

Effects of synbiotic supplementation on inflammatory and anti-inflammatory markers in adults: A GRADE-assessed systematic review and meta-analysis of randomized controlled trials

Mohammad Vesal Bideshki^{1,2}, Naimeh Mesri Alamdari³, Hossein Bahari⁴, Zahra Asadi⁵, Behrad Sadeghi⁶, Tohid Salehi⁷, Hannane Jozi⁷, Mehrdad Behzadi^{5,8}, Seyed Fazel Zinat Motlagh⁹, Zahra Sohrabi^{10,8*}, Ali Rashidinejad^{11*}

¹Bio Environmental Health Hazards Research Center, Jiroft University of Medical Sciences, Jiroft, Iran

²Clinical Research Development Unit, Imam Khomeini Hospital, Jiroft University of Medical Sciences, Jiroft, Iran

³Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁴Transplant Research Center, Clinical Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

⁶Department of Agricultural, Forest and Food Science (DISAFA), University of Torino, Grugliasco, Torino 10095, Italy

⁷Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

⁸Department of Community Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

⁹Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran

¹⁰Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

¹¹Riddet Institute, Massey University, Private Bag 11222, Palmerston North, New Zealand

Article Info



Article Type:

Systematic Review

Article History:

Received: 11 Oct. 2025

Revised: 28 Jun. 2026

Accepted: 8 Jul. 2026

ePublished: 4 Oct. 2026

Keywords:

Synbiotics, Inflammatory markers, Anti-inflammatory markers, CRP, IL-6, TNF- α

Abstract

Introduction: Systemic inflammation contributes to chronic diseases, and synbiotics may modulate these pathways via gut microbiota. This systematic review and meta-analysis evaluates synbiotic supplementation effects on adult inflammatory and anti-inflammatory markers.

Methods: A comprehensive search of PubMed/MEDLINE, Web of Science, Scopus, Embase, and CENTRAL, supplemented by Google Scholar and manual reference-list searches, identified 63 randomized controlled trials involving 3,725 participants. Eligible studies administered synbiotics for at least 3 weeks. Data were pooled using random-effects models to calculate standardized mean differences (SMDs). Risk of bias was assessed using the Cochrane risk-of-bias tool, and the certainty of evidence was evaluated using the GRADE approach.

Results: Synbiotic supplementation was associated with a reduction in C-reactive protein (CRP) (SMD: -0.49, 95% CI: -0.67 to -0.31), interleukin-6 (IL-6) (SMD: -0.33, 95% CI: -0.61 to -0.05), IL-8 (SMD: -0.62, 95% CI: -1.15 to -0.09), and tumor necrosis factor- α (TNF- α) (SMD: -0.38, 95% CI: -0.65 to -0.11). Conversely, anti-inflammatory IL-10 significantly increased (SMD: 0.30, 95% CI: 0.002 to 0.59). No significant changes occurred in IL-1 β , IFN- γ , lipopolysaccharide (LPS), or adiponectin. Publication bias was detected for CRP, and evidence certainty ranged from very low to low.

Conclusion: Synbiotic appears to modulate inflammatory status by reducing key pro-inflammatory biomarkers (CRP, IL-6, IL-8, and TNF- α), and increasing the anti-inflammatory cytokine IL-10. Nevertheless, the strength of these conclusions is limited by the low to very low certainty of the available evidence, as well as potential publication bias affecting the CRP estimate. Future standardized, adequately powered RCTs are required to validate these clinical findings.

Introduction

Probiotics, which are live microorganisms, could bear health-promoting effects when they are consumed in sufficient amounts. The beneficial effects of probiotics are pertinent to their protective effects against various metabolic or cognitive diseases, cancers, and the like, through improving gut microbiota.¹⁻⁴ Moreover, synbiotic supplementation (the combination of prebiotics and

probiotics) may affect the gastrointestinal microbiota more effectively than the single supplementation of probiotics or prebiotics.⁵

Various healthful effects of probiotics include immunomodulatory effects,⁶ anti-inflammatory properties (by a reduction in inflammatory cytokine levels and suppression of Toll-like receptor 4 (TLR-4) activation),⁷ weight modulation,⁸ and other related conditions. On the



