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Authors' Affiliation:
[1]Grochowski Hospital, address Grenadierów 51/59, 04-073 Warsaw, Poland
[2]Nowodworskie Centrum Medyczne, address Miodowa 2, 05-100 Nowy Dwór Mazowiecki, Poland
[3]University Clinical Center of the Medical University of Warsaw, address Banacha 1a, 02-097 Warsaw, Poland
[4]Independent Public Healthcare Complex in Wyszków, address Komisji Edukacji Narodowej 1, 07-200 Wyszków, Poland
[5]Independent Public Clinical Hospital named after prof. W. Orłowski CMKP, Czerniakowska 231, 00-416 Warsaw, Poland
[6]Independent Public Multispecialty Healthcare Centre of the Ministry of the Interior and Administration in Bydgoszcz, 4/6 Księdza Ryszarda Markwarta St, 85-015 Bydgoszcz, Poland.

***Corresponding author:**
Paulina Zegarska, Grochowski Hospital, address Grenadierów 51/59, 04-073 Warsaw, Poland, email: paulinka160300@gmail.com

Contact List

Paulina Zegarska	paulinka160300@gmail.com
Eliza Mędrek	elizamusician@gmail.com
Natalia Brzozowska	natalkab79@gmail.com
Natalia Sałkowska	nat.kawczynska@gmail.com
Barbara Wardzyńska	barbaramick23@gmail.com
Jakub Magdziak	kuba.magdziak@wp.pl
Oliwia Borowska	oliwkaborowska23@gmail.com
Sara Awad	saraawad3a@gmail.com
Hanna Markowska	hmarkowska8@gmail.co

Orcid List

Paulina Zegarska	0000-0001-6727-8128
Eliza Mędrek	0009-0001-2830-014X
Natalia Brzozowska	0009-0003-6580-1714
Natalia Sałkowska	0009-0005-2518-3493
Barbara Wardzyńska	0009-0002-4521-8911
Jakub Magdziak	0009-0006-0297-7423
Oliwia Borowska	0009-0006-1260-5711
Sara Awad	0009-0004-0942-6240
Hanna Markowska	0009-0006-7837-1989

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Pro-inflammatory cytokines as biomarkers in schizophrenia: a systematic review

Paulina Zegarska[1*], Eliza Mędrek[2], Natalia Brzozowska[2], Natalia Sałkowska[3], Barbara Wardzyńska[4], Jakub Magdziak[5], Oliwia Borowska[5], Sara Awad[5], Hanna Markowska[6]

ABSTRACT

Introduction: Schizophrenia's now linked to immune system problems, especially inflammation. This review examines research from 2018 to 2025 on the potential use of these pro-inflammatory cytokines as biomarkers for schizophrenia, with a focus on their role in the onset, progression, symptom presentation, and treatment response of the illness. *Results*: Higher levels of certain cytokines have been found in people with different stages of schizophrenia. These cytokines lead to ongoing inflammation in the body and brain, nerve cell damage, and problems with brain chemicals. These are linked to cognitive impairment and poorer health outcomes. Additionally, gender-based differences affect cytokine levels and treatment efficacy. Studies show that cytokine levels can indicate current and long-term illness. Checking cytokine levels in medical care could facilitate early diagnosis, inform prognosis, and enable the development of personalised treatment plans that address brain inflammation. *Conclusion*: Pro-inflammatory cytokines are key indicators that can help to explain the link between the immune system and the brain in schizophrenia. They can also guide more personalised treatment. Research should aim to make tests more consistent. It should involve studying how these cytokines function to improve patient care.

Keywords: Schizophrenia, Cytokines, Neuroinflammation, IL-6, TNF-alpha, IL-1 beta, IFN-gamma, Personalized psychiatry, Immune dysregulation

1. INTRODUCTION

Schizophrenia is a long-term and serious mental illness. It affects how people think, perceive reality, and behave. About 1% of people worldwide have schizophrenia. Despite significant research, the exact causes of schizophrenia remain unclear. This lack of understanding makes early diagnosis and effective treatment difficult. Recent studies indicate that issues with the immune system and brain inflammation are crucial in the development of schizophrenia. Researchers have closely examined specific immune proteins called pro-inflammatory cytokines as potential indicators of inflammation associated with the onset, progression, and symptoms of schizophrenia (Fond et al., 2018).

