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Effect of probiotics on C-reactive protein levels in schizophrenia: Evidence from a systematic review and meta-analysis

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ABSTRACT

Background: Inflammatory markers play a pivotal role in schizophrenia, as they provide insight into the neuroinflammatory processes occurring in the context of the disorder. Elevated levels of these markers, particularly C-reactive protein (CRP), can indicate an underlying immune system dysregulation, potentially influencing symptom severity and progression. Recognizing these markers has led to investigate the use of probiotics as an adjuvant to improve the treatment of schizophrenia. The main objective of this study is to rigorously evaluate the efficacy of probiotics in reducing plasma levels of CRP in patients with schizophrenia.

Methods: A systematic search and meta-analysis were conducted to review randomized clinical trials following the PRISMA methodology. The following search strategy ((SCHIZO* OR PSYCHOTIC OR PSYCHOSES) AND (PROBIOTIC* OR BIFIDOBACTER* OR LACTOBACILL*)) was used for searching publications between June-December 2024 on the PubMed, Web of Science, and APA PsycINFO databases. Individual study quality was assessed with the Cochrane risk of bias (RoB2) and the certainty of total evidence was assessed with the GRADE system.

Results: The primary outcome assessed was the impact of probiotic supplementation on plasma CRP levels. Out of 78 studies initially identified, 4 were finally included in the meta-analysis. Three out four studies found a significant reduction in high-sensitivity C-reactive protein levels in the supplemented compared with the placebo group. The pooled analysis revealed a significant reduction in CRP levels with probiotic supplementation, with a standardized mean difference (SMD) of −0.46, (95 % CI −0.719; −0.201; $p = 0.001$).

Conclusions: The synthesis and meta-analysis of available literature provide evidence for the potential role of probiotics in the reduction of serum CRP in schizophrenia compared with placebo. However, more clinical trials with better control of experimental design are needed before a clear recommendation as adjuvant therapy can be made.

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1. Introduction

Schizophrenia is a complex neuropsychiatric disorder characterized by a wide spectrum of clinical manifestations, including negative, positive and cognitive symptoms. Affecting approximately 1 % of the global population,[1] people with schizophrenia (PWS) face a mortality risk two to three times higher than the general population[2] and experience an average reduction in life expectancy of about 15 years.[2] This disorder significantly impacts functional capacity and quality of life. Despite extensive research, its etiopathogenesis remains poorly understood.[3,4] Emerging evidence has highlighted the microbiota-gut-brain axis (MGBA) as a potential etiological factor in various neuropsychiatric disorders, including schizophrenia.[5] This bidirectional axis comprises the gastrointestinal microbiota, the enteric nervous system, the autonomic nervous system, the neuroendocrine system, the immune system (IS) and the central nervous system (CNS).[6] The MGBA is a bidirectional communication network encompassing the gastrointestinal microbiota, the enteric nervous system, the autonomic nervous system, the neuroendocrine system, the immune system (IS), and the central nervous system (CNS). The gut microbiota influences brain function through multiple mechanisms, including the production of neurotransmitters, modulation of the immune response, and maintenance of gut barrier integrity. The vagus nerve plays a central role in this axis, acting as a key communication pathway between the gut and the brain. Dysbiosis, or an imbalance in the microbiota composition, has been associated with several CNS disorders such as depression, bipolar disorder, or schizophrenia.[7,8] Specific bacterial populations within the gut microbiota, may contribute to intestinal dysbiosis, potentially serving as endogenous factors that promote inflammation linked to neuropsychiatric.[9–11] In fact, schizophrenia is widely recognized as a multifactorial disorder with a genetic component that predisposes patients to inflammatory processes.[12] Notably, immune dysregulation appears to play a pivotal etiological role in schizophrenia.[13] One prevailing hypothesis posits that schizophrenia is a neurodevelopmental disorder potentially linked to prenatal infection.[14] Such infections are thought to increase the production of specific interleukins, particularly interleukin-6 (IL-6), among other humoral factors, which subsequently activate microglial cells in the fetal brain, leading to neuroinflammation.[15] In addition to immune dysregulation, disruptions in classical neurotransmitter systems, dopaminergic, serotonergic, noradrenergic, and glutamatergic pathways, have been observed in the context of low-level neuroinflammation. These changes are proposed to be critical triggers for the onset and persistence of psychotic symptoms in schizophrenia.[11]

Recent research has underscored the critical role of inflammation not only in the onset but also in the persistence of schizophrenia.[16] Meta-analyses have consistently reported elevated levels of both pro-inflammatory and anti-inflammatory cytokines in the peripheral blood of patients experiencing their first episode of schizophrenia as well as in those with relapse when compared to healthy controls.[17] Furthermore, these studies have demonstrated that peripheral anti-inflammatory cytokine levels tend to normalize in parallel with symptomatic improvement following the initiation of antipsychotic treatment.

