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SYSTEMATIC REVIEW

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Inflammation in first-episode psychosis: The contribution of inflammatory biomarkers to the emergence of negative symptoms, a systematic review and meta-analysis

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Abstract

Objective: To provide a comprehensive analysis of cytokine perturbations in antipsychotic-naïve first-episode psychosis (FEP) populations and assess the relationship between inflammatory biomarkers and negative symptom severity.

Methods: A systematic review and meta-analysis following PRISMA guidelines were conducted. A total of 1042 records were identified via systematic search of EMBASE, MEDLINE and APA PsycInfo databases. Sixteen studies met the inclusion criteria and were eligible for inclusion in the review. Ten of these studies had sufficient data for inclusion in a random effects, pooled-effect meta-analysis.

Results: A significant and large effect size was reported for IFN-γ, IL-6 and IL-12, and a moderate effect size reported for IL-17 ($p = <0.05$) in people with antipsychotic naive first episode psychosis, compared to healthy controls, suggesting a significant elevation in proinflammatory cytokine concentration. Non-significant effect sizes were reported for TNF-α, IL-1β, IL-2, IL-4, IL-8 and IL-10 ($p = >0.05$). Regarding proinflammatory cytokines and relationships to negative symptomology, moderate positive relationships were reported for negative symptoms and IL-1β, IL-2, IL-6 and TNF-α, across four studies. For anti-inflammatory cytokines, one strong and one weak-to-moderate negative relationship was described for IL-10 and negative symptoms. Contrastingly, a strong positive relationship was reported for IL-4 and negative symptoms.

Conclusion: There is evidence of significantly elevated proinflammatory cytokines in antipsychotic-naïve FEP populations, alongside promising findings from cohort data suggesting an interaction between inflammation and primary negative symptomology. Future studies should seek to come to a consensus on a panel of cytokines that relate most specifically to negative symptoms, and consider longitudinal studies to investigate how cytokine fluctuations may relate to exacerbation of symptoms.

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KEYWORDS
cytokines, immune response, inflammation, negative symptoms, schizophrenia

1 | INTRODUCTION

Schizophrenia (SCZ) is a highly debilitating mental illness that affects over 20 million individuals globally, associated with a reduced quality of life, severe cognitive dysfunction and substantially increased mortality rates.[1,2] SCZ is widely recognised as a neurodevelopmental disorder that often becomes apparent at a critical period in early adulthood.[3] Through the interaction of genetic predisposition and environmental stressors, an individual may be particularly vulnerable to developing SCZ.[4] Typically, risk factors for SCZ can trigger a first episode of psychosis (FEP), which is an acute period whereby an individual begins to experience some loss of contact with reality. This may include sporadic hallucinations, delusions, disturbances in behaviour, thought processes and functioning.[5] Following treatment, most individuals may initially achieve remission of symptoms. However, for approximately one in three, persistence and relapse of symptoms occur and this increases the risk of transition to more persistent SCZ pathology.[6]

A common feature associated with FEP is the emergence of negative symptoms. Negative symptomology is associated with a significantly reduced quality of life and social functioning,[7,8] and is classically described as a 'loss of function'. This includes two subdomains concerned with 'diminished expression' and 'avolition-amotivation'. The former involves the absence of drive, interest and deficits in affective responses.[9] The second subdomain, 'avolition-amotivation', are symptoms that manifest as asociality and specifically motivational anhedonia.[10,11] Negative symptoms can be further defined as primary negative symptoms which are intrinsic to disease pathology, or secondary negative symptoms which may present as a side-effect of other conditions such as comorbidity, concomitant psychotic symptoms, or medication status.[12] Primary negative symptoms can emerge at any time throughout the duration of disease, display poor response trajectory to treatment,[13] and have been suggested as present in approximately 26% of FEP cohorts.[14] However, this figure may vary dependent upon subdomains and specific items assessed, as well as control of confounding factors.[14] The role of antipsychotic medication in the generation of negative symptoms remains controversial, as research suggests that antipsychotic drugs can cause presentation of sedatory, akinetic and amotivational behaviours which may be interpreted as a negative symptom, making primary symptoms increasingly difficult to identify and estimate.[12,15,16] Furthermore, It is well established that antipsychotic medication possesses the capacity to alter biomarkers that are perturbed in FEP and may be implicated with the pathophysiology of primary negative symptoms, therefore medication status must be considered when investigating negative symptomology.[15,17]

Summations

- Proinflammatory cytokines are significantly elevated in drug naïve first-episode psychosis populations, display subtle relationships with primary negative symptom severity.
- Inflammatory cytokines may represent a panel of biomarkers that could be used to stratify patients into subgroups experiencing primary negative symptoms or deficit schizophrenia, who may benefit from anti-inflammatory treatment.

Limitations

- Future research should seek to acknowledge a common method for cytokine quantification to allow more accurate cross-study comparisons and consider immune cell phenotyping techniques to further elucidate the 'immune profile' in psychosis.
- Forthcoming studies should also consider cytokine measurement over time and correlate cytokine changes/exacerbations with specific primary negative symptoms, in order to establish a causal relationship between the two and differentiate from secondary negative symptoms and depression.