*Corresponding authors: Zahra Sohrabi, Email: Zahra_2043@yahoo.com and Ali Rashidinejad, Email: a.rashidinejad@massey.ac.nz



© 2026 The Author(s). This work is published by BioImpacts as an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>). Non-commercial uses of the work are permitted, provided the original work is properly cited.

other hand, it was asserted that synbiotic consumption in the form of foods or supplements could positively affect various processes, including gut microbiota, lipid metabolism, liver enzymes, and insulin sensitivity, to a greater extent than probiotics or prebiotics alone.⁹ Anti-inflammatory properties of the synbiotics could improve various diseases as well.¹⁰ It was reported that gut microbial dysbiosis and higher translocation bacteria and their components in the intestine could promote systemic inflammation.¹¹ It was mentioned that synbiotic consumption could slow down the inflammatory process by modulating the gut microbiome.¹² The prebiotics present in synbiotics, such as inulin, can be fermented, which leads to the formation of short-chain fatty acids (SCFAs). These SCFAs could reduce the expression of genes related to inflammation, such as cyclooxygenase-2, interleukin-8, and interleukin-6.¹³ Moreover, these compounds could also increase IL-18 expression,¹⁴ which can in turn reduce hepatic C-reactive (CRP) production. Moreover, some compounds with anti-inflammatory properties from the methylketone family are produced following synbiotic consumption.¹⁵

Considering the anti-inflammatory characteristics of synbiotics, various studies evaluated the effects of synbiotics alone or compared to probiotics on inflammatory markers. However, there has been some disagreement among studies considering the anti-inflammatory effects of pro/synbiotics. A meta-analysis by Kazemi et al assessed the effects of pro/synbiotics on inflammatory markers and concluded that these supplementations had promising effects only on CRP and tumor necrosis factor-alpha (TNF-α) in healthy and unhealthy individuals. They found that pro/synbiotic supplementation could effectively alleviate inflammation in inflammatory bowel disease (IBD), arthritis, and fatty liver.¹⁶ In addition, Naseri and colleagues showed decreasing trends in CRP and TNF-α after synbiotic supplementation in pre-diabetes and type 2 diabetic patients.¹⁷ However, a recent meta-analysis did not find any changes in IL-6 and CRP following synbiotic supplementation in healthy adults.¹⁸ Therefore, given the potential beneficial effects of synbiotics on inflammation and the controversial findings on this topic, the present systematic review and meta-analysis aimed to address this gap by assessing the effects of synbiotic supplementation on both inflammatory and anti-inflammatory markers in healthy and unhealthy individuals.

Materials and Methods

The present systematic review was conducted and reported in compliance with PRISMA protocols¹⁹ and is registered in the PROSPERO database (registration number: CRD42024616716).

Search strategy

In order to find relevant randomized controlled trials that met the study inclusion criteria, a comprehensive systematic search was conducted in PubMed/MEDLINE, Web of Science, SCOPUS, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The

search strategy was designed to be highly inclusive to minimize the risk of omitting relevant trials. Peer-reviewed articles published up to March 2026 and written in English were included. The systematic search, conducted according to PRISMA guidelines, utilized a combination of keywords and MeSH terms including: “Synbiotic supplementation”, “probiotic AND prebiotic”, “Inflammatory markers”, “anti-inflammatory”, “interleukin*”, and “gut microbiota”. Additionally, reference lists of similar review articles were manually searched and screened, and an additional search was performed using Google Scholar, with the first 200 results sorted by relevance screened.

Study selection

Following the PICO (Population, Intervention, Comparator, Outcome) framework (Table 1), studies were included based on the following criteria: (1) randomized controlled trials (RCTs) with either a crossover or parallel design; (2) a minimum of 3 weeks of synbiotic supplementation; (3) differentiation between placebo and intervention groups solely by the use of the synbiotic supplement; (4) participants aged 18 years or older, including both healthy individuals and those with health-related conditions; (5) reported effects of synbiotic supplementation on assessment criteria, including baseline and follow-up values along with their corresponding standard deviations (SDs), standard errors (SEs), or 95% confidence intervals (CIs) for the intervention and placebo groups; (6) oral administration of the synbiotic supplement; and (7) publication in peer-reviewed journals.