Among the immune-inflammatory disturbances in schizophrenia, IL-6 stands out as one of the most frequently disrupted cytokines.[18] On the one hand, linked to the hypothesis of prenatal infection, it has been observed that lipopolysaccharide (LPS) from the bacterial walls of various infectious agents elevates IL-6 levels.[19] Beyond infection, additional factors, including genetic predispositions, environmental stressors, and disruptions in the hypothalamic-pituitary-adrenal (HPA) axis, further contribute to increased IL-6 levels in individuals with schizophrenia.[20] This growing body of evidence underscores the multifactorial nature of immune dysregulation in schizophrenia, highlighting IL-6 as a pivotal mediator in the inflammatory processes associated with the disorder.[21–23] In addition to its direct role in immune signaling, IL-6 drives the hepatic production of C-reactive protein (CRP), a widely recognized biomarker of systemic inflammation. Elevated maternal CRP levels during pregnancy, often resulting from nonspecific viral or bacterial infections, have been associated with an increased risk of schizophrenia in adult offspring. This relationship underscores the relevance of prenatal inflammation in the pathogenesis of the disorder.[24–26] Furthermore, a high prevalence of elevated CRP levels has been reported in patients with schizophrenia.[24] Abnormal CRP levels have been associated with positive symptoms and a broad range of cognitive impairments as demonstrated in a recent systematic review,[27] supporting the link between neuroinflammatory processes and symptomatology in schizophrenia.

[28–3233–36373839–43]While the exact aetiology of schizophrenia remains uncertain, dopamine dysregulation has traditionally been considered a central factor, guiding the development of antipsychotics. These medications, though effective in mitigating positive symptoms, have limited impact on negative and cognitive symptoms, which are critical for functionality and quality of life.[28–32] Furthermore, antipsychotics often carry significant side effects, including metabolic disturbances such as weight gain, dyslipidaemia, and insulin resistance, which exacerbate systemic inflammation and increase the risk of comorbid somatic illnesses.[33–36] These adverse effects can reduce treatment adherence and overall therapeutic outcomes.[37]

Given the growing evidence linking inflammation to symptom severity in schizophrenia, targeting inflammation—potentially through dietary interventions and probiotics—has emerged as a promising adjunctive strategy.[38–43]

Given the above, therapies aimed at restoring the MGB axis and regulating the IS are particularly promising candidates for the adjunctive treatment of schizophrenia symptoms. Probiotics, which modulate gut microbiota and reduce systemic inflammation, may offer a promising adjunctive treatment for schizophrenia by potentially alleviating neuroinflammation and improving overall symptoms. These effects may be mediated through the restoration of gut barrier integrity.[44] Probiotics also promote the production of short-chain fatty acids (SCFAs) like butyrate, which possess anti-inflammatory properties and are known to regulate microglial activation in the brain.[45] In fact, probiotics have proved their effect through metanalytic reviews on serum CRP levels in other inflammatory health issues such as osteoarthritis, autoimmune diseases or neurological disorders.[46–48] To date, there are few randomized controlled trials (RCTs) studying the effect of probiotics on inflammatory markers in schizophrenia. However, despite the literature being limited, the results so far are very promising. The general objective of this study is to conduct the first systematic review with a meta-analysis of the effects of probiotics on the pro-inflammatory marker C-reactive protein (CRP) in schizophrenia.

2. Methods

The present study was prepared following the Preferred Reporting Items for Systematic reviews and Meta-Analysis PRISMA guidelines 2020 version[49] (see Appendix 1) The research question was framed according to the criteria of population (patients with schizophrenia), intervention (probiotics), comparison (placebo-controlled), and outcome (symptoms) (PICO).

The protocol was registered on PROSPERO https://www.crd.york.ac.uk/prospero/ (registration number: CRD 42023491573).

2.1. Search Strategy and Eligibility Criteria

A systematic search of articles was conducted in PubMed (Medline), Web of Science, and APA PsychInfo to identify studies relevant to the current review. We applied the following search criteria: ((SCHIZO* OR PSYCHOTIC OR PSYCHOSES) AND (PROBIOTIC* OR BIFIDOBACTER* OR LACTOBACILL*)). The complete search strategy can be found in Appendix 2. The electronic search was conducted from June 2024 to December 2024, both inclusive. The inclusion criteria were: (i)

randomized clinical trials, (ii) Low or medium risk of bias, which ensures the methodological quality of clinical trials, (iii) placebo-controlled (not medical advice), (iv) published in peer-reviewed journals, (v) administration of probiotics (alone or in combination with prebiotics or other supplement or vitamin), and (vi) participants with a diagnosis of schizophrenia according to ICD-11 or DSM-5 criteria, or previous international diagnostic classifications. In addition, we searched the reference lists of previous reviews and relevant studies as well as grey literature for additional relevant studies. The flow chart of studies can be seen in Fig. 1.