Contemporary evidence suggests a link between perturbed inflammatory processes and negative symptoms in FEP, and points to immune cell dysfunction within the brain and more globally in peripheral tissues. An exacerbated inflammatory cascade characterised by increased in immune activation, proinflammatory cytokine production and oxidative distress is present in both FEP and established SCZ, and may be a key mediator underlying negative symptom presentation.[17–19] It is suggested that peripheral immune responses are representative of the neuroimmune status of the brain, therefore systemic cytokine concentrations are increasingly relevant for revealing how inflammation may confer specific symptom profiles in FEP. Multiple studies have suggested relationships between peripheral inflammatory biomarkers and the emergence of negative symptoms in particular, with dysregulation of immune

cells and aberrations in proinflammatory cytokines noted as important.[15,20–23] The interaction between dysfunctional cytokine secretion and oxidative stress can result in tissue damage and neurodegeneration that may contribute to SCZ pathology, through the impairment of downstream signalling pathways including serotonergic, dopaminergic and glutamatergic neurotransmission, ultimately leading to the presentation of negative symptomology.[15]

Balance between the peripheral Th1, and Th2 inflammatory responses and overall cytokine production is crucial for an efficient and regulated immune response, and perturbation of this balance can result in chronic inflammation and deterioration into disease (see Figure 1).[24] Previous research supports the notion that proinflammatory cytokines in the peripheral body systems are elevated in FEP and SCZ.[15,17,25,26] However, evidence of a direct link between inflammation and the emergence of specifically negative symptoms is mixed, which may be due to small sample sizes, heterogeneity in illness duration, methodological variations in cytokine quantification and management of confounding factors.[27] For example Zhu et al. (2018)[28] reported significantly elevated plasma TNF-α concentrations that were positively correlated with negative symptomology in a chronic SCZ cohort, however, these findings were not replicated in a drug-naive FEP population. Elsewhere, however, correlations between TNF-α and negative symptoms have been identified across CHR,[21] first episode[29] and chronic medicated SCZ cohorts.[23]

In order to most accurately identify the relationship between cytokines and negative symptoms, the current review utilises a specific FEP definition that includes an established F20 diagnosis status via a validated clinical tool (DSM-5, ICD-10, etc.), absolute medication naivety and less than 5 years of total illness duration. Using these criteria enable a greater understanding of pathogenic processes that underlie the presentation of negative symptomology in FEP, where disease pathology is still in its infancy and unconfounded by chronicity of disease or side effects of antipsychotic medication, both of which are known to influence cytokine concentration. This could enable the future stratification of patients experiencing negative symptoms, which may be critical in determining more effective therapeutic treatments for negative symptoms specifically.

1.1 | Aims of the study

The aim of this systematic review was to provide a comprehensive overview of cytokine perturbations in antipsychotic naïve FEP populations and assess the relationship between inflammatory markers and negative symptom severity.

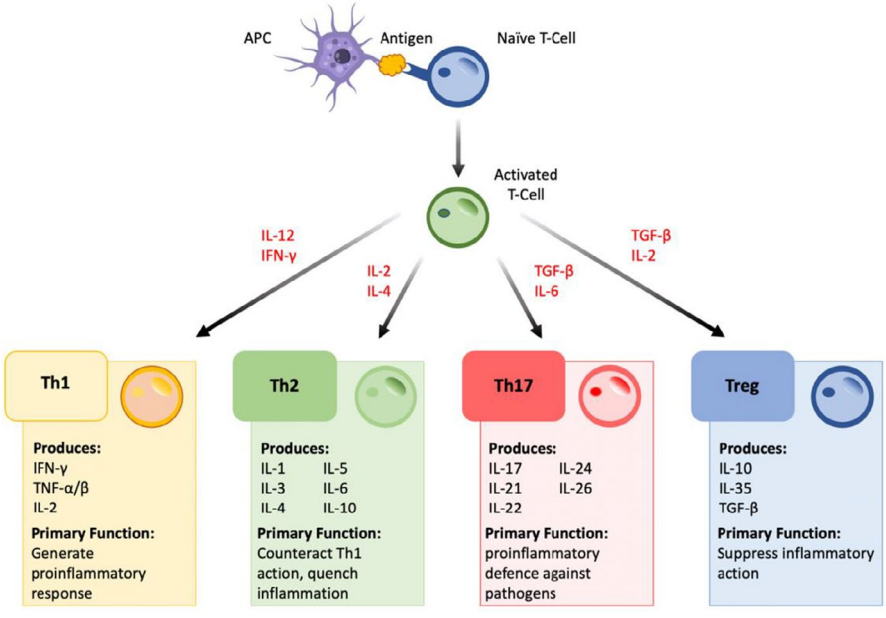

FIGURE 1 Under physiological conditions, the immune system protects the body from invading pathogens or damaged tissues through a highly regulated process, divided into generalised 'innate' response to infection, and specialised 'adaptive' defence associated with antibody production and memory function. Cytokines including TNF-α, IL-1, IL-6 and IL-8 constitute the initial exacerbation of inflammation against pathogens. IFN-γ and IL-12 promote further inflammation to kill intracellular parasites, constituting the T-Helper 1 immune response. IL-4, IL-5 and IL-13 function to compensate and extinguish neuroinflammation via anti-inflammatory action, termed the T-Helper 2 immune response. IL-17 and IL-23 further exacerbate the inflammatory state as part of the T-Helper 17 response. Finally, IL-10 and TGF-β dampen the inflammatory response of the aforementioned cytokines and represent the T-Regulatory response. APC, Antigen Presenting Cell; IFN, interferon; IL, Interleukin; TGF, Transforming Growth Factor; TNF, Tumour Necrosis Factor

2 | MATERIALS AND METHODS

2.1 | Study selection

Studies were systematically searched on the 1st September 2021 via the Ovid database system, using Medline, EMBASE and PsycInfo databases, in accordance with the PRISMA guidelines to ensure high-quality reporting of systematic reviews.[30] The search was conducted using keywords which were adjusted appropriately to subject headings/MeSH headings dependent on the database being searched, with the Ovid 'explode' function implemented where appropriate. Keywords that were mapped to subject headings were also separately searched as a keyword in order to collect all potentially relevant studies and negate any human error regarding database study input or keyword mapping, as advised by a library technician. An asterisk '*' marks a truncated keyword where any alternative ending of a word is retrieved.