The following studies were excluded if they met one or more of the following criteria: (1) observational studies, animal studies, or review articles; (2) lack of baseline and/or follow-up data for the specified assessment criteria; (3) trials with acute duration or short-term supplementation; (4) retracted publications; (5) non-English language publications; (6) studies with unspecified probiotic strains or prebiotic types; (7) studies involving pregnant women; and (8) Studies in which the independent effect of synbiotic supplementation could not be isolated.

Data extraction

The identification of eligible trials, data extraction, and risk of bias assessment was independently performed by two

Table 1. Population, intervention, comparison, outcome, and study design (PICO) criteria for inclusion and exclusion of studies

Parameter	Criteria
Participant	Adults
Intervention	Synbiotic
Comparator	Matched control group
Outcomes	CRP, IL-1β, IL-6, IL-8, IFN-γ, TNF-α, LPS, IL-10, Adiponectin
Study design	Controlled clinical trial

Abbreviations: CRP, C-reactive protein; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-8, Interleukin-8; IFN-γ, Interferon-gamma; TNF-α, Tumor necrosis factor-alpha; LPS, Lipopolysaccharide; IL-10, Interleukin-10.

researchers (B.S. and Z.A.). Any conflicts were resolved through discussion with a third investigator (T.S). The following data were extracted from the included articles: name of the first author, article title, year of publication, sample sizes of the intervention and placebo groups, study location, study design, participants' health status, gender distribution, the mean age at baseline, body mass index (BMI) of the individuals, details of the synbiotic supplement (daily dose, prebiotic type and dose, probiotic strain and colony count), supplementation duration, placebo type, and any co-interventions.

Quality assessment

The Cochrane quality assessment tool was utilized to evaluate the quality of the studies included in this analysis, classifying them into low, high, or unclear risk categories based on identified biases. To assess the overall quality and certainty of evidence across studies, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was employed. GRADE uses methodologically sound and transparent criteria to evaluate recommendations and evidence, categorizing the quality of evidence as High, Moderate, Low, or Very Low. The certainty of evidence can be downgraded due to factors such as: (1) publication bias, (2) imprecision, (3) inconsistency, (4) indirectness, and (5) risk of bias. Conversely, it can be upgraded in specific circumstances, such as when a large magnitude of the effect is observed, there is a dose-response gradient, or all plausible confounders or other biases increase confidence in the estimated effect. The GRADE approach ensures systematic assessment and rating of evidence, guiding the development of recommendations that balance the benefits and harms of interventions with clarity and confidence.²⁰

Statistical analysis

The effects of synbiotic supplementation on the predefined outcomes were quantified using a random-effects model and presented as standardized mean differences (SMDs) and their corresponding 95% CIs. The use of SMDs was considered appropriate because the included studies employed heterogeneous laboratory assays and reported outcomes in different measurement units, thereby precluding meaningful pooling using weighted mean differences (WMDs). For this review, the mean differences (MDs) and SD of inflammatory biomarkers, including IL-1 β , IL-8, IL-6, TNF, IL-10, and IFN- γ , as well as metabolic and adipose-related biomarkers such as CRP and LPS, before and after the intervention were calculated. Additionally, the changes in the anti-inflammatory biomarkers, including IL-10 and Adiponectin, were assessed to evaluate changes in the inflammatory and Anti-inflammatory balance following supplementation.

In instances where a mean difference was not reported in the article, it was calculated using the following formula: (value at the endpoint of the synbiotic group - value at the baseline of the synbiotic group) and (value at the endpoint of the placebo group - value at the baseline of the

placebo group). For missing SDs of mean differences, the following formula was used: $SD = \sqrt{[(SD \text{ pre-treatment})^2 + (SD \text{ post-treatment})^2 - (2 \times R \times SD \text{ pre-treatment} \times SD \text{ post-treatment})]}$, where R (correlation coefficient) of 0.8 was assumed.²¹ For studies reporting standard error of the mean (SEM) instead of standard deviation, SD was calculated using the formula: $SD = SEM \times \sqrt{n}$, where n is the number of participants in the group. Between-study heterogeneity was assessed using Cochran's Q test and the I² statistic, with $P < 0.05$ and $I^2 \geq 50\%$ considered indicative of significant heterogeneity.²² A predefined subgroup analysis was conducted to identify potential sources of heterogeneity, considering the study location, characteristics of participants (mean BMI, health status, mean age and sex composition), intervention features (colony types, prebiotic types, and duration of intervention) and duration, and study quality levels.