2.2. Evaluation of studies

Studies were evaluated by two independent reviewers (VRF and LGF) using the revised Cochrane risk-of-bias tool (RoB 2 tool).[50] This tool assesses and categorizes possible sources of bias arising from the randomization process, deviations from intended interventions, missing outcome data, the measurement of the outcome, and the selection of reported results. Ratings per item were compared and disagreements discussed. In case of discrepancies, a third one evaluated the studies (RRJ). Additionally, we evaluated the reliability of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, which assesses factors such as risk of bias, imprecision, inconsistency, and indirectness to classify the evidence into high, moderate, low, and very low quality,[51] reflecting the level of uncertainty regarding the estimated impact. The quality of evidence resulted as "moderate" (see Table S1).

Study population. Participants were adult men and women (aged ≥18) diagnosed with schizophrenia. Diagnosis should be based on the World Health Organization (ICD-11 or earlier) or the American Psychiatric Association (DSM-5-TR or earlier) classification systems.

Intervention and comparison. The intervention consisted of daily treatment with probiotics administered for at least 4 weeks with or without simultaneous antipsychotic medications. Comparison should be made with placebo. Studies with no placebo, for example, 'usual medical advice' were excluded. All probiotic formulations were considered regardless of species, strain, or concentration.

Results. The primary outcome was the reduction of CRP levels after the intervention.

Quality assessment. Two independent evaluators (VRF, LGF) assessed each study using the the Cochrane risk of bias (RoB2). When any incongruence was found, it was resolved by a third expert (RRJ). The reasons for exclusion are listed in Table 1.

Study design. Clinical trials were reviewed, regardless of publication date. Randomized, placebo-controlled, double-blind trials were preferred, but those that did not meet one of these requirements (for

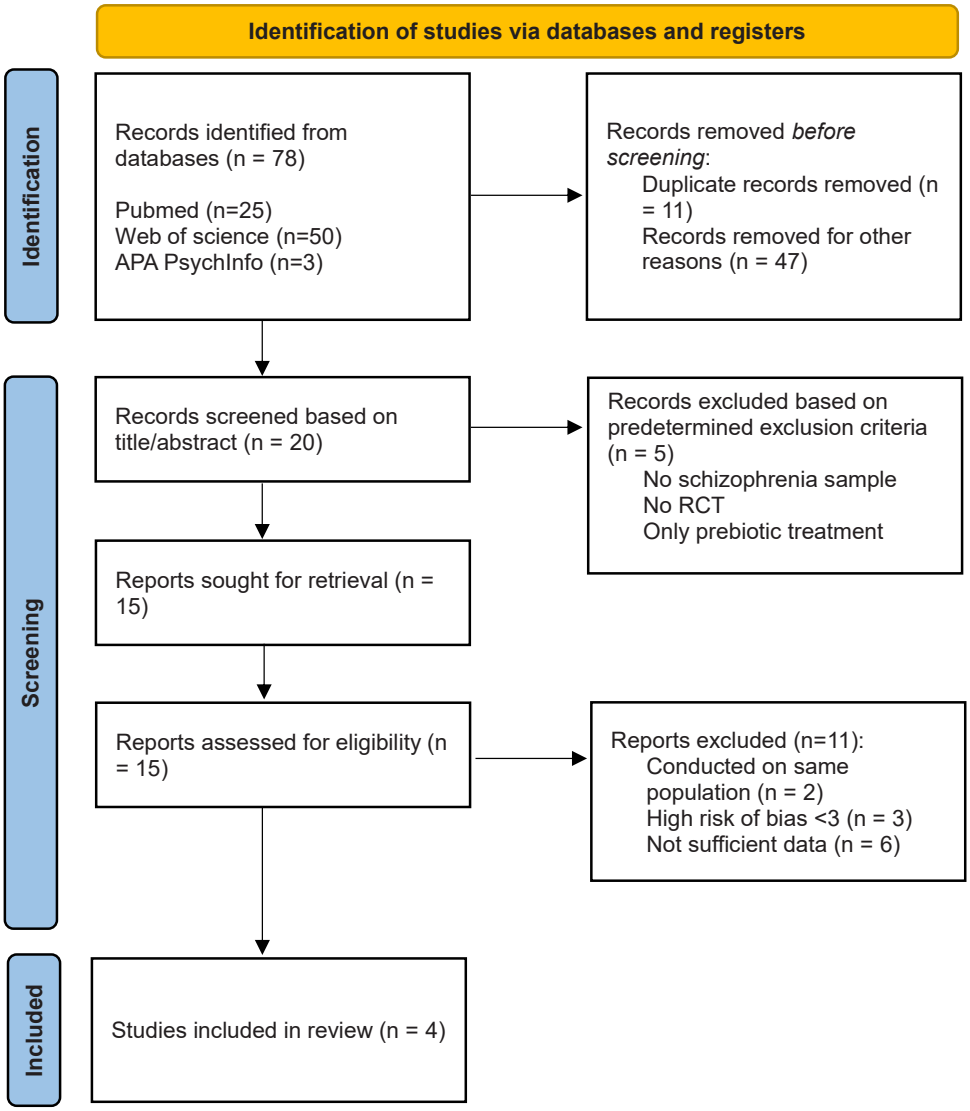

Fig. 1. PRISMA flowchart.