Pro-inflammatory cytokines, like interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ), are key mediators of inflammation in both the systemic and central nervous systems. Studies have shown higher levels of these cytokines in the blood, spinal fluid and brain tissue of people with schizophrenia at different stages, like first-episode psychosis, acute exacerbations, chronic phases. These changes to the cytokines are thought to be a contributing factor to the neurodevelopmental disturbances, neuronal damage, neurotransmitter imbalances, and cognitive dysfunction seen in schizophrenia (Shafiee-Kandjani et al., 2023; Upthegrove & Khandaker, 2019; Lv et al., 2024). A significant body of research has indicated a correlation between schizophrenia and systemic inflammation. This condition is characterised by elevated levels of pro-inflammatory cytokines and an imbalance between pro- and anti-inflammatory mediators (Momtazmanesh et al., 2019; Bini et al., 2023). Longitudinal studies further demonstrate that cytokine levels fluctuate dynamically with disease activity and treatment phases, supporting their relevance as both state and trait markers (Delaney et al., 2019; Feng et al., 2020).

Due to these new findings, this review carefully examines and synthesizes current research on pro-inflammatory cytokines as markers in schizophrenia. It focuses on how these cytokines are involved in the illness, what symptoms they are connected to, the different stages of the disease, and what this means for using these markers to guide personalized care in psychiatry. By gathering results from recent high-quality studies and combining information from laboratory work, patient care, and treatments, this review aims to clarify the utility of pro-inflammatory cytokines as markers and suggest future research to help improve the diagnosis and treatment of schizophrenia.

2. REVIEW METHODS

This systematic review utilises a comprehensive and rigorous methodology to synthesise current evidence regarding pro-inflammatory cytokines as biomarkers in schizophrenia, building upon previous systematic approaches. The review protocol was established to ensure transparency, reproducibility, and unbiased selection of relevant studies.

Search strategy

A systematic literature search was completed across multiple electronic databases, including PubMed, Google Scholar for studies published up to 2025. The search terms possessed keywords and Medical Subject Headings (MeSH) relating to schizophrenia, pro-inflammatory cytokines, biomarkers and inflammation (e.g. 'schizophrenia', 'pro-inflammatory cytokines', 'biomarkers', 'IL-6', 'TNF-alpha', 'IL-1beta', 'inflammation', 'systemic inflammatory response'). Boolean operators (AND and OR) were used to refine the search queries, to maximise sensitivity and specificity. The reference lists of contained articles were manually screened for eligible studies. The present study only considers studies published in English.

Inclusion criteria targeted peer-reviewed original research articles, clinical studies, and previously conducted systematic reviews and meta-analyses that investigated the expression levels or clinical utility of pro-inflammatory cytokines in schizophrenia patients across different stages (first episode, chronic, treatment-resistant). Research that looked at samples of blood, fluid from the brain and nervous system samples were all included. The principal objective of the studies was to examine alterations in cytokines with respect to symptom severity, treatment response, and cognitive functioning.

Exclusion criteria

The following types of studies were left out: (1) studies on animals or in the lab that did not have direct data from patients, (2) case reports, opinion pieces, letters, conference summaries, and articles that were not reviewed by other experts, (3) studies that did not clearly define how they diagnosed schizophrenia or mixed schizophrenia with other mental illnesses without looking at them separately, (4) studies that did not give specific data about cytokine levels or did not have proper comparison groups, (5) articles not written in English, and (6) repeated publications or studies using the same data without new results. Also, studies that only looked at anti-inflammatory cytokines and did not include pro-inflammatory markers were left out to keep the focus on the inflammatory markers linked to the body's overall inflammatory response in schizophrenia. The article screening process followed the PRISMA guidelines (Figure 1).