Egger's regression tests, and funnel plots were used to detect potential publication bias in the included studies. If publication bias was detected, the trim-and-fill method and fail-safe N method were applied to adjust for it.²³ Sensitivity analysis was performed according to the leave-one-out sensitivity analysis to assess the influence of each included effect size on the overall effect size. Statistical analyses in this meta-analysis were performed using Stata version 17 (Stata Corp, Texas, USA). A p-value of less than 0.05 was considered statistically significant for all tests.

Results

Flow and characteristics of included studies

As presented in Fig. 1, there were 19081 initial identifications. Upon removing duplicate articles (n = 6817), 12264 articles remained. 12187 articles were excluded after reviewing their titles and abstracts because they were not RCTs or directly related to the inclusion criteria. As a result, 77 articles were selected that may be relevant for further full-text evaluation. 18 more articles were excluded for the following reasons: Retracted articles (n = 6),²⁴⁻²⁹ No measurements of the factors (n = 3),³⁴⁻³⁶ short-term synbiotic supplementation (n = 4),³⁴⁻³⁷ limited data on supplementation (n = 4),³⁷⁻⁴⁰ and studies involving pregnant women (n = 1).⁴¹ Additionally, four studies were found by performing a manual search of the literature.⁴²⁻⁴⁵ Following the inclusion criteria, 63 qualified RCTs were selected for analysis.^{12,42-103}

Characteristics of included studies

Across 63 eligible studies encompassing 69 treatment arms, a total of 3,725 individuals were randomly allocated to receive either synbiotic supplementation (n = 1,876) or a placebo/control (n = 1,849) (Table S1). Sample sizes ranging from 10⁴⁹ to 221 participants.¹⁰¹ The probiotic colony dosage varied from 11×10^6 to 4×10^{11} CFU. Prebiotics used in the studies included dextran, inulin, oligofructose, arabinogalactan, xylo-oligosaccharides, FOS (Fructooligosaccharides), galactooligosaccharides, dietary fiber, and barley β -glucans.

