL-1β, IL-1RA, soluble IL-2 receptor, IL-6, IL-8, IL-10, TNF-α, and C-reactive protein) that were consistently altered in both acute and chronic schizophrenia-spectrum disorders, and a second group (IL-2, IL-4, IL-12, and interferon-γ) that were differentially altered between acute and chronic illness.

Implications of all the available evidence

These results provide an entry point for more advanced research into stage-specific inflammatory marker patterns in schizophrenia-spectrum disorders. Clarifying alteration patterns of peripheral biomarkers can facilitate the search for clinically useful biomarkers that might be used to stratify individuals who are more likely to develop chronic and treatment-resistant illness. Understanding how immune aberration occurs in schizophrenia-spectrum disorders might also facilitate the development of targeted interventions that can modulate these inflammatory processes for a subgroup of patients, potentially reducing symptoms in individuals not achieving symptomatic remission with current treatments.

Once in the CNS, cytokines have been shown to have neurochemical and further immunological effects, as well as to stimulate neuroendocrine processes.[8]

Previous meta-analyses have demonstrated aberrant concentrations of peripheral cytokines in people with schizophrenia-spectrum disorders compared with healthy controls,[1,7,13] and have shown that some antipsychotics might have broad anti-inflammatory effects.[14,15] Aberrant cytokine concentrations have also been identified in the cerebrospinal fluid (CSF) of people with schizophrenia-spectrum disorders compared with healthy controls.[1,7] However, inconsistencies remain over which specific cytokines are affected, and how cytokine concentrations change over the course of the illness. For example, while Goldsmith and colleagues[1] reported a statistically significant increase of peripheral interleukin (IL)-1β, IL-8, and IL-10 concentrations in people with first-episode psychosis versus healthy controls, Fraguas and colleagues[16] reported no significant change in concentrations of peripheral interleukins.

Inconsistencies between these previous meta-analyses are suspected to stem, in part, from heterogeneity in the methods of studies measuring cytokine concentrations. Many analyses have not tested for the impact of variation in measuring and reporting of covariates, including participant (smoking, BMI, illness duration, antipsychotic medication status) and cytokine sampling (fasting status, timing of sampling) factors.[11] Furthermore, few previous meta-analyses have compared how cytokine concentrations might change between acute and chronic illness stages of schizophrenia.[1,7] Addressing this issue is important, not only for methodological rigor, but also as identification of stage-specific inflammatory markers might allow for prediction of recurrence and treatment resistance.[11] Such markers might also facilitate patient stratification for early interventions.[11]

This systematic review and network meta-analysis aims to examine studies that measured peripheral cytokine and other inflammatory protein concentrations (in plasma or serum) in people with schizophrenia-spectrum disorders at a defined stage of acute or chronic illness, compared with a healthy control population. Notably, there have been multiple large studies published over the past 5 years that have not been included in past meta-analyses. Because there is little newly published evidence on CSF markers since Orlovska-Waast's review in 2019,[10,17,18] this Article addresses only peripheral proteins. We hope to gain clarity, not only from a study of greater size, but through examination of the impact of cytokine sampling and covariate variability on the results.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, the databases PubMed, PsycINFO, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched from inception to March 31, 2022, using terms connected to schizophrenia-spectrum disorders and cytokines or associated biomarkers of inflammation (appendix p 2). No language restrictions were applied in the initial searches and full-text articles were digitally translated for screening purposes. After excluding duplicate articles collected through the search process, the remaining articles were screened at title, abstract, and full-text level by two authors independently (SH and MA), with any conflict resolved by two other authors (DS and NW).

For studies to be included, the following criteria were required: (1) an observational or experimental design; (2) a population consisting of adults diagnosed with schizophrenia-spectrum disorders (ie, schizophrenia or other primary psychotic disorders under the schizophrenia spectrum), with a specified indicator of acute or chronic stage of illness; (3) a comparable healthy control population without mental illness; (4) a study outcome that measured the peripheral protein concentration (in plasma or serum) of either a cytokine, associated inflammatory marker (eg, cytokine antagonists and soluble receptor proteins), or C-reactive protein (for studies that measured the protein through a high-sensitivity C-reactive protein test) through a quantitative method (eg, ELISA). Studies that did not measure cytokine proteins or associated biomarkers in blood were excluded—for example, studies measuring genetic material (such as cytokine mRNA), *in vitro* cytokine production, or cytokines in post-mortem tissue. Although relevant, such other outcomes were not included here due to the already large scope of this study.

Study subpopulations, including people with a first episode of psychotic illness, acute exacerbation of chronic schizophrenia-spectrum disorders, acute psychosis not otherwise specified, and hospital inpatients with a primary psychotic illness, were categorised as acute schizophrenia-spectrum disorders. The category of chronic schizophrenia-spectrum disorders consisted of individuals with chronic (including treatment-resistant cases) schizophrenia-spectrum disorders on stable psychopharmacological treatment, and also community outpatients with the condition.

Given the vast heterogeneity in the methods of included studies, restriction by antipsychotic medication status of cohorts (ie, whether cohorts were antipsychotic medication-naïve, off antipsychotic medication, newly medicated, or on stable medication) did not occur. Instead, the percentage of individuals with schizophrenia-spectrum disorders on antipsychotics was recorded and meta-regression, to examine the influence of this covariate, was performed.

Articles without published data contained in the results or supplementary material were excluded (ie, authors were not contacted) and grey literature and unpublished studies were not sought.

See Online for appendix

Data extraction

Data extraction was done by one author (SH) and reviewed by two other authors (DS and NW). The primary outcome measure was peripheral concentration of inflammatory proteins, with a list of included proteins presented in the appendix (p 3). For the primary outcome, mean protein concentration with SD, sample size, and the source of the protein sample (serum or plasma) were transcribed directly from the results section (ie, from tables, figures, and text) from the included full-text articles. When inflammatory marker concentration data were not contained within the full-text itself, associated supplementary material was used. Data conversions, as per Cochrane recommended formulae,[19] were performed on studies reporting medians with first and third quartile values, logarithmic mean and SD values, and stratified cohort values (appendix p 3). Graphically presented data were extracted with the online tool WebPlotDigitizer.