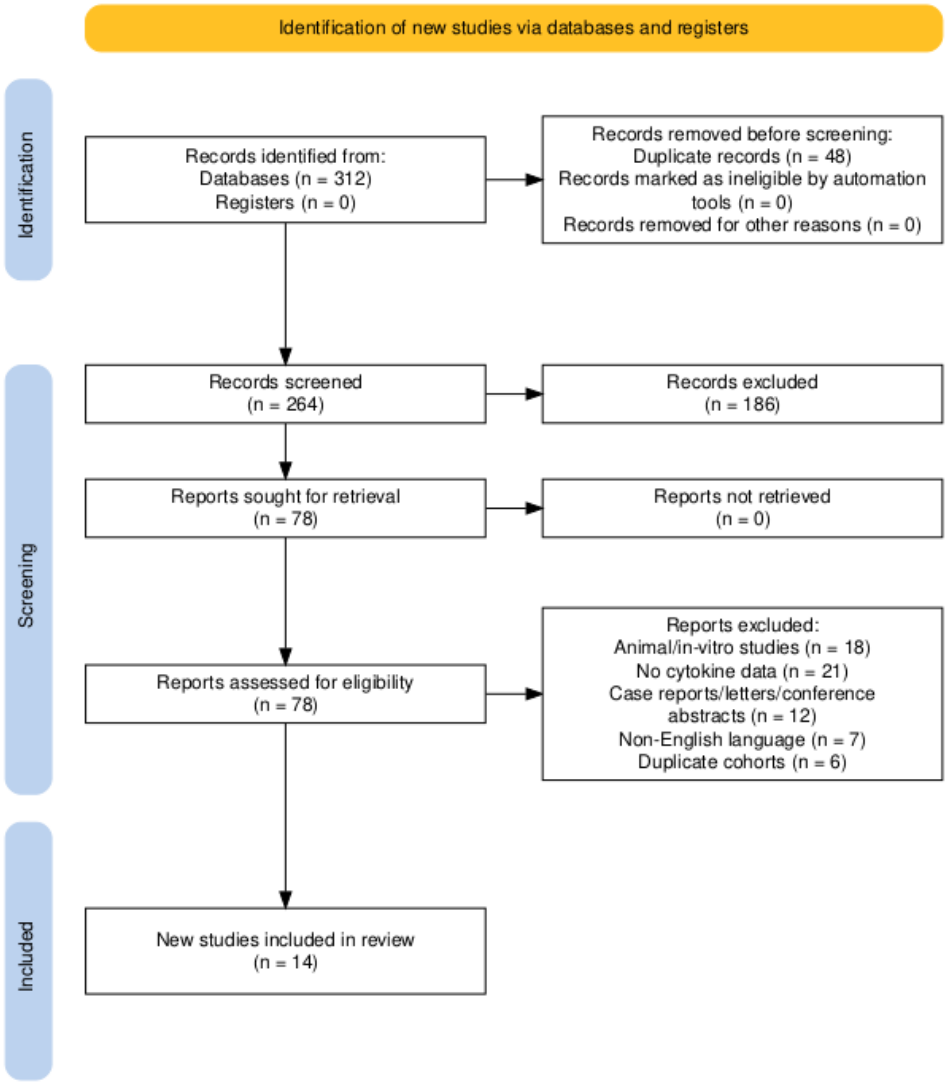

Figure 1. PRISMA flow diagram.

3. RESULTS AND DISCUSSION

Studies from 2018 to 2025 show that certain inflammation-related proteins are higher in people with schizophrenia, which supports their use as signs of body-wide inflammation and disease processes. Important proteins like IL-6, IL-1β, TNF-α, and IFN-γ are found at higher levels in blood, spinal fluid, and brain samples from people at different stages of schizophrenia, including first episodes, relapses, long-term illness, and cases that do not respond to treatment.

Higher levels of IL-6 and TNF-α are some of the most common findings and are linked to worse symptoms, thinking problems, and poor results in treatment. IL-1β is usually high in the early stages of psychosis and goes down when symptoms improve and with medication. IFN-γ changes over time, going up during sudden episodes but dropping in long-term schizophrenia. These proteins trigger immune responses that lead to brain inflammation, nerve cell damage, and problems with brain chemicals, all of which affect how schizophrenia develops and gets worse (Kozyrev et al., 2023).

Differences between men and women in these protein levels and how they affect treatment have been found. For example, women with higher starting levels of TNF-α tend to have worse symptom improvement after six months, showing that doctors should pay attention to these differences (Kim et al., 2023). Also, these protein levels are linked to changes in the brain's structure, like less gray matter and a thinner front part of the brain, suggesting a connection between body-wide inflammation and changes in the brain in schizophrenia (Miller & Goldsmith, 2019).

Studies over time show that these protein levels go up during active illness and usually return to normal when symptoms improve, but some problems remain even in people who get treatment, especially those who do not respond well to it. This means that ongoing inflammation might be behind long-lasting symptoms and poor treatment results for some people.

All this evidence shows that these inflammation-related proteins could be useful indicators for the early detection and tracking of the illness, as well as for predicting how someone will respond to treatment. They could help to create more personalised treatments that target brain inflammation and improve outcomes for people with schizophrenia (Table 1).