The key word search terms included were as follows: ("schizo*" **OR** "psychosis" **OR** "psychoses" **OR** "first episode" **OR** "first episode psychosis" **OR** "first psychotic episode" **OR** "FEP" **OR** "psychotic disorder" **OR** "early onset" **OR** "early intervention" **OR** "drug naïve" **OR** "medication naïve") **AND** ("inflammat*" **OR** "cytokin* **OR** "interleukin*" **OR** "tumour necrosis factor" **OR** "TNF-alpha" **OR** "interferon" **OR** "immune response" **OR** "immune dysregulation" **OR** "cytokine production) **AND** (negative symptom* **OR** "negative syndrome" **OR** "alogia" **OR** "anergia" **OR** "anhedonia" **OR** "avolition" **OR** "apathy" **OR** "asociality" **OR** "affective flattening" **OR** "blunted affect" **OR** "diminished expression" **OR** "social withdrawal" **OR** "lossADJ1interest" **OR** "lackADJ1interest" **OR** "lossADJmotivat* **OR** "lackADJ1motivat*").

Additional limits were also implemented into each search, limited to (1) human-based studies, (2) exclude conference abstracts, (3) search limits from 1982 to 2021, in line with the implementation of the Scale for the Assessment of Negative Symptoms (SANS) questionnaire (1982) and the Positive and Negative Syndrome Scale (PANSS) questionnaire (1987), widely recognised as the 'gold-standard' for quantitative assessment of negative symptoms.[9,31] Studies were then retained or discarded based on an agreed inclusion/exclusion criterion.

2.1.1 | Inclusion criteria

1. Published between 1982 and 2021
2. Patients with an established diagnosis of FEP
3. Within first 5 years of duration of illness (explicit measurement in years, or deemed within criteria based on text information, as assessed by author)
4. Antipsychotic naïve (or a subset with fully stratified data for medication naïve FEP)
5. Assessed peripheral circulating cytokines (via blood, serum, plasma)
6. Assessed negative symptoms
7. Apparently healthy control group
8. Human-based only

2.1.2 | Exclusion criteria

1. In vitro studies
2. Genetic studies
3. Animal-based studies
4. Review articles, Posters, Conference Abstracts
5. Studies not measuring peripheral proinflammatory cytokines
6. Studies not measuring negative symptoms
7. Full text not available
8. Not written in English

2.2 | Data extraction and analysis

Information was extracted by two authors (C. Dunleavy & S. Aldred) from each study for a 'three-phase exclusion' process of studies for full review. In phase one (Identification), any duplicates, posters and conference abstracts were excluded. Phase two (Screening) comprised the exclusion of records based on the title and/or abstract, in accordance with the agreed inclusion/exclusion criterion. In phase three (Eligibility), articles were assessed at the full-text level, in which population demographic data, duration of illness, study type, medication status, cytokine concentration, symptom scale measurement and outcome measures were extracted in order to determine eligibility in the systematic review, see Figure 2. If specific data required to determine inclusion/exclusion were not available in the online version of a study, an attempt was made to contact the author for supplementary data. If sufficient data were still not available, the study was excluded. Studies were also examined for overlapping/duplicate samples or measurements and excluded accordingly. Mean, standard deviation and sample size data were extracted separately from each study for each proinflammatory cytokine assessed, for both FEP and control groups, and converted to picograms per millilitre (pg/ml) where necessary. Some studies divided the FEP group into sub-groups based on certain characteristics of interest, therefore in order to combine mean, standard deviation and sample size of the relevant subgroups into one homogenous FEP group, the formulas proposed by Cochrane Reviews were implemented.[32]