Table 1
Reasons for exclusion from of studies reviewed.

Reference	Reasons for exclusion
[84]	High risk of bias; It's not double-blind; it's not randomized
[85]	High risk of bias; It's not double-blind; it's not randomized; it doesn't have a control group
[86]	Same sample as[56]
[87]	Same sample as[56]
[88]	Insufficient data; The intervention is only dietetic.
[89]	High risk of bias; It is not double-blind; the method of randomization is not indicated
[90]	Insufficient data
[91]	Insufficient data; included patients diagnosed with bipolar disorder
[92]	Insufficient data
[93]	Insufficient data; included patients diagnosed with bipolar disorder
[94]	Insufficient data

example, non-computer-generated randomization) were not excluded.

2.3. Data extraction

For all studies, data were extracted independently by two investigators (VRF and CR). Sample sizes (experimental and placebo) as well as means and standard deviations (SDs) before and after the intervention, were collected. When data shared in a relevant study was insufficient for analysis (e.g., data in diagrams, lack of post-treatment values), efforts were made to contact the study authors to ask them for data required to perform the meta-analysis.

2.4. Data synthesis, statistical analysis, and meta-analysis

The CRP levels, expressed as mean and SD, was the main outcome, that was. The change in CRP levels was calculated by subtracting the pre-treatment mean CRP (mg/L) from the post-treatment, when this difference was not already indicated in the publication. The standard deviation of that mean difference, which was not usually indicated, was calculated following the procedure described in a previous study.[52] Heterogeneity between studies was assessed using the I^2 statistic and was classified as low ($I^2 \approx 25$ %), medium ($I^2 \approx 50$ %), and high ($I^2 \approx 75$ %) according to Higgins.[53] Random-effect models were generated when high heterogeneity was observed ($I^2 \geq 75$ %), and fixed-effect models were otherwise used. Cohen's standardized mean difference (SMD) was used as the primary index of effect size and was calculated in such a way that negative values indicated a reduction in CRP levels after treatment. Statistical analyses were performed using Stata 14.0 (Stata-Corp, College Station, TX), and results were considered statistically significant when $p < 0.05$. Confidence intervals are also provided.

3. Results

3.1. Review and selection of studies

Initially, 76 records were identified from database searches. Two new studies were found during the second search. After removing duplicates and articles that were not clinical trials or did not include patients diagnosed with schizophrenia, 20 records remained, which were screened based on titles, abstracts, and methods sections. Five of these records were excluded according to preset exclusion criteria. At this point, 15 records were screened based on the full texts, and finally, 4 clinical trials were included in this systematic review.[54–57] The excluded studies are listed in Table 1.

3.2. Risk of bias assessment

The quality of the studies was assessed using Risk of Bias 2 tool mentioned above (see Fig. 2). Cohen's weighted kappa was used to measure the agreement between the two raters. Results showed a Kappa = 0.706, 95 %CI [0.454; 0.958], $p < .001$, which is a substantial agreement. All studies were clinical trials, all reported dropouts and withdrawals and included data from participants who completed the trial. The dropout rate ranged from 2.9 % to 16.0 %, with an average of 10.5 %. Publication bias was assessed using Egger's linear regression test, which is more specific than Begg's test when the number of primary studies is small.[58]

3.3. Synthesis of results

Full study characteristics are presented in Table 2. In one of the first clinical trials conducted by Tomasik et al.[56] a combination of 10^9 colony-forming units (CFU)/day of *Lacticaseibacillus rhamnosus* (in the article indicated as *Lactobacillus rhamnosus GG) and Bifidobacterium*