Table 1. Key Pro-Inflammatory cytokines associated with schizophrenia

Cytokine	Association with Schizophrenia	Key evidence sources
IL-6	Elevated in the first episode, severe symptoms, cognitive deficits	Shafiee-Kandjani et al., 2023; Lv et al., 2024
IL-1β	High in early psychosis; decreases after remission and treatment	Shnayder et al., 2022; Mednova et al., 2022
TNF-α	Linked to symptom severity, cognitive impairment, and poorer remission in females	Frydecka et al., 2018
IFN-γ	Increased in acute phases; decreased in chronic schizophrenia	Lv et al., 2024

Research conducted between 2018 and 2025 on specific immune system proteins has shown a consistent pattern of inflammation in people with schizophrenia. This inflammation relates to the severity of their symptoms and how well they respond to treatment. These biological markers help us understand the immune system's role in schizophrenia and could guide the development of new treatment options.

Discussion

This review shows that certain pro-inflammatory proteins are important indicators of schizophrenia. These proteins are linked to the onset, progression, the symptoms the disease, as well as the treatment response. Many studies from 2018 to 2025 have found higher levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ) patients with schizophrenia compared to healthy individuals. These proteins also show different concentrations at various stages of the illness, indicating their active role in the development of schizophrenia.

These proteins help explain how problems with the immune system and brain inflammation are connected in schizophrenia. Higher levels of IL-6 and TNF-α, which are important in the body's inflammation process, are linked to worse symptoms, thinking problems, and lower chances of getting better, especially in women. IL-1β is involved in early stages of the illness and usually returns to normal with treatment, which means it could be a sign of how active the disease is. IFN-γ levels change with different stages of the illness, showing that the immune system changes over time.

Also, the differences in these protein levels between men and women show that treatment for schizophrenia should be more personalized, matching care to each person's type of inflammation and other traits. These custom approaches could make treatments work better and help avoid problems with treatment not working. The link between these inflammation proteins and changes in the brain supports the idea that they play a direct role in brain damage and symptoms, making them even more useful as signs of the disease.

Using these inflammation proteins as tools to help diagnose and predict schizophrenia could help make mental health care more precise. Checking these protein levels during regular doctor visits could help doctors find the illness earlier, track how active it is, guess how well someone will respond to treatment, and spot people who might have a relapse or not respond to treatment. Also, creating medicines that target these proteins could lead to new ways to treat brain inflammation and improve results for patients.

However, there are still problems. Different laboratories use different methods to measure these proteins - there is not so much long-term data and patients vary greatly from one another. Future research should focus on ensuring that everyone uses the same methods to measure these proteins, studying how their levels change over time and testing these markers in many different groups of people. A closer examination of the interaction between these inflammatory proteins, genes, body chemistry and the environment will help to make treatments even more personalised.

4. CONCLUSION

This review clearly shows that certain inflammation-related proteins in the body are important signs of schizophrenia. These proteins point to ongoing inflammation throughout the body, which affects when the disease starts, how severe it is, how it develops, and how people respond to treatment. Higher levels of proteins like IL-6, TNF-α, IL-1β, and IFN-γ have been found in many different groups of patients and at different stages of the disease from 2018 to 2025.

In summary, these inflammation-related proteins are important signs that link problems with the immune system to the development of schizophrenia. Learning more about how they work will help turn this knowledge into more personal and targeted care for patients. Future studies should focus on following patients over time and using more personalized approaches to make the most of these proteins for better diagnosis, prediction, and treatment of schizophrenia. Pro-inflammatory cytokines are important biomarkers that link problems with the immune system to the development of schizophrenia. Learning more about how they work will help turn this knowledge into more personal and targeted care for patients. Future research should focus on following patients over time and using more personalized approaches to make the most of these biomarkers for better diagnosis, prediction, and treatment of schizophrenia.

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Authors' Contributions

Paulina Zegarska - Conceptualization; writing - rough preparation; supervision
Eliza Mędrek - Writing - rough preparation
Natalia Brzozowska - Writing - rough preparation
Natalia Sałkowska - Writing - rough preparation
Barbara Wardzyńska - Writing - rough preparation
Jakub Magdziak - Writing - rough preparation
Oliwia Borowska - Writing - rough preparation
Sara Awad - Writing - Review and editing
Hanna Markowska - Writing - review and editing

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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