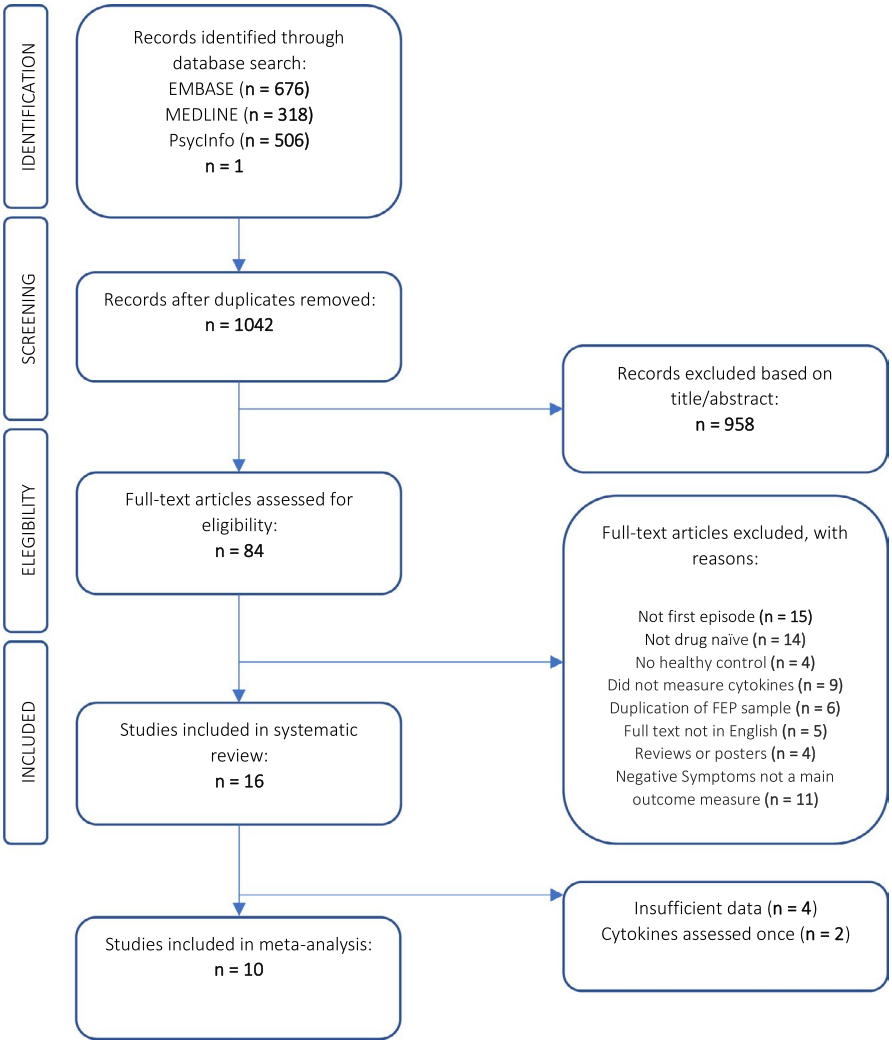

FIGURE 2 A flow chart displaying the selection process of studies included in the systematic review and meta-analysis

Mean and standard deviation values were also extracted for the negative symptom measurements for the patient groups only. Where appropriate, values presented in a format other than PANSS scale were converted into PANSS Negative values based on a formula proposed by Van Erp et al. (2014), to allow for comparison of the values across a normalised scale.

SANS—PANSS negative conversion equation

PANSS Negative = 7.1196 +(0.3362×SANS [composite] Total score).[33]

2.3 | Data analysis

Mean, standard deviation and sample size for each cytokine assessed in two or more studies were entered into Revman 5.0 for subsequent analysis. A 'random effects' model was selected as this statistical methodology considers heterogeneity that may be present between studies, as well as the variance in potential study effect during the prediction of overall effect size.[34] The 'inverse variance' method was implemented to assign specific weighting to each study based on the variance of the effect, therefore more comprehensive studies with smaller standard error account for higher overall weights. This was done in attempt to lessen error or inaccuracy of the overall effect size in meta-analysis.[32] Individual standardised mean difference (SMD) was calculated for each cytokine from each study included in meta-analysis with 95% confidence intervals, in addition to an overall effect size for cytokine concentration favouring an increase in FEP or control (displayed by Z score) with overall 95% confidence intervals, and significance values noted ($p < 0.05$). SMD calculation was implemented due to the expectance of high study heterogeneity, and potential differences in sensitivity of cytokine measurements. This minimised the methodological differences between studies, and provide a standardised result on a uniform scale based on the variability within a given study.[35] Meta-regression analyses were performed to assess the contribution of various socioeconomic and clinical factors that may further perturb cytokine concentrations in FEP. Mean, standard deviation and sample size for each cytokine were inputted into Comprehensive Meta-Analysis (CMA) 3.0 software and SMD calculated.

Numerical values for potential confounding factors were then extracted from papers, converted to relevant units and inputted into CMA for meta-regression analysis.

Inter-study heterogeneity was evaluated by the *Tau²* and *Chi-square* tests. These tests determine if statistical heterogeneity is present between all studies for a given cytokine to determine if the change in cytokine concentration is similar across papers. The I^2 statistic was also calculated in order to display the percentage of variability in cytokine change across studies that is due to heterogeneity, which gives the reader an indication of the proportion of variance between studies. Data from RevMan 5.0 were displayed graphically via forest plots, with $p < 0.05$ denoting a significant effect of the diagnosis of FEP on cytokine concentration, when compared to an apparently healthy control population. In order to assess the potential relationship between cytokine concentration and FEP symptomology, mean, standard deviation and sample size for cytokine concentration and PANSS Negative from each study included in the meta-analysis, was entered into GraphPad Prism 8.0 for subsequent regression analysis.

3 | RESULTS

Following PRISMA guidelines, a primary systematic search identified 1500 studies. After the removal of 458 duplicate records, 1042 studies were retrieved, and the title and abstracts screened against the identified inclusion criteria. Subsequently, 958 records were excluded. Full-text analysis was then undertaken on the remaining 84 records. Articles were then excluded as follows: Condition not classified as FEP ($n = 15$), negative symptoms not used as a main outcome measure ($n = 14$), participants were not drug naïve ($n = 12$), study didn't measure/report peripheral cytokines ($n = 9$), no apparently healthy control group ($n = 5$), not in English language ($n = 5$), poster abstract only ($n = 2$), review article ($n = 2$). Finally, six studies were excluded due to duplication of the participant sample with another identified paper already included in this review.[36–41] Where duplicate participant samples were identified, the paper that was included was selected based upon (1) largest panel of cytokines assessed and (2) largest sample size respectively. The study selection process is displayed in Figure 2.

Data reviewed herein are included from FEP patients only, as identified by the prespecified inclusion criteria. Where studies included data for participants in other disease groups (e.g. clinical high risk, chronic SCZ, depression), only data on participants with FEP and healthy controls were extracted. Altogether, 16 studies met the inclusion criteria for the current systematic review (see Table 1). Within the 16 included studies, the data from four studies were not provided in sufficient detail to be included in meta-analysis. The authors of these four studies were contacted and additional data were requested, but not received. These studies were therefore included in the narrative section of the review only. Rationale for exclusion from meta-analysis were as follows: standard deviation not given for cytokine values ($n = 2$), Over 50% cytokines at or below limit of detection ($n = 1$), actual cytokine values not given ($n = 1$). Furthermore, an additional two studies measured cytokines that were only featured once (IL-3, IL-18), therefore were not assessed via meta-analysis ($n = 2$).

3.1 | Meta-analysis

Ten studies met the inclusion criteria and were therefore included in the meta-analysis to assess cytokine concentrations in FEP, where cytokines were measured across two or more studies.[28,29,42–49] Data from the 10 included studies provided information on 651 antipsychotic naïve FEP patients. The mean age of FEP patients was 25.18 ± 4.09 years, ranging from 14.7 to 29.07 years. From the same ten studies, data were extracted for 521 apparently healthy control subjects, with a mean age of 26.01 ± 4.78 years, ranging from 14.5 to 32.9 years.