Demographic information about participants was extracted, including mean age, sex ratio, percentage of smokers, and mean BMI. Where available, demographic data were directly transcribed from the methods (ie, description of study cohort) and results (ie, table of demographic data) sections of the included full-text studies. For studies that did not publish data for these variables, the appropriate values were listed as "not otherwise specified". From these data, a control comparability index was calculated between 0 and 1, as a fraction of how many of these four variables were similarly distributed between the case and control populations (eg, studies that controlled for age, sex, BMI, and smoking were given a score of 4/4: an index of 1). Other extracted participant data included: location (by country), diagnostic composition of the cohort (eg, schizophrenia-only, or mixed schizophrenia-spectrum disorder diagnoses), diagnostic criteria used, antipsychotic treatment status (eg, antipsychotic-naïve), percentage of unmedicated cases, percentage of cases on clozapine, mean duration of illness, mean age at illness onset, mean total Positive and Negative Syndrome Scale (PANSS) score,[20] and mean chlorpromazine equivalent. As per the demographic data extraction, where available, data were directly transcribed from the methods (eg, for information about the cohort such as diagnostic criteria, diagnostic composition of cohort, medication status) and results (eg, for measures such as mean total PANSS and mean chlorpromazine equivalent) sections of the included full-text studies. Studies that did not report these variables were listed as not otherwise specified for each unreported variable.

To evaluate the methodological validity of cytokine measurement, assay process details were recorded: type of assay, fasting status, and plasma or serum. Given the heterogeneity in the reporting of assay methodology, an assay validity index was created that was scored out of two for each protein included in a study, giving one mark each for (a) if mean concentrations were above the sensitivity or lower limit of detection for both the psychosis and control groups, and (b) if the intra-assay coefficient was lower than 10% and the inter-assay coefficient was lower than 15%. This index was based upon recognised criteria for assay validity.[1,7]

Study quality appraisal (assessed by SH and reviewed by DS and NW) was done via a seven-item adapted scale based on the Joanna Briggs Institute critical appraisal tool for case-control studies (appendix p 4).[21] Quality adjudications for individual studies were formatted into a quality index from the seven-item scale. Quality index scores were utilised in meta-regression tests to determine if differences in quality between studies biased overall meta-analysis results. Further sensitivity and meta-regression tests were performed for various cohort factors and methodological elements that might have also introduced bias between studies to determine if these significantly impacted the observed results.

Statistical analysis

For all analyses, p values less than 0·05 were considered significant. Each of the individual included studies was scrutinised for details such as location of the study (eg, city, region, or hospital), year of the study, cohort details (eg, average age, sex ratio), and study results (ie, inflammatory marker concentration) to determine if duplicate data had been published multiple times between different studies. In cases in which multiple studies had used the same population to report on the same inflammatory protein, the study with the largest sample was used for that individual meta-analysis. Studies with no unique data (ie, no data for a new marker that was not already included in previous studies for that population) were excluded at full-text level as duplicate study populations.

For all inflammatory proteins with at least three eligible studies, pairwise meta-analyses comparing the standardised mean difference (SMD) in protein concentration between the pooled population with schizophrenia-spectrum disorders and healthy control populations were done, using random effects and Hedges' g as the effect size. These pairwise analyses combined acute and chronic groups from the included studies into a pooled schizophrenia-spectrum disorder group to be able to study a wider range of cytokines. The aforementioned Cochrane formulae were used to combine means and SDs of separate acute and chronic groups (appendix p 3) when individual studies contained both. Subgroup sensitivity analyses were performed to determine if separating the sample according to acute and chronic subgroups impacted these pairwise meta-analysis results. I^2 and χ^2 were used to characterise heterogeneity in each of the pairwise meta-analyses.

To appraise the alterations in inflammatory protein concentrations between acute schizophrenia-spectrum disorder and chronic schizophrenia-spectrum disorder, a frequentist network meta-analysis was performed. For

For more on **WebPlotDigitizer** see https://automeris.io/WebPlotDigitizer

each protein, a network meta-analysis was only done if both acute schizophrenia-spectrum disorder and chronic schizophrenia-spectrum disorder groups had at least five studies contributing data. A random-effects network meta-analysis model was used, given anticipated heterogeneity. For each of the three comparisons in the model, the network meta-analysis calculated the SMD as the effect size. Model inconsistency was examined through consulting the network meta-analysis I^2 as well as the Q statistic and p value from a design-by-treatment interaction model. A funnel plot and Egger's regression test were used to ascertain publication bias for proteins with at least ten studies. Under a design-by-treatment interaction model, the between-design Q statistic (Q_{bd}) was specifically examined to evaluate inconsistency arising between the evidence of each of the three arms of the network meta-analysis model (the three arms and strength of direct evidence are depicted visually in the appendix (pp 97–98).

When appraising the network meta-analysis results, the statistical significance and direction of effect sizes were compared between the acute schizophrenia-spectrum disorder versus healthy control and chronic schizophrenia-spectrum disorder versus healthy control arms of the network meta-analysis. Markers that had both of these arms producing similar results were labelled as consistent (eg, both arms had a statistically significant and positive effect size), and markers where similarity was not met were labelled as inconsistent (eg, only one arm had a statistically significant effect size but in opposite directions). This grouping adjudication was employed to improve the analytical interpretation of the results.

Sensitivity analyses (for categorical variables) and meta-regression modelling (for continuous variables) were used to examine the influence of the following covariates: age, sex, BMI, smoking, antipsychotic treatment status, clozapine use, illness duration, age of onset, country, year of publication, language of article, source of blood sample (plasma or serum), fasting status, symptom severity (total PANSS score), control comparability index, assay validity index, and study quality appraisal. These covariate analyses were only done for proteins with at least ten studies.