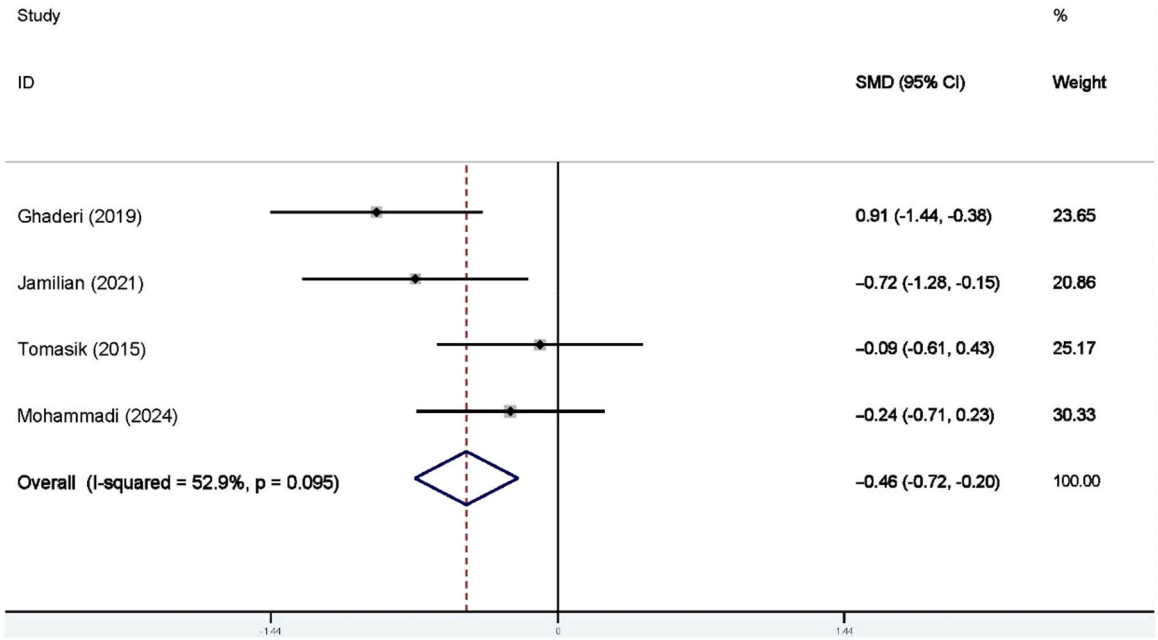

Fig. 2. Meta-analysis of the change in serum C-reactive protein between post- and pre-treatment in the probiotics versus placebo groups.

Table 2
Characteristics of the included studies. UI = International Units; CFU = Colony Forming Units; PANSS = *Positive and Negative Syndrome Scale* (P = Positive symptom subscale; N = Negative symptom subscale; GP = General Psychopathology subscale). *In the original article they are indicated by their old genera names. Significant P values ≤ 0.05 are in boldface.

First Author, Year	N (Probiotic/ Control)	Age Range (Years)	Diagnosis	Probiotics (daily dose)	Duration (weeks)	C-reactive protein reduction
Ghaderi, 2019	30 / 30	25–65	Schizophrenia of at least two years of duration, with a total PANSS score ≥ 55, treated with chlorpromazine (300–1000 mg/day, excluding clozapine) and anticholinergic agents (trihexyphenidyl, 4–8 mg/day) during the past 6 months	50,000 IU of Vitamin D3 every 2 weeks plus *Lactobacillus acidophilus, Bifidobacterium bifidum, Limosilactobacillus reuteri** and *Limosilactobacillus fermentum** (each 2 × 10^9 CFU)	12	hs-CRP − 2.3 mg/L ± 3.0 supplemented vs. −0.3 ± 0.8 mg/L placebo, $p = 0.001$)
Jamilian, 2021	25 / 26	18–60	Schizophrenia (any type) that meets the DSM-IV-TR criteria. Authors do not say anything about the medication, but neither they say that patients are drug naïve	200 μg/day of selenium as selenium yeast plus *Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium bifidum, and Bifidobacterium longum* (each 2× 10^9 CFU)	12	Mean difference reduction = − 1.44 mg/L (95 %CI − 2.22; − 0.66, $p = 0.001$)
Tomasik, 2015	31 / 27	18–65	Schizophrenia or schizoaffective disorder in outpatient treatment with at least moderately severe psychotic symptoms through PANSS scores. Antipsychotic use for at least 8 weeks prior to the study, unchanged from the previous 21 days	10^9 UFC de *Lacticasei rhamnosus** GG and 10^9 UFC of *Bifidobacterium animalis* subsp. *lactis* BB12	14	CRP start (μg/ml) 6.7 ± 8.2 (supplemented), 6.3 ± 7.6 (placebo); CRP end 7.1 ± 7.9 (supplemented), 7.3 ± 10.1 (placebo)
Mohammadi, 2024	35/35	18–65	Schizophrenia having at least a fifth-grade elementary education, having no GI problem at the study baseline, and being stable on the current psychotropics for at least 6 months	Probiotic/vitamin D supplement (BioZenD) was containing *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus**, *Limosilactobacillus reuteri**, *Lacticaseibacillus paracasei**, *Bifidobacterium longum*, and *Weizmannia coagulans**(2 × 10^9 CFU), and 400 IU vitamin D per one capsule.	12	Marginal Mean Difference = −2.33 mg/L, $p < .001$

animalis subsp. *Lactis* BB12 was administered to a group of medicated patients diagnosed with schizophrenia (n = 31) for 14 weeks. All patients received antipsychotic treatment for at least eight weeks prior to starting the trial and had not changed their medication within the previous 21 days. The results showed a reduction of 0.44 μg/ml from baseline in the supplemented group and 1 μg/ml in the placebo group. However, they did not calculate the *p*-value for this comparison.[56]