Twenty-four different cytokines were assessed peripherally via ELISA, or similar assay. The following cytokines were assessed in more than one study: TNF-α, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17, (proinflammatory), IL-4 and IL-10 (anti-inflammatory). The data for each cytokine were included in a random-effects, pooled effect size model to determine which cytokines are significantly altered in FEP. After transformation into SMD to avoid potential differences in ELISA sensitivity, a random-effect, pooled-effect analysis suggested that four cytokines were significantly upregulated in the FEP population, when compared with control.

A significant effect size was reported for IFN-γ (4 studies, 168 patients, SMD = 1.22, 95% CI 0.14 to 2.31, Z = 2.21, $I^2 = 94\%$), IL-6 (5 studies, 251 patients, SMD = 1.38, 95% CI 0.54 to 2.22, Z = 3.21, $I^2 = 94\%$), IL-12 (2 studies, 87 patients, SMD 3.43, 95% CI 2.12 to 4.73, Z = 5.15, $I^2 = 80\%$) and IL-17 (3 studies, 130 patients, SMD = 0.72, 95% CI 0.07 to 1.37, Z = 2.16, $I^2 = 81\%$) in patients with FEP (all <0.05). Six cytokines were not significantly altered in the FEP population when compared with control subjects. Non-significant effect sizes were reported for TNF-α (5 studies, 287 patients), IL-1β (4 studies, 218 patients), IL-2 (3 studies, 99 patients), IL-4 (3 studies, 99 patients) IL-8 (2 studies, 69 patients) and IL-10 (4 studies, 227 patients). Forest plots are presented in Figure 3, broken down by study and cytokine of interest.

TABLE 1 Studies included in review

Author	Nationality	Drug Naïve FEP (*n*)	Healthy control (*n*)	Cytokines assessed	Methodology	Negative Symptoms Instrument	Comment
Borovcanin et al., 2012	Serbia	88	36	TNF-α, IFN-γ, IL-4, IL-6, IL-.10, IL-17, IL-27, TGF-β	ELISA	PANSS	Not included in meta-analysis
Crespo-Facorro et al., 2008	Spain	56	28	IL-12	ELISA	SANS	Included
Dai et al., 2020	China	83	60	IL-1β, IL-6	ELISA	PANSS	Included
Ding et al., 2014	China	69	60	IFN-γ, IL-6, IL-17	ELISA	PANSS	Included
Haring et al., 2015	Estonia	38	37	TNF-α, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10	Sandwich Assay	PANSS	Included
Joaquim et al., 2018	Brazil	28	30	IL-1β	Multiplex Assay	PANSS	Included
Karanikas et al., 2017	Greece	25	23	TNF-α, TNF-β, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12	Immunoassay	PANSS	Not included in meta-analysis
Noto et al., 2019	Brazil	31	22	TNF-α, sTNF-R1/R2, IFN-γ, IL-1β, IL-1RA, IL-2, sIL-2r, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, GM-CSF	Immunoassay	PANSS	Included
Pesce et al., 2014	Italy	54	38	TNF-α, IL-1β, IL-2	ELISA	PANSS, SANS	Not included in meta-analysis
Petrikis et al., 2015	Greece	39	39	IL-2, IL-6, IL-10, IL-17, TGF-β	ELISA	PANSS	Not included in meta-analysis
Simsek et al., 2016	Turkey	30	26	TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10, IL-17	Flow Cytometry Bead Array	PANSS	Included
Xiu et al., 2012	China	78	78	IL-18	ELISA	PANSS	Not included in meta-analysis
Xiu et al., 2014	China	128	62	IL-10	ELISA	PANSS	Included
Yang et al., 2016	China	55	43	IL-3	ELISA	PANSS	Not included in meta-analysis
Zhu et al., 2018	China	69	61	TNF-α, IL-1β	ELISA	PANSS, SANS	Included
Zhu et al., 2020	China	119	135	TNF-α	ELISA	PANSS	Included