Data analysis was done in *R studio* (version 2022.07.1+554); pairwise meta-analyses were done using the *meta* (version 5.5) and *metafor* (version 3.4) packages, while network meta-analysis was done with the *netmeta* package (version 2.5). Because this was a systematic review containing only secondary data, no ethical permission or patient consent was obtained. This systematic review was prospectively registered with PROSPERO (CRD42022320305) and conducted in accordance with PRISMA guidelines.[22]

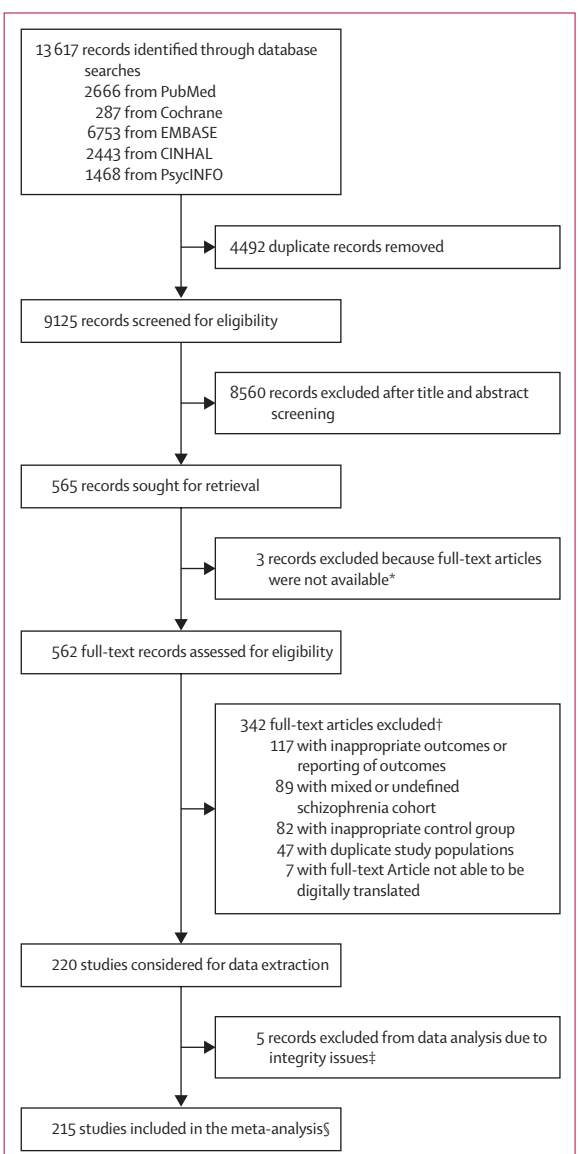

Figure 1: **Study profile**
*Studies listed in the appendix p 24. †Studies listed in the appendix pp 14–22. ‡Studies listed in the appendix p 23. §Studies listed in the appendix pp 5–13.

Role of the funding source
There was no funding source for this study.

Results
13 617 records were identified in the database searches, of which 4492 duplicate records were removed. 9125 records were screened for eligibility, 8560 were excluded after title and abstract screening, and 565 were then sought for full-text retrieval. Three records were then excluded due to the full-text article not being available, and 562 full-text records were assessed for eligibility. 342 full-text articles were excluded due to an inappropriate outcome, mixed or undefined schizophrenia cohorts, or duplicate study populations. During data-analysis, five studies were removed due to concerns over data integrity (appendix p 23), resulting in 215 studies being included in the meta-analysis (figure 1).

From the 215 studies included for analysis (appendix pp 5–13), there was a total of 24 921 participants, comprising 13 952 cases and 10 969 controls (table 1). Acute schizophrenia-spectrum disorder was studied more frequently (130 groups) than was chronic schizophrenia-spectrum disorder (95 groups); ten studies had both acute and chronic groups. From the studies that reported age and sex, the mean age of the cohort with schizophrenia-spectrum disorders was 34·6 years (SD 12·2) and 33·9 years (11·7) for the control cohort, and the male to female ratios were 62%:38% for the cohort with schizophrenia-spectrum disorders and 56%:44% for the control cohort (table 2). Data on ethnicity were not obtained due to inconsistent reporting in the included articles. The most frequently studied inflammatory proteins were IL-6 (106 studies) and tumour necrosis factor (TNF)-α (84 studies) (table 3).

A pairwise meta-analysis was done for 31 cytokines and associated markers (table 3; forest plots in appendix pp 83–96). No meta-analyses were performed for the following proteins due to insufficient data: interferon (IFN)-α, soluble IL-1 receptor antagonist (sIL-1RA), IL-3, IL-9, IL-21, IL-27, IL-33, sIL-33R, and transforming growth factor (TGF)-α. Pairwise meta-analysis demonstrated significantly elevated concentrations of IL-1β, IL-1RA, IL-2, sIL-2R, sIL-2Rα, IL-6, IL-8, IL-10, IL-18, TGF-β (not otherwise specified [NOS]), TNF-α, and C-reactive protein in the pooled schizophrenia-spectrum disorder case population compared with healthy controls (table 3).

Sufficient data were collected to perform individual network meta-analyses for 13 markers. Network meta-analysis (figure 2) demonstrated that concentrations of several inflammatory proteins were consistently significantly elevated in both acute schizophrenia-spectrum disorder and chronic schizophrenia-spectrum disorder, compared with healthy controls: IL-1β, IL-1RA, sIL-2R, IL-6, IL-8, IL-10, and TNF-α. C-reactive protein, which is not regarded as a cytokine but is an associated acute-phase protein, was also significantly elevated in both groups. Conversely, IL-17 showed no difference in concentration in both acute and chronic schizophrenia-spectrum disorders, compared with healthy controls. For nearly all these inflammatory markers, no significant difference was identified between the acute schizophrenia-spectrum disorder and chronic schizophrenia-spectrum disorder groups, with only IL-6 concentration being significantly higher in acute schizophrenia-spectrum disorders compared with chronic schizophrenia-spectrum disorders (SMD 0·29 [95% CI 0·11 to 0·47]).