In a more recent study by Ghaderi et al.,[55] a supplement of 50,000 international units (IU) of vitamin D3 every 2 weeks and a probiotic containing 8 × 10^9 CFU/day of *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Limosilactobacillus reuteri* (in the article indicated as *Lactobacillus reuteri*) and *Limosilactobacillus fermentum* (in the article indicated as *Lactobacillus fermentum*) was administered during 12 weeks to a group of 30 patients with schizophrenia treated with chlorpromazine. The authors found a significant decrease in high-sensitivity CRP in the supplemented group (-2.3 ± 3.0) compared with placebo (-0.3 ± 0.8 mg/L), ($p = .001$).[55]

In the study carried out by Jamilian and Ghaderi,[54] a combination of 8 × 10^9 CFU/day containing *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Bifidobacterium bifidum* and *Bifidobacterium longum* in addition to 200 μg/day of selenium was administered during 12 weeks to a group of patients with schizophrenia (n = 30). These authors found a significant reduction in high-sensitivity C-reactive protein levels in the supplemented compared with the placebo group (−1.44 mg/L, $p = .001$).[54]

Finally, in the study by Mohammadi, participants diagnosed with schizophrenia (n = 34) received a probiotic supplement containing *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus* (in the article indicated as *Lactobacillus rhamnosus*), *Limosilactobacillus reuteri* (in the article indicated as *Lactobacillus reuteri*), *Lacticaseibacillus paracasei* (in the article indicated as *Lactobacillus paracasei*), *Bifidobacterium longum*, and *Weizmannia coagulans* (in the article indicated as *Bacillus coagulans*) (2×10^9 CFU), and 400 IU of vitamin D per day for 12 weeks. After that, they found a significant decrease in C-reactive protein compared to the placebo-receiving group (Marginal Mean Difference = −2.33, $p < .001$).[57]

No adverse effects secondary to probiotic administration have been reported in any of the reviewed studies. None of the studies explicitly mention having tested the purity of products. However, although there are variations depending on the country and its legislation, generally a probiotic product should contain more than 10^6–10^8 CFU/dose of viable cells.[59] All studies included have at least 10^9 CFU from each strain administered.

3.4. Meta-analysis on the C-reactive protein levels

The I^2 value was 52.9 % ($p = 0.095$), so a fixed-effects model was applied. No risk of publication bias was observed according to the results of Egger's test (coefficient = −11.9, $p = 0.358$). The total pooled SMD was −0.46 mg/L (95 % CI −0.719; −0.201), $p = 0.001$ (see Fig. 3).

4. Discussion

The main objective of this study was to systematically review the existing literature and conduct a meta-analysis on the effects of probiotic supplementation in reducing CRP levels in patients with schizophrenia.

The meta-analysis was performed on data from four of the 15 eligible studies, which provided evaluable pre- and post- treatment serum levels of CRP. Summary of results revealed a significant reduction in CRP levels following 12–14 weeks of probiotic intake, compared to the control group, with an overall standardized mean difference (SMD) of −0.46 mg/L (95 % CI −0.719 to −0.201; $p = 0.001$). Some previous meta-analysis conducted in general population show significant reductions in serum CRP following probiotic administration (−1.35 mg/L; 95 % CI −2.15 to −0.55),[60] and (-1.02 mg/L; 95 % CI −1.23 to −0.80),[61] as well as other inflammatory markers such as IL-10 or TNF-α, and even, blood pressure.[62] The evidence unequivocally demonstrates that probiotic supplementation leads to a significant reduction in C-reactive protein (CRP) levels across healthy populations,[61,63] those with neurological disorders,[46] and people with schizophrenia. Notably, a comparison of these findings reveals that the reduction inflammatory parameters is more pronounced in the general population than in people with schizophrenia (−1.35 mg/L vs. −0.46 mg/L). It is important to