Studies included in the analysis were published between

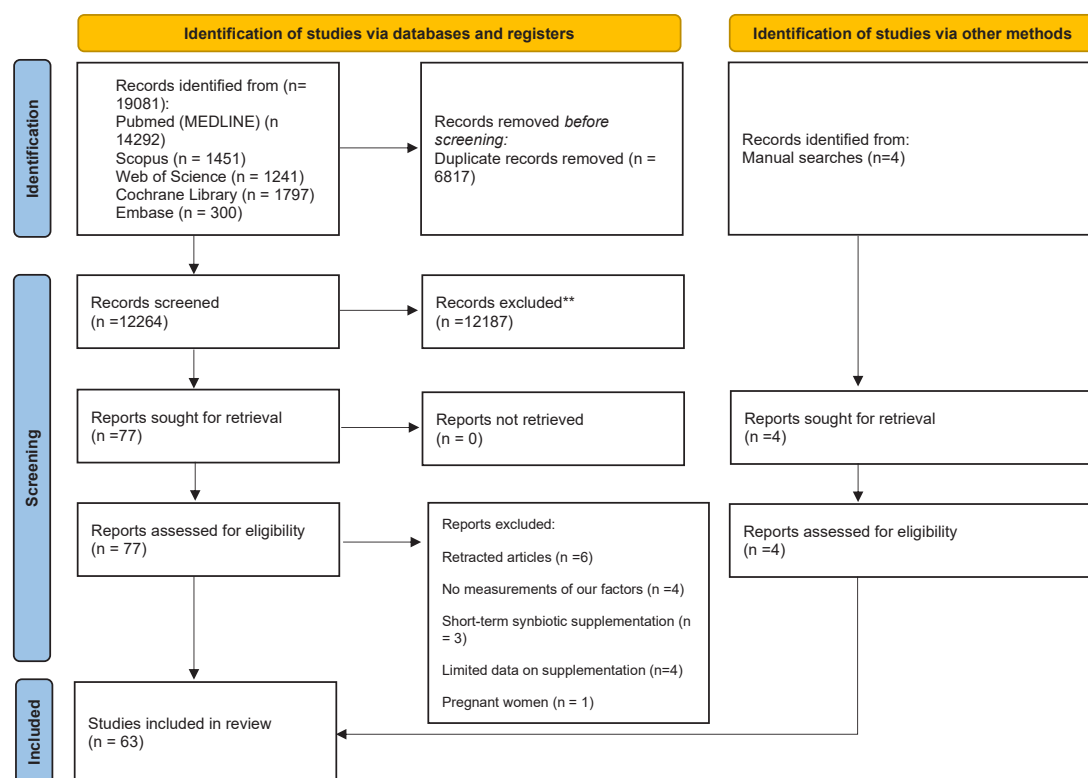


Fig. 1. PRISMA 2020 flow diagram illustrating the study selection process from database searches, trial registries, and other sources

2006 and 2026 and were from a variety of countries: Iran (n = 28),^{42,44,53,56,57,59,63-67,70,71,73,74,76,80,81,83,84,86,89,93,94,96-98,103} Brazil (n=6),^{43, 60-62, 72, 75} Italy (n=4),^{45,48,69,79} the United Kingdom (n=3),^{50,52,100} Japan (n = 2),^{46,77} Spain (n=2),^{43,82} Mexico (n=2),^{12,49} India (n=2),^{54,87} Indonesia (n=2),^{85,99} China (n=2),^{88,90} Serbia (n=2),^{91,92} Ireland (n = 1),⁴⁷ Thailand (n=1),⁷⁸ Chile (n = 1),⁵⁵ Finland (n = 1),⁵⁸ Turkey (n = 1),⁶⁸ Denmark (n = 1),⁹⁵ the United States (n = 1),¹⁰¹ and Egypt (n = 1).¹⁰² The mean age of participants ranged from 20.66⁸² years to 79.5 years.⁷² Two trials involved only male participants,^{82,93} nine trials were exclusively conducted on female participants,^{63,76,80,81,83,89,90,97,101} and the remaining trials included both genders.

The duration of supplementation ranged from 3 weeks⁵² to 51 weeks.¹⁰¹ Three studies employed a crossover design,^{50,52,95} while the remaining 60 studies were conducted using a parallel design. In terms of blinding, four studies were open-label or unblinded,^{68,77,100,102} two were single-blinded,^{54,69} five were triple-blinded RCTs,^{65,80,82,84,98} and the others were double-blinded RCTs.

In terms of the participant population, 13 studies involved healthy participants,^{43,46,50-52,54,61,69,72,75,82,88,100} while nine studies targeted patients with liver diseases, including non-alcoholic fatty liver disease (NAFLD),^{42, 44,53,57,59,98} non-alcoholic steatohepatitis,⁴⁵ and metabolic dysfunction-associated steatotic liver disease.^{91,103} Also, nine studies involved adults with overweight or obesity.^{55, 58,69,77,78,80,83,87,89} Eight studies focused on patients with diabetes.^{56,64,66,71,77,94,95,98} Seven focused on hemodialysis or chronic kidney disease patients,^{12,66,67,70,73,80,91} and six studies were conducted on patients with cancer

(including breast, colon, and nasopharyngeal cancer).^{47, 76,80,83,97,99} Additionally, five studies were conducted on patients with metabolic syndrome,^{62,65,79,84,96} and two studies involved individuals with ulcerative colitis.^{48,68} Other specific patient populations, each addressed in a single study, included women with polycystic ovary syndrome (PCOS),⁶³ individuals with recurrent aphthous stomatitis,⁶⁰ HIV-infected individuals,⁴⁹ hypothyroidism,⁷⁴ migraine sufferers,⁸¹ systemic lupus erythematosus,⁸⁵ heart failure,⁸⁶ coronary artery diseases,⁹⁰ postmenopausal women,¹⁰¹ dyslipidemia,⁹³ and Parkinson's disease.¹⁰²