The cytokines IL-2, IL-4, IL-12(NOS), and IFN-γ were inconsistent in the direction and significance regarding alterations of concentrations for acute and chronic schizophrenia-spectrum disorders when compared with healthy controls (figure 3). IL-4, IL-12(NOS), and IFN-γ conformed to a similar pattern, whereby the cytokine concentrations were increased in acute schizophrenia-spectrum disorder compared with chronic schizophrenia-spectrum disorder, and decreased in chronic schizophrenia-spectrum disorder compared with healthy controls. However, for the acute schizophrenia-spectrum disorder versus healthy control comparison, only IFN-γ demonstrated a significant difference. IL-2 showed an increased concentration in acute schizophrenia-spectrum disorder, but not in chronic schizophrenia-spectrum disorder, when compared with healthy controls. Three of these differentially altered markers (IL-2, IL-12[NOS], and IFN-γ) have been visually depicted in figure 4, with attention to the potential physiological implications in acute and chronic illness stages of schizophrenia-spectrum disorder.[6]

The network meta-analysis comparisons against healthy controls were based primarily on direct data from included studies, while the acute versus chronic schizophrenia-spectrum disorder comparisons were based mainly on indirect data, because only ten studies contained both an acute and chronic schizophrenia-spectrum disorder group (appendix p 36).

	Number of studies
Included studies	215
Single-arm studies	205
Multi-arm studies (acute and chronic)	10
Illness groups	225
Acute schizophrenia spectrum disorder	130
Chronic schizophrenia spectrum disorder	95
Diagnostic composition	
Schizophrenia only	180
Schizophrenia spectrum*	45
Total sample size	24 921
Schizophrenia spectrum disorder sample	13 952
Healthy control sample	10 969

Data are absolute values. *Includes other schizophrenia spectrum disorders such as schizoaffective disorder, brief psychotic disorder, and first-episode psychosis.

Table 1: **Overview of included studies**

	Cohort with schizophrenia spectrum disorder	Healthy controls
Mean age (years)	34·6 (2·2); 209/225	33·9 (11·7); 195/215
Males	62%; 217/225	56%; 203/215
Females	38%; 217/225	44%; 203/215
Smokers	35%; 99/225	27%; 79/215
Mean BMI	25·2 (5·8); 112/225	24·4 (4·6); 95/215

Data are mean (SD) unless otherwise specified. n/N corresponds to a fraction of how many of the included schizophrenia spectrum disorder or control groups had available demographic data (eg, only 99 of the 225 schizophrenia spectrum disorder groups had data on percentage of smokers).

Table 2: **Demographics of participants in schizophrenia spectrum disorder cohorts and healthy controls**

	Marker category	Number of studies	Number of schizophrenia-spectrum disorder cases*	Number of healthy controls	SMD (95% CI)	p value	χ^2	p value	I^2
IL-1α	Interleukin (cytokine)	4	270	227	0·09 (–0·17 to 0·34)	0·51	5·32	0·15	43·58%
IL-1β†	Interleukin(cytokine)	46	2877	2231	0·44 (0·23 to 0·66)	0·0001	498·07	<0·0001	90·97%
IL-2†	Interleukin (cytokine)	37	2229	1700	0·41 (0·12 to 0·7)	0·0056	531·54	<0·0001	93·23%
IL-4	Interleukin (cytokine)	33	2152	1885	–0·12 (–0·46 to 0·22)	0·49	361·36	<0·0001	91·14%
IL-5	Interleukin (cytokine)	9	575	480	0·17 (–0·18 to 0·53)	0·34	37	<0·0001	78·38%
IL-6†	Interleukin (cytokine)	106	6637	5204	0·66 (0·48 to 0·84)	<0·0001	1164·53	<0·0001	90·98%
IL-7	Interleukin (cytokine)	7	422	392	0 (–0·19 to 0·19)	0·99	12·48	0·052	51·90%
IL-8†	Interleukin (cytokine)	37	1912	1641	0·26 (0·09 to 0·43)	0·0020	149·96	<0·0001	75·99%
IL-10†	Interleukin (cytokine)	48	3190	2626	0·24 (0·01 to 0·48)	0·044	381·18	<0·0001	87·67%
IL-12 (NOS)	Interleukin (cytokine)	12	789	665	–0·07 (–0·31 to 0·16)	0·54	47·2	<0·0001	76·69%
IL-12p40	Interleukin (cytokine)	4	322	280	0·31 (–0·07 to 0·7)	0·11	14·01	0·0029	78·58%
IL-12p70	Interleukin (cytokine)	7	422	311	0·39 (–0·41 to 1·19)	0·34	80·1	<0·0001	92·51%
IL-13	Interleukin (cytokine)	7	394	392	0·3 (–0·08 to 0·68)	0·12	24·23	0·0005	75·24%
IL-15	Interleukin (cytokine)	3	205	178	–0·1 (–0·91 to 0·72)	0·82	16·22	0·0003	87·67%
IL-17	Interleukin (cytokine)	16	1153	823	0·17 (–0·06 to 0·4)	0·14	78·05	<0·0001	80·78%
IL-17A	Interleukin (cytokine)	4	267	251	0·13 (–0·04 to 0·31)	0·14	1·48	0·69	0%
IL-18†	Interleukin (cytokine)	5	413	320	0·48 (0·3 to 0·66)	<0·0001	5·96	0·20	32·87%
IL-23	Interleukin (cytokine)	4	196	170	1·41 (–0·08 to 2·90)	0·063	64·74	<0·0001	95·37%
IL-2R (NOS)	Interleukin receptor	3	90	75	0·33 (–0·51 to 1·17)	0·44	13·90	0·0010	85·62%
sIL-2R†	Soluble interleukin receptor	14	1200	1142	0·62 (0·18 to 1·06)	0·0054	72·53	<0·0001	82·08%
sIL-2Rα†	Soluble interleukin receptor	4	96	95	1·25 (0·54 to 1·96)	0·0006	14·76	0·0020	79·67%
sIL-6R	Soluble interleukin receptor	5	149	138	0·11 (–0·55 to 0·77)	0·74	23·29	0·0001	82·83%
IL-1RA†	Interleukin antagonist	16	740	732	0·46 (0·23 to 0·7)	0·0020	74·52	<0·0001	79·87%
IFN-γ	Interferon (cytokine)	46	2726	2355	0·08 (–0·22 to 0·38)	0·61	489·29	<0·0001	90·80%
TGF-β (NOS)†	Transforming growth factor (cytokine)	7	749	726	0·73 (0·29 to 1·16)	<0·0001	50·42	<0·0001	88·10%
TGF-β1	Transforming growth factor (cytokine)	10	573	401	0·31 (–0·5 to 1·13)	0·45	133·91	<0·0001	93·28%
TNF-α†	Tumour necrosis factor (cytokine)	84	5190	4281	0·55 (0·38 to 0·73)	<0·0001	1001·98	<0·0001	91·72%
TNF-β	Tumour necrosis factor (cytokine)	4	348	268	0·09 (–0·14 to 0·33)	0·44	5·08	0·17	40·95%
sTNF-R1	Tumour necrosis factor receptor	5	328	407	1·48 (–0·23 to 3·19)	0·090	197·09	<0·0001	97·97%
sTNF-R2	Tumour necrosis factor receptor	5	263	324	1·47 (–0·03 to 2·98)	0·054	152·95	<0·0001	97·38%
C-reactive protein†	Acute-phase protein	35	2128	1622	0·65 (0·45 to 0·86)	<0·0001	285·14	<0·0001	88·08%