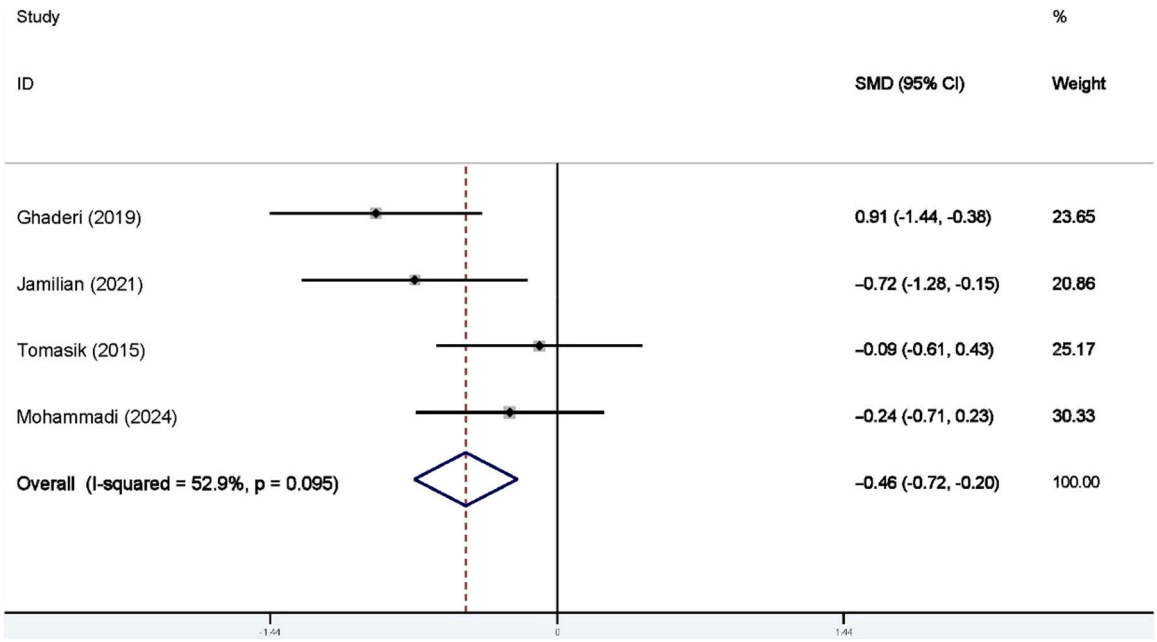

Fig. 3. Meta-analysis of the change in serum C-reactive protein between post- and pre-treatment in the probiotics versus placebo groups.

highlight, however, that while two studies employed high-sensitivity CRP measurements, the other two utilized the standard CRP test. Given that standard CRP is designed for detecting acute infections and has lower sensitivity to subtle inflammation, this methodological difference may lead to an underestimation of the overall effect.[64] Despite this limitation, the observed capacity of probiotics to reduce CRP, a key inflammatory biomarker, in a complex disorder such as schizophrenia represents a highly relevant finding as well as a novel contribution to current literature. Among the studies reviewed, the only study that did not find a significant effect is one of the two studies that used the standard CRP measurement and also included a mixed population of patients with schizophrenia and schizoaffective disorder, which may have influenced its results.[56] The heterogeneity within this mixed group could introduce variability in response to the intervention, as the pathophysiological mechanisms and inflammatory profiles in schizophrenia and schizoaffective disorder might differ.

The most commonly administered strain in the studies included in the present meta-analysis was *Lactobacillus acidophilus*, which was administered in three of the four studies.[54,55,57] In the involving *Lactobacillus acidophilus*, significant findings were observed. Notably, these three studies also co-administered vitamin D3 or selenium. This concurrent supplementation makes it challenging to isolate the effects of probiotics alone, which have been shown to reduce inflammation,[65] from those of vitamin D3, which also correlate with lower levels of C-reactive protein,[66] although a causal relationship has not been established.[67] Furthermore, a study suggests that vitamin D3 may more effectively reduce inflammation in patients with inflammatory-related conditions compared to those with non-inflammatory conditions, which could imply that the observed reduction in inflammation might be more attributable to vitamin D3 than to the probiotics themselves.[68] Likewise, selenium supplementation has been shown to significantly reduce CRP levels, especially in patients with elevated values.[69] However, since selenium was only administered in one of the studies and given the substantial differences in vitamin D3 dosages used in the other two studies (50,000 IU every two weeks in[55] vs. 400 IU/day, equating to 5600 IU every two weeks, in[57]), it is challenging to attribute the observed reduction in CRP levels solely to these supplements. While these differences complicate the assessment of the specific effects of probiotics, it is important to acknowledge that both vitamin D3 and selenium may have contributed to the observed outcomes. In this sense, other meta-analysis shows the ability of natural supplements -in absence of probiotics- of reducing CRP serum levels.[63]