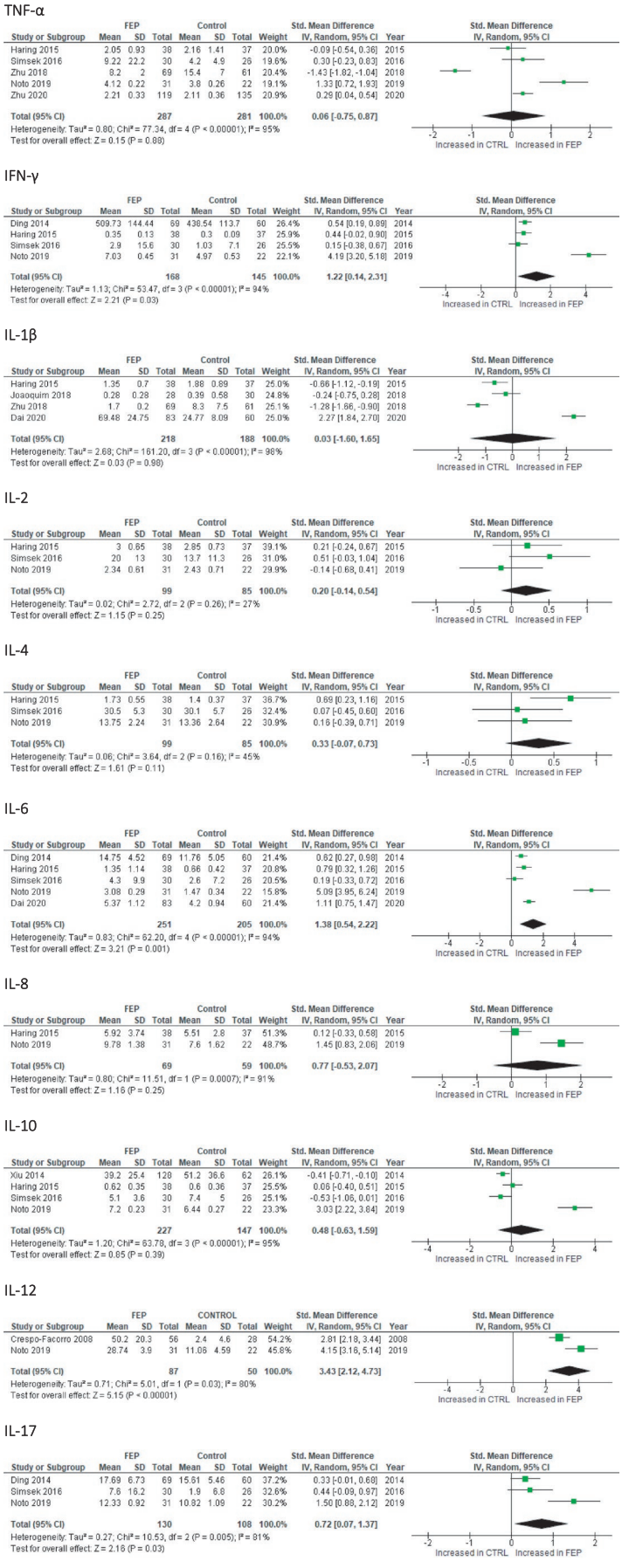

FIGURE 3 Forest plots displaying the standardised mean difference between first-episode psychosis(FEP) and control for each cytokine. Tests for heterogeneity in effect size for each cytokine, as well as overall effect size given for each cytokine. Also plotted graphically per cytokine, with the box size relating to the weight of each study, position relating to the difference in FEP vs. control, and the emanating lines relating to the 95% confidence intervals. The diamond represents the overall effect size

3.2 | Meta-regression analysis

Meta-regression analyses were conducted to assess the effect of various clinical and sociodemographic factors that may influence the significant changes in cytokine concentration exhibited in the current meta-analysis. Due to insufficient data, meta-regression analysis could only be conducted for potential moderators of IFN-γ and IL-6, and not IL-12 or IL-17. Across the four studies assessing IFN-γ, a significant association between Body Mass Index (BMI) and IFN-γ was found ($Z = 1.98$, $p = 0.048$). Specifically, as BMI increased in FEP populations, IFN-γ also increased. Furthermore, a significant association between IFN-γ and percentage male sex was reported ($Z = 2.18$, $p = 0.029$). Within the six studies that measured IL-6, meta-regression analyses revealed a significant association between IL-6 and BMI ($Z = 2.89$, $p < 0.01$) and IL-6 and percentage male sex ($Z = 3.07$, $p = <0.01$). For both cytokines, no significant associations were reported for age ($p = >0.05$), and there were no enough data made available by included studies to assess the effects of smoking on cytokine concentration.

Meta-regressions were also conducted to assess the effects of psychopathology on the meta-analysis results. No significant associations were found for positive symptoms, negative symptoms or general psychopathology (all $p = >0.05$).

3.3 | Cytokine and negative symptom analysis

Due to the lack of available data, extensive analysis of the relationship between cytokine concentrations and individual negative symptom items could not be performed. Therefore, a narrative review was conducted to assess the relationship between cytokine concentration and severity of negative symptoms. Significant correlations between the PANSS Negative sub-score and change in inflammatory markers were reported seven times, in six different studies, with reference to six different cytokines. An overview of these findings is presented in Table 2. Moderate correlation strengths were reported for IL-6 ($r = 0.48$), IL-2 ($r = 0.409$), TNF-α ($r = 0.37$) and the PANSS Negative sub-score. Furthermore, Dai et al.[44] reported a significant and positive β-coefficient for the relationship between IL-1β and the PANSS Negative sub-score ($\beta = 0.486$), which suggests that an increase in IL-1β caused an increase in the PANSS Negative subscale. In terms of anti-inflammatory cytokines, a strong positive correlation between IL-4 and the PANSS Negative sub-score were reported ($r = 0.67$).

Furthermore, two correlations were reported between IL-10 and the PANSS Negative sub-score, including a strong negative correlation ($r = -0.65$) reported by Simsek et al.,[46] and a weak-to-moderate negative correlation ($r = -0.195$) reported by Xiu et al.[43] IL-10 was reported as correlated with the PANSS Negative subscale in 50% of studies measuring this cytokine. No other significant relationships were reported ($p < 0.05$). IL-10 was reported as correlated with the PANSS Negative subscale in 50% of studies measuring this cytokine.

4 | DISCUSSION

The relationship between inflammatory biomarkers and negative symptom severity in antipsychotic naïve FEP populations is an area of research interest as it may offer further insight into FEP aetiology. Previous literature has identified alterations in cytokine concentration in FEP and SCZ populations,[17,25,50–52] which is supported in this meta-analysis. The findings presented demonstrate that IFN-γ, IL-6, IL-12 and IL-17 are all significantly increased in medication naïve FEP. This is indicative of a perturbed inflammatory response in the very early stages of psychosis. We add additional evidence here, bringing further contemporary studies that suggest specific proinflammatory cytokine aberrations are evident in early SCZ pathology, unconfounded by antipsychotic medication and chronicity of disease. Although sufficient raw data to allow in-depth analysis were not made available from many studies, significant relationships between negative symptoms and IL-1β, IL-2, IL-4, IL-6 IL-10 and TNF-α were identified from cohort data provided in each study independently. This review further supports the hypothesis of a dysregulated immune system as a key component of SCZ pathology, and the current analysis implicates immune perturbations within the very earliest stages of psychosis.