SMD=standardised mean difference. IL=interleukin. NOS=not otherwise specified. sIL=soluble interleukin. IFN=interferon. TGF=transforming growth factor. TNF=tumour necrosis factor. sTNF=soluble tumour necrosis factor. *Total number of individuals in the pooled population of the schizophrenia-spectrum disorder cohort (ie, combining all available acute and chronic schizophrenia-spectrum disorder groups) for each respective pairwise meta-analysis. †Markers calculated to be significantly (p<0·05) increased through pairwise meta-analysis in individuals with schizophrenia-spectrum disorders compared with healthy controls.

Table 3: **Pairwise meta-analysis results of comparison of peripheral marker concentrations between people with schizophrenia-spectrum disorders and healthy controls**

The network meta-analysis findings were broadly consistent with the pairwise results of the combined schizophrenia-spectrum disorder sample (table 3); however, because of the statistical tests used in network meta-analyses, these results had more precise confidence intervals. As such, some cytokines that were not reported to be significantly altered in the pairwise results were reported to be significantly altered in the network results, such as IL-4, IL-12(NOS), and IFN-γ.

On study quality assessment (appendix pp 25–33), 44 studies were rated as high quality (meeting six to seven criteria), 114 as moderate quality (meeting three to five criteria), and 57 as low quality (meeting two or fewer of the seven criteria). The lowest quality domains concerned the comparability between patient and control

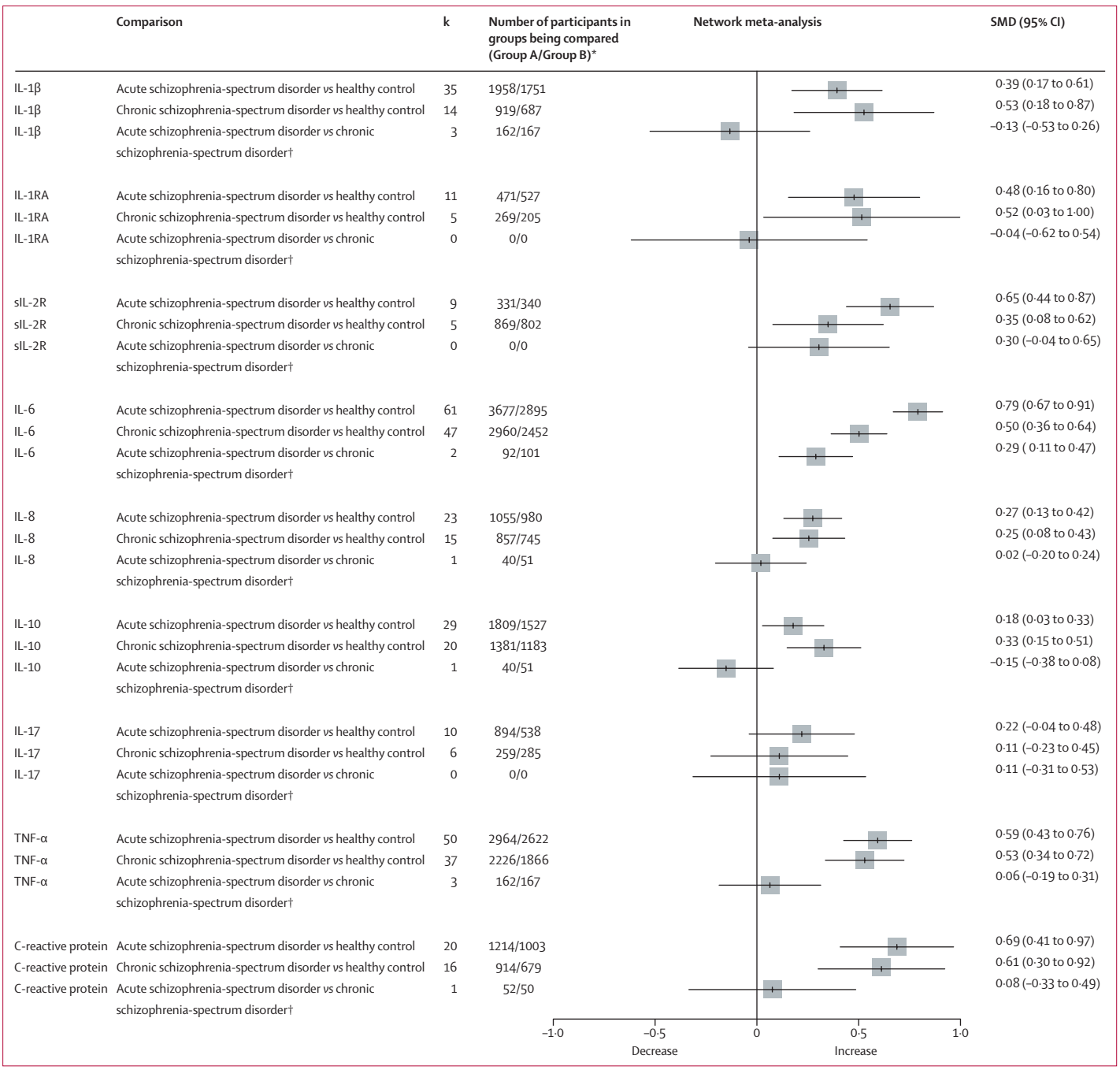

Figure 2: **Network meta-analysis results of inflammatory proteins with consistent alteration patterns in schizophrenia-spectrum disorders for acute and chronic illness, compared with healthy controls**