Regarding the pathway through which probiotics can affect serum CRP levels, several mechanisms have been suggested. On the one hand, short chain fatty acids (SCFAs), which are products of anaerobic bacteria fermentation in the intestine, have the ability to regulate various leukocyte functions including the production of the cytokines TNF-α, IL-2, IL-6 and IL-10. The capacity of leukocytes to migrate to the foci of inflammation and to destroy microbial pathogens also seems to be affected by the SCFAs.[70] Specifically, the SCFAs acetate and butyrate have demonstrated anti-inflammatory properties.[71] Thus, the reduction of inflammation would result in decreased enzymatic synthesis of hepatic CRP. The decreased serum CRP levels might also result from decreased colonic concentration of IL-6.[72] It has also been suggested that decreased inflammation and oxidative stress produced by some specific strains of lactic acid bacteria could be due to their effects on decreasing expression of interleukin-6 (IL-6) in adipocytes.[73] On the other hand, the anti-inflammatory properties of some strains of probiotics are thought to act by preventing or repairing the leaky epithelial barriers, which reduces intestinal permeability and improves tight-junction integrity.[74] They also enhance synthesis of antimicrobial peptides that influence inflammation resolution pathways in the mucosa.[75] Nevertheless, the significant reduction in serum levels of CRP observed in schizophrenia patients receiving antipsychotic treatment supplemented with probiotics is hypothesized to stem from the beneficial effects demonstrated by these supplements in both *in vitro* and *in vivo* studies.[76,77]

It is also noteworthy that all patients included in this study received antipsychotics in addition to the supplement administered. This should not be a concern, given that a meta-analysis has demonstrated that CRP levels were moderately elevated in individuals with schizophrenia independent of antipsychotic usage. Furthermore, these levels did not increase following the initiation of either first- or second-generation antipsychotic medication.[78] In addition, the associations between CRP levels and psychiatric symptoms in schizophrenia have also been studied, but mixed results have been found. Some studies have found that elevated serum levels of C-reactive protein in schizophrenia were associated with the severity of cognitive impairment –especially working memory deficits- but not with psychotic symptoms.[79,80] By contrast, others have found associations between CRP levels and psychiatric symptoms, such as the severity of illness, negative symptoms and

aggressiveness[81] auditory hallucinations and anhedonia,[82] or the severity of positive -but not negative- symptoms.[83] These mixed results highlight the complexity of the relationship between inflammation and schizophrenia, suggesting that more research is needed to fully understand the role of CRP levels in the presentation and severity of psychiatric symptoms.

Moreover, probiotics are well-tolerated with minimal adverse effects, leading to a wide acceptance among patients and the general public. This favourable risk-benefit balance, supported by positive meta-analyses, justifies their use in clinical practice.

Our review has some strengths and limitations. As strengths, we can point out that this is the first meta-analytic review on the use of probiotics to assess their effect on serum CRP levels. Also, the use of the PRISMA model, according to which only randomized trials that compare probiotics administration with placebo were selected. Individual study quality was assessed with the Cochrane risk of bias (RoB2) and the certainty of total evidence was assessed with the GRADE system, being rated as "moderate". Also, grey literature has been sought for retrieval, although available information did not meet inclusion criteria. For all this, although there were only four eligible studies, a meta-analysis was performed. Regarding the limitations, they have more to do with those of the included studies: small samples, heterogeneity of probiotic strains, CRP determination (high-sensitive vs. standard) and the addition of other micronutrients such as vitamin D3 or selenium. Also, when there are a small number of studies, publication bias tests such as Egger test are not wrong but have low statistical power. More studies are needed to increase statistical power and draw solid conclusions.

In conclusion, this systematic review and meta-analysis explored the effects of probiotic supplementation on CRP levels in patients with schizophrenia. Although it involves a small number of studies, results suggest the potential anti-inflammatory benefits of probiotics. However, it is important to acknowledge that the concurrent administration of other substances, such as vitamin D or selenium, may also contribute to the observed effects and their potential influence of the results cannot be entirely ruled out. The meta-analysis included four randomized controlled trials and found a significant reduction in CRP levels following 12–14 weeks of probiotic supplementation compared to placebo. This result suggests that probiotics could serve as an adjunctive treatment to manage inflammation in schizophrenia. However, the variability in probiotic strains and the co-administration of micronutrients like vitamin D3 and selenium in the studies analysed suggest that the specific mechanisms by which probiotics exert their effects on inflammation in schizophrenia need further investigation. Future studies should focus on larger sample sizes and standardized probiotic formulations to validate these findings and clarify the role of probiotics in the treatment of schizophrenia.

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CRediT authorship contribution statement

Roberto Rodriguez-Jiménez: Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Rolf Wynn:** Writing – review & editing, Supervision. **Miguel Ángel Álvarez-Mon:** Writing – review & editing, Supervision. **Mónica De la Fuente:** Writing – review & editing, Supervision, Conceptualization. **Rocío González-Soltero:** Writing – original draft, Validation, Methodology. **Carmen Romero Ferreiro:** Software, Formal analysis, Data curation. **José Miguel Biscaia:** Writing – original draft, Validation, Methodology. **Lorena García-Fernández:** Writing – original draft, Validation, Data curation. **Verónica Romero-Ferreiro:** Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Roberto Rodriguez Jimenez reports a relationship with University Hospital October 12th that includes: consulting or advisory, funding grants, and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2025.103126.

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