Aberrations in the peripheral concentration of cytokines can manifest in, and indicate a state of, chronic neuroinflammation.[53] This has been described in the 'vulnerability-stress-inflammation' model as fundamental for SCZ development.[54] It is suggested that stressor-induced proinflammatory cytokine elevations that occur in early life, for example elevations in IFN- γ, can cause proliferation of immune cells within the brain and central nervous system (CNS) and exacerbated proinflammatory cytokine release. Chronic inflammation can then perturb neurotransmitter systems, cause neurodegeneration and lead to eventual psychotic symptom presentation.[55,56] Cytokines do not work independently and may operate through an inflammatory network to reciprocally upregulate other cyto- and chemokines and exacerbate inflammation. This may explain why cytokines appear to be upregulated simultaneously in patterns and

TABLE 2 Cytokine concentration in antipsychotic-naïve FEP per study, PANSS Negative sub-score and relationship between cytokine and negative symptoms

Cytokine	Author	Cytokine (Pg/ml, mean)	PANSS negative (mean)	Analytical method	Findings	Cytokine/ Negative symptom relationship
IL-1β	Haring et al., 2015	1.35	22.97	Pearson correlation	$r = 0.232$	NS
	Joaquim et al., 2018	0.28	18.00	Pearson correlation	Not stated	NS
	Zhu et al., 2018	1.70	25.60	Partial correlation	Not stated	NS
	Dai et al., 2020	**69.48**	**22.16**	Multivariate regression	$\boldsymbol{\beta = 0.486}$	***Positive**
IFN-γ	Ding et al., 2014	509.73	18.23	Pearson correlation	$r = 0.074$	NS
	Haring et al., 2015	0.35	22.97	Pearson correlation	$r = 0.162$	NS
	Simsek et al., 2016	2.90	26.30	Pearson correlation	$r = 0.30$	NS
	Noto et al., 2019	7.03	20.59	Multiple regression	Not stated	NS
IL-2	**Haring et al., 2015**	**3.00**	**22.97**	Pearson correlation	$\boldsymbol{r = 0.409}$	***Positive**
	Simsek et al., 2016	20.00	26.30	Pearson correlation	$r = -0.12$	NS
	Noto et al., 2019	2.34	20.59	Multiple regression	Not stated	NS
IL-4	Haring et al., 2015	1.73	22.97	Pearson correlation	$r = 0.073$	NS
	Simsek et al., 2016	**30.5**	**26.30**	Pearson correlation	$\boldsymbol{r = 0.67}$	***Positive**
	Noto et al., 2019	13.75	20.59	Multiple regression	Not stated	NS
IL-6	Ding et al., 2014	14.75	18.23	Pearson correlation	$r = 0.168$	NS
	Haring et al., 2015	1.35	22.97	Pearson correlation	$r = 0.227$	NS
	Simsek et al., 2016	4.30	26.30	Pearson correlation	$r = -0.57$	NS
	Noto et al., 2019	**3.08**	**20.59**	Multiple regression	$\boldsymbol{r = 0.48}$	***Positive**
	Dai et al., 2020	5.37	22.16	Multivariate regression	$\beta = 0.130$	NS
IL-8	Haring et al., 2015	5.92	22.97	Pearson correlation	$r = 0.04$	NS
	Noto et al., 2019	9.78	20.59	Multiple regression	Not stated	NS

TABLE 2 (Continued)

Cytokine	Author	Cytokine (Pg/ml, mean)	PANSS negative (mean)	Analytical method	Findings	Cytokine/ Negative symptom relationship
IL-10	**Xiu et al., 2014**	**39.20**	**18.90**	Pearson correlation	***r* = −0.195**	***Negative**
	Haring et al., 2015	0.62	22.97	Pearson correlation	*r* = 0.097	NS
	Simsek et al., 2016	**5.10**	**26.30**	Pearson correlation	***r* = −0.65**	***Negative**
	Noto et al., 2019	7.20	20.59	Multiple regression	Not stated	NS
IL-12	Crespo-Facorro et al., 2018	50.2	10.11	Pearson correlation	Not stated	NS
	Noto et al., 2019	28.74	20.59	Multiple regression	Not stated	NS
IL-17	Ding et al., 2014	17.69	18.23	Pearson correlation	*r* = 0.204	NS
	Simsek et al., 2016	7.60	26.30	Pearson correlation	*r* = 0.23	NS
	Noto et al., 2019	12.33	20.59	Multiple regression	Not stated	NS
TNF-α	Haring et al., 2015	2.05	22.97	Pearson correlation	*r* = 0.034	NS
	Simsek et al., 2016	9.20	26.30	Pearson correlation	*r* = −0.46	NS
	Zhu et al., 2018	8.20	25.60	Partial correlation	Not stated	NS
	Noto et al., 2019	4.12	20.59	Multiple regression	Not stated	NS
	Zhu et al., 2020	**2.21**	**26.89**	Multiple regression	***r* = 0.37**	***Positive**

Studies in bold, and marked with an asterisk (*) report a significant correlation between variables ($p < 0.05$). 'NS' indicates no significant correlation between variables.

not in isolation, as reported in the current review and elsewhere.[26]