K denotes the number of studies with data for direct network comparison. IL=interleukin. sIL=soluble interleukin. SMD=standardised mean difference. TNF=tumour necrosis factor. *Number of participants in the respective first and second groups of each comparison (from studies with direct data). †Because there were few studies (or 0, for IL-1RA, sIL-2R, and IL-17) with direct participant data for the acute schizophrenia-spectrum disorder vs chronic schizophrenia-spectrum disorder comparisons, these network meta-analysis results were primarily based on indirect data from the other two comparisons (appendix p 36).

groups and methodological validity of cytokine measurement. Egger's regression tests for publication bias were generally non-significant, with the exception of IL-1RA, sIL-2R, IL-6, and TNF-α for the pairwise analyses (appendix pp 35). Both the pairwise and network meta-analyses encountered significant heterogeneity with I^2 values frequently higher than 80% (table 3; appendix p 34).

Sensitivity and meta-regression analyses (appendix pp 37–39) were undertaken for the entire

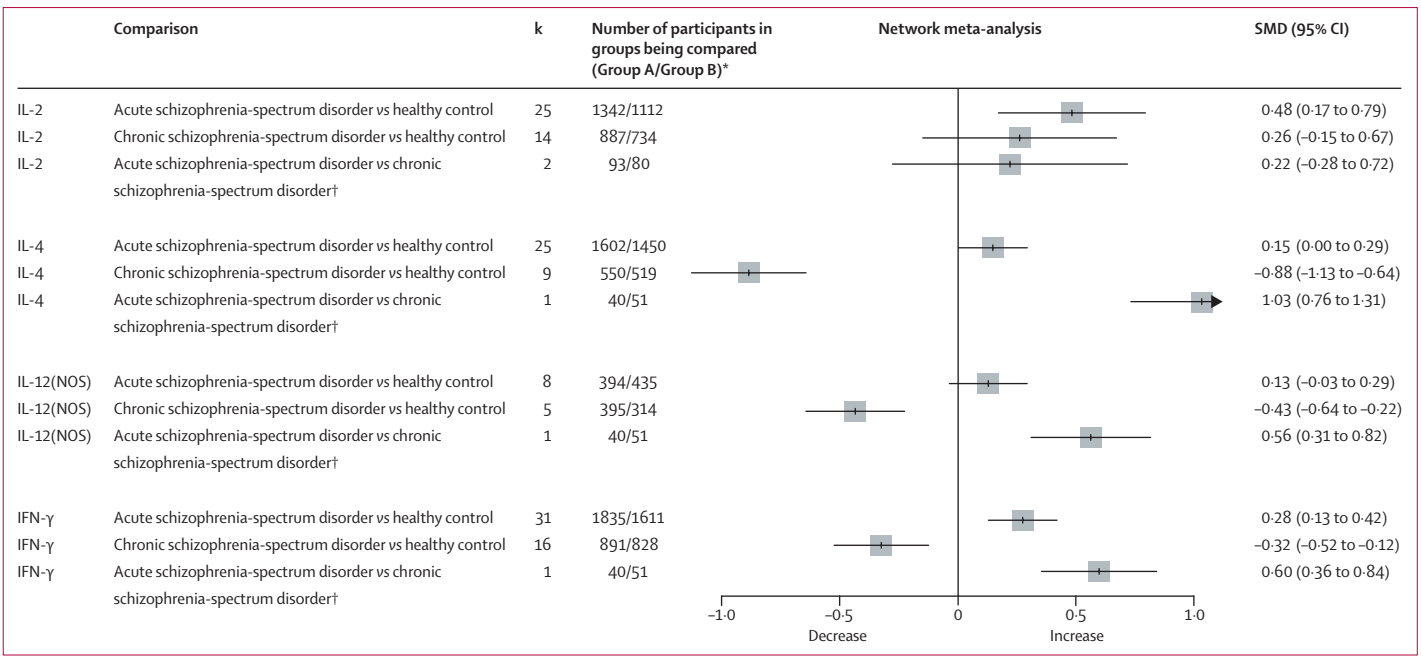

Figure 3: **Network meta-analysis results of inflammatory proteins with inconsistent alteration patterns in schizophrenia-spectrum disorders for acute and chronic illness, compared with healthy controls**

K denotes the number of studies with data for direct network comparison. IL=interleukin. IFN=interferon. SMD=standardised mean difference. *Number of participants in the respective first and second groups of each comparison (from studies with direct data). †Because there were few studies with direct participant data for the acute schizophrenia-spectrum disorder vs chronic schizophrenia-spectrum disorder comparisons, these network meta-analysis results were primarily based on indirect data from the other two comparisons (appendix p 36).

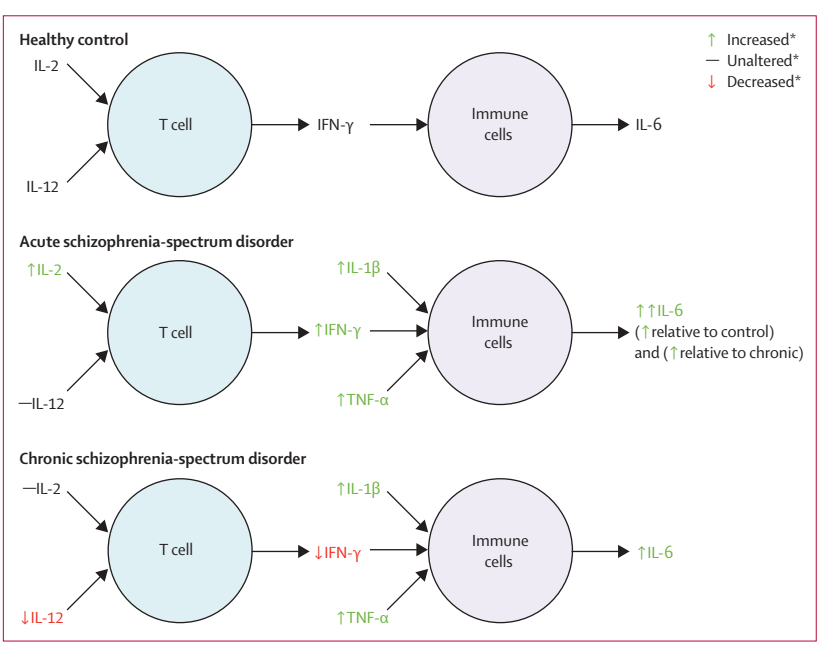

Figure 4: **Hypothetical illustration of the influence of trait and state cytokines on inflammation in acute and chronic schizophrenia-spectrum disorders**

IFN-γ has been used as an example in this diagram. IL=interleukin. IFN=interferon. TNF=tumour necrosis factor. *Compared with healthy control.

schizophrenia-spectrum disorder sample examined in the pairwise meta-analyses. Overall, these analyses revealed no pervasive confounding factors; however, some factors were found to be significant for specific proteins. Methodological factors were routinely demonstrated not to have a significant effect on results. Exceptions were assay source for IL-2 and IL-8, study quality for TGF-β1, and assay validity for IL-1β. Similarly, demographic factors did not have a significant influence on results; the exceptions being age for IFN-γ and IL-12(NOS), and age, smoking, and BMI for IL-4. Meta-regression against sex ratios revealed no significant impact for the majority of markers tested, but was significant for IFN-γ and IL-12(NOS). Control comparability was not a significant factor for any of the proteins. Diagnostic factors, such as diagnostic criteria, antipsychotic use, clozapine use, and illness duration were mostly non-significant. Sensitivity analyses of diagnostic composition led to significant group differences for IL-1β, IL-2, IL-6, and TNF-α. The percentage of cases free of antipsychotics was only significant for IL-4 and IL-1RA; illness duration, symptom severity, and subgroup composition were also significant for IL-4.

Discussion

This is the largest systematic review and the first network meta-analysis to provide cytokine-based evidence that schizophrenia-spectrum disorders are associated with immunological aberration. Through investigating the peripheral concentration of circulating cytokines and other associated proteins compared with healthy controls, this study has identified discrete groups of biomarkers

that adhere to distinct patterns of alteration in acute and chronic schizophrenia-spectrum disorders. IL-1β, IL-6, IL-8, IL-10, IL-1RA, sIL-2R, TNF-α, and the inflammatory marker C-reactive protein were consistently elevated in both acute and chronic schizophrenia-spectrum disorders compared with healthy controls. IL-2 and IFN-γ were elevated in acute but not chronic schizophrenia-spectrum disorder, while IL-4, IL-12, and IFN-γ were decreased in chronic schizophrenia-spectrum disorder.

Although there have been previous meta-analyses of cytokines in schizophrenia-spectrum disorders, the large sample size, with approximately four times the included participants than the next largest meta-analysis,[13] addresses several of the previous inconsistencies within the literature. The findings of this review largely corroborate the results of Goldsmith and colleagues,[1] with the exception of the results for IL-2, IL-4, and IL-10. There is less agreement with smaller meta-analyses focused on antipsychotic-naïve first-episode psychosis cohorts,[12,13] and without appropriate healthy control comparators.[7] The elevated concentrations of C-reactive protein in schizophrenia-spectrum disorders shown in this study broadly corroborate the findings of Fernandes and colleagues;[23] however, this was the first study to identify this alteration in distinct acute and chronic illness groups.

Discussions on cytokine involvement in schizophrenia-spectrum disorders have often sought to categorise specific cytokines as either "trait" or "state" markers. Trait markers are associated with genetic and developmental factors corresponding to an individual's susceptibility to illness. For cytokines to constitute a trait marker for schizophrenia-spectrum disorders, they need to be consistently altered in all phases of illness when compared with healthy controls.[12,24] By comparison, state markers are associated with active disease pathology in symptomatic individuals,[24] and cytokines considered to be state markers should have differential alteration patterns between acute illness and periods of remission. Using these concepts as a theoretical framework, the markers with consistent alteration patterns (IL-1β, IL-6, IL-8, IL-10, IL-1RA, sIL-2R, TNF-α, and C-reactive protein) can be hypothesised to be trait markers, and the differentially altered markers (IL-2, IL-4, IL-12, and IFN-γ) can be hypothesised to be potential state markers.

Of the proposed trait markers, IL-1β, IL-6, IL-8, TNF-α, and C-reactive protein are associated with major pro-inflammatory function, largely through triggering and signalling in inflammatory cascades.[6] IL-1RA concentrations will reflect the concentration of IL-1β as it is secreted in response to the same stimuli and counteracts the pro-inflammatory actions by binding to the same receptor.[6] Similarly, IL-10 has an important role in suppressing T-cell activation and communication through reducing the secretion of pro-inflammatory cytokines from macrophages and T-helper-1 lymphocytes.[6] Finally, as a soluble receptor, sIL-2R is secreted by activated T-cells, and can be involved in both enhancement and inhibition of IL-2 activity.[25] With increased concentrations in both acute and chronic phases of illness, these hypothesised trait markers might indicate low-grade inflammation caused by pro-inflammatory cytokines with a homoeostatic anti-inflammatory response. In line with this hypothesis, evidence from longitudinal studies suggests that increased serum concentrations of some pro-inflammatory proteins precede psychosis onset.[26]

Despite a limited understanding of the precise mechanisms that underpin the cross-talk between peripheral inflammation and impact on the CNS, there is an array of evidence from animal, imaging, and CSF studies that demonstrate interconnectedness.[27–29] For example, diffusion-weighted magnetic resonance imaging of people with schizophrenia showed an association between increased peripheral IL-6 and TNF-α concentrations with neuroinflammatory processes characterised by increased micro-vessel permeability and production of reactive oxygen species.[28] Within the CNS, prolonged exposure to pro-inflammatory cytokines might lead to neuronal apoptosis and is detrimental to neurogenesis, especially in areas such as the hippocampus.[30–32] Inflammatory cytokines might also mediate oligodendrocyte cytotoxicity, impairing myelin production and resulting in abnormal myelination, a pathology seen in both autopsy and animal model studies of schizophrenia-spectrum disorders.[33,34]