Several studies included in the review reported a significant relationship between cytokines and negative symptoms (displayed in Table 2). Proinflammatory cytokine concentrations of IL-1β, IL-2, IL-6 and TNF-α were all significantly related to the PANSS negative subscale, whereby an increase in proinflammatory cytokine concentration was related to an increase in the severity of negative symptoms. These findings have been replicated across the SCZ spectrum, occurring as early as at-risk of psychosis,[21,57] through FEP,[44,48] and into chronic SCZ.[23] It is suggested that proinflammatory cytokines that induce a 'neuroinflammatory state' within the CNS, may lead to brain volume reductions in areas that are important for negative symptom emergence, including prefrontal and hippocampal regions of the brain.[15,58] Proinflammatory cytokines can perturb neurotransmitter pathways to alter brain signalling, and negative symptoms may be induced in this way. Evidence suggests that proinflammatory cytokines may be responsible for the induction of N-Methyl-D-Aspartate receptor antagonist kynurenic acid, which can cause dysfunction in glutamatergic signalling and subsequent motivational and reward processing deficits.[15] Similarly, anti-inflammatory cytokine alterations have been reported to be related to the emergence of negative symptoms across all stages of schizophrenia, whereby typically lower anti-inflammatory cytokine concentrations are associated with increased negative symptom severity.[43] Overall, this may represent a more generalised imbalance of the T-helper system, causing a polarisation to a chronic proinflammatory state that is insufficiently quenched by anti-inflammatory responses.[24] Therefore, chronic low-grade inflammation that is present in psychosis, could cause eventual presentation of symptoms via perturbation in neurotransmission.

The relationship between specific cytokines and negative symptom severity in FEP show significant heterogeneity, despite the overall disruption of immune function. This could be apparent for various reasons. First, FEP and eventual SCZ is polygenic by nature, meaning that individuals with psychosis may possess varied profiles of susceptibility genes implicated with SCZ pathology.[59] For example some FEP populations may not have certain immune-related polymorphisms that confer increases the production of a specific cytokine, and therefore patients may display normal plasma protein concentration. Given that the included studies did not genetically screen participants, this could be responsible for a lack of consistent correlations of a given cytokine with negative symptoms. Furthermore, the extent of the interaction between cytokines within signalling cascades in ongoing immune responses is not known, and plasma concentrations may vary between individuals. Heterogeneity may also arise because of confounding environmental factors including smoking status, diet and stress exposure, which may obscure cytokine concentrations and mask genuine relationships between cytokines and symptoms. Due to insufficient data and lack of studies investigating certain cytokines, meta-regression analysis could only be conducted for potential moderators of IFN-γ and IL-6, and not IL-12 or IL-17. The relationship between IFN-γ or IL-6 and negative symptoms was significantly affected by BMI and in studies with a higher proportion of male participants. Evidence elsewhere suggests that tobacco smoking is common amongst the FEP population and may interact with immune functioning peripherally,[60,61] however, discrepancies in data reporting meant that this could not be investigated on a larger scale. This highlights a key consideration when designing studies looking at cytokine profiles in FEP and SCZ population, in addition to the need for better demographic reports in papers. Insufficient available data may be responsible for the lack of an overall relationship of a specific cytokine with negative symptoms, as meta-regressions typically require high numbers of studies to determine genuine relationships. Recently, attempts to resolve some of these issues surrounding heterogeneity have utilised immunophenotyping and genetically stratifying patient cohorts into 'high' or 'low' inflammation.[62,63] Stratification of patients into high and low inflammatory subtypes may better reveal the relationship between inflammation and negative symptoms, as opposed to individual cytokine concentrations which vary considerably between individuals. Better characterisation of FEP subgroups into 'high' or 'low' inflammation, as well as subgroups of cytokines that are typically upregulated together will reveal more about the relationship between cytokines and symptomology.

More definitive criteria for FEP diagnosis are required, as circulating cytokine concentration in FEP and SCZ appears to be affected by the duration of illness, antipsychotic medication, and associated comorbidities. This systematic review utilised the operationalised definitions described by Breitborde et al., in order to classify an individual as within a period of 'first episode of psychosis', accounting for the entire 'critical period' of deterioration that defines FEP.[64] Furthermore, this systematic review ensured absolute drug naivety in included studies, to provide an accurate and minimally confounded overview of the relationship between cytokines and primary negative symptomology within FEP.

Although the current meta-analysis was largely in agreement with other studies, there were some key differences, for example the changes in IL-1β and TNF-α reported herein were not significant. This may in part be explained by the specific definition of FEP used in this study to accurately represent the early stages of disease. Our approach may offer a more accurate representation of the early psychosis spectrum, which includes all patients with FEP. This is key, as the 'critical period' of deterioration in FEP can occur for up to five years and therefore it is logical to assess cytokines over this entire timeframe.[65] This may result in differences with reviews elsewhere based upon FEP definitions, as some cytokines that are identified as a 'state' cytokines which are increased upon acute exacerbations of disease, may have somewhat normalised in concentration if a longer time period has elapsed since their first psychotic episode.[17] Alternatively, the discrepancy in findings between studies included and elsewhere may be a consequence of methodological differences across studies, including researcher competence, experimental error and protocol variations.[66] Within the current review, several different cytokine assay platforms are used between studies, varying from single cytokine measures to multiplex systems, which can significantly impact assay sensitivity. These factors make comparison of cytokine concentration between studies difficult.

The current systematic review suggests that several cytokines are elevated in FEP, providing further evidence for a central role of perturbed inflammation in early SCZ pathology. The review highlighted several relationships between different cytokines and the severity of negative symptomology, whereby elevated proinflammatory immune activation and inability to mount an anti-inflammatory response appear to confer worse negative symptom presentation. Future research should focus on identifying the cytokines most relevant to negative symptomology, investigate cytokine concentration fluctuations and symptom profiles over a longitudinal period, and consider phenotyping of peripheral immune cells to better

define immune dysregulation profiles in psychosis. It may be that longer periods of persistent inflammation are the driving factors for negative behaviours, rather than the effects of a given cytokine, the majority of which possess a multitude of pleiotropic effects. This may assist in identifying individuals experiencing primary negative symptoms, for the delivery of anti-inflammatory medication to better manage symptomology and improve outcomes in FEP.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13416.

DATA AVAILABILITY STATEMENT

This data will be made available and provided in full on suitable request.

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