The proposed state markers IL-2, IL-4, IL-12, and IFN-γ, which were differentially altered between acute and chronic illness stages, have integral roles in T-cell functioning and activity. IL-2, which is elevated in acute schizophrenia-spectrum disorder, is responsible for stimulaing the proliferation of lymphocytes and natural killer (NK) cells, and also induces the release of inflammatory mediators such as IFN-γ.[6,12] In turn, IFN-γ stimulates cytokine release and in particular, it increases concentrations of IL-6 in acute schizophrenia-spectrum disorder beyond chronic schizophrenia-spectrum disorder.[12] IL-6 is postulated to have a role in disrupting the blood–brain barrier's integrity, which can lead to influx of peripheral cytokines and immune cells and exacerbate microglial-mediated CNS inflammatory processes.[11,12] Decreased IL-4, IL-12, and IFN-γ concentrations in chronic stages of illness might suggest that a different type of lymphocyte cellular activity occurs, or these might be the result of the immunomodulating effect of antipsychotics.[35,36] Other immunomodulating conditions seen in schizophrenia-spectrum disorders are weight gain, smoking, and medical comorbidities (such as autoimmune conditions and metabolic syndrome).[37–39] This might explain why IL-4, a hypothesised state marker potentially more prone to immunomodulation between acute and chronic illness stages than markers that were consistently elevated throughout illness stages (eg, TNF-α, or IL-1β), was significantly associated, through

regression analysis, with factors such as age, BMI, illness duration, illness severity, and antipsychotic medication status, compared with the majority of trait markers which did not replicate these associations. Understanding how such illness-related factors relate to inflammatory markers requires primary research that compares inflammatory marker concentrations between subgroups of people with schizophrenia-spectrum disorders, as categorised by the presence of factors such as obesity, medical comorbidities, and antipsychotic treatment-resistance.

There are several limitations that need to be considered when interpreting the results of this review. Firstly, seven articles (published in languages other than English) that could not be digitally translated were excluded during full-text screening. Publication bias might have been introduced from the decision to include papers in which there was selective reporting of cytokine results, frequently occurring in studies for which cytokine assays had been performed as secondary outcomes. This publication bias might have differentially affected unaltered cytokines (such as IL-17) with non-significant results less likely to be reported. Meta-analyses for some proteins were not performed due to an insufficient number of studies, which particularly affect lesser studied proteins in schizophrenia-spectrum disorders, such as IL-33.

The groupings of acute schizophrenia-spectrum disorder and chronic schizophrenia-spectrum disorder were somewhat general and non-specific; this concession was made due to limited subgroup data that prohibited more specific analyses (appendix pp 80–81). As expected, significant heterogeneity in both the pairwise and network meta-analyses was encountered and although sensitivity and meta-regression analyses for potential confounders were conducted and generally did not indicate significant impact on results, this should be noted. Other unevaluated variables for which data were not collected, such as ethnicity, might have also biased results. Moreover, as this review focused on exploring the breadth of available evidence, more advanced and nuanced research which utilises alternative statistical methodologies is recommended to explore this topic in greater depth. For example, deeper exploration of other important factors, such as illness duration and severity, will be crucial.

The network meta-analysis was limited in its ability to detect differences in the acute schizophrenia-spectrum disorder versus chronic schizophrenia-spectrum disorder comparisons due to the reliance on indirect data, especially for IL-1RA, sIL-2R, and IL-17, for which there were no direct data (appendix p 36).

Q_{bd} values were assessed to test for network consistency under a full design-by-treatment interaction random-effects model. These revealed significant inconsistency for IL-4 and TNF-α, in conjunction with high heterogeneity (as per I^2 values) throughout all network meta-analyses (appendix p 34). Random-effects was used in part to attenuate these issues. However, the network meta-analysis results should be interpreted with caution due to the possible effects of inconsistency on network transitivity.

The limitations of so-called state and trait markers should be noted, as it is a classification system that can reduce dynamic biological mediators into binary categories. However, this study proposes that framing markers with hypothesised state and trait roles is useful under a theoretical model that facilitates communication and speculation on an otherwise complex, and largely unknown, biological subject. Reference to these terms is not intended as a precise commentary on the specific biological roles of individual cytokines. Moreover, because only peripheral cytokines in those with established psychotic diagnoses were studied, no direct comment could be made on whether the hypothesised state and trait markers are present in the CNS, and in individuals at high risk for psychosis. Altogether, these findings should be regarded as an entry point into illness-stage based exploration of inflammatory markers in schizophrenia-spectrum disorders, rather than a conclusive description of inflammatory marker mechanisms in schizophrenia-spectrum disorders.

There is a distinct peripheral inflammatory signature of cytokines and associated proteins in people with schizophrenia-spectrum disorders, with different alteration patterns observed between acute and chronic stages of the illness. This study provides guidance for the framing of cytokines as potential state and trait biomarkers or to indicate a subgroup of cases with a greater inflammatory phenotype. These findings might lead to the repurposing of drugs, such as anti-inflammatory medications, as treatment adjuncts in schizoprenia-spectrum disorder. Ultimately, greater clarity of how inflammation is involved in the cause and pathophysiology of schizophrenia could foster the development of new targeted interventions aimed at illness prevention.

Contributors

NW, DS, SH, and EW devised this study with assistance from KW and ZL. SH and MA did the systematic search and study selection, with assistance and supervision by DS, NW, and EW. SH performed data extraction, data analysis, and quality assessment, with verification and support by DS and NW. Upon completion of data analysis, authors EW, VY, KW, and ZL assisted with interpretation of the results with correlation to the existing scientific literature on cytokines and schizophrenia. SH wrote the first draft of the manuscript with assistance from NW and DS. All authors edited the final manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

DS is supported by a National Health and Medical Research Council Investigator Fellowship (GNT 1194635). EW has been invited to advisory boards from Recordati. NW has received speaker fees from Otsuka, Lundbeck, and Janssen. All other authors declare no competing interests.

Data sharing

Study data are available from the corresponding author upon reasonable request.

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