Data quality

Table S2 presents the results of the Cochrane risk of bias assessment for the 63 included studies. Based on the evaluation, the studies were categorized into three quality levels: Good, Fair, and Poor, according to the number of domains with a low risk of bias. The majority of the studies (n = 47 studies) were classified as having good quality, characterized by more than two domains exhibiting a low risk of bias. These studies reflect a robust methodological framework, enhancing the reliability of their findings. A smaller subset of 4 studies was identified as fair quality, with exactly two domains demonstrating a low risk of bias. Lastly, 12 studies were determined to have poor quality, with fewer than two domains indicating a low risk of bias. These studies present a higher likelihood of methodological limitations, necessitating careful consideration when synthesizing their results.

The GRADE framework was used to assess the certainty of evidence concerning the effects of synbiotic

Table 2. GRADE profile of synbiotic supplementation on inflammatory and anti-inflammatory markers

Quality assessment						Quality of evidence
Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
CRP	No serious limitation	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b	⊕○○○ Very low
IL-1β	No serious limitations	Serious limitations ^c	No serious limitations	Serious limitations ^d	No serious limitations	⊕⊕○○ Low
IL-6	No serious limitations	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	⊕⊕○○ Low
IL-8	No serious limitations	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	⊕⊕○○ Low
IL-10	No serious limitations	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	⊕⊕○○ Low
IFN-γ	No serious limitations	Very serious limitations ^a	No serious limitations	Serious limitations ^d	No serious limitations	⊕○○○ Very low
TNF-α	No serious limitations	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	⊕⊕○○ Low
LPS	No serious limitations	Very serious limitations ^a	No serious limitations	Serious limitations ^d	No serious limitations	⊕○○○ Very low
Adiponectin	No serious limitations	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations	⊕⊕○○ Low

^a There was high heterogeneity ($I^2 > 75\%$).

^b There was significant publication bias.

^c Downgraded one level for substantial unexplained heterogeneity.

^d There was moderate heterogeneity ($50\% < I^2 < 75\%$).

supplementation on inflammatory and anti-inflammatory markers (Table 2). Overall, the certainty of evidence ranged from low to very low across outcomes. CRP, IFN-γ, and LPS were classified as very low certainty (⊕○○○), primarily due to very serious inconsistency and, in some cases, imprecision or publication bias. IL-1β, IL-6, IL-8, IL-10, TNF-α, and adiponectin were rated as low certainty (⊕⊕○○), with inconsistency being the main limiting factor and imprecision contributing in some outcomes. Overall, the evidence was limited mainly by heterogeneity across studies, with additional concerns regarding imprecision and publication bias for selected outcomes.

Meta-analysis

Findings from the meta-analysis of synbiotic supplementation on pro-inflammatory markers

Effect of synbiotic supplementation on CRP

CRP levels were assessed in 41 studies encompassing 43 treatment arms. According to the pooled estimates from the random-effects model, synbiotic supplementation demonstrated a significant effect on reducing CRP levels (SMD: -0.49, 95% CI: -0.67 to -0.31, $P < 0.001$) (Fig. 2A).

However, substantial heterogeneity was detected among the studies ($I^2 = 79.7\%$, $P < 0.001$). Subgroup analysis identified that the type of prebiotics (P -between = 0.04) and quality of studies (P -between = 0.003) could be the source of this heterogeneity. Also, the results of the subgroup analysis were significant for all subgroups, except for studies conducted in South America ($P = 0.13$) and North America ($P = 0.35$), the unreported age group ($P = 0.23$), the specific strains of probiotic bacteria (*L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. longum*, and *L. bulgaricus*) ($P = 0.30$), as well as for females ($P = 0.25$), obese individuals ($P = 0.14$), and poor quality of studies ($P = 0.60$) (Table S3).

Effect of synbiotic supplementation on IL-1β

IL-1β data were collected from eleven studies, which included thirteen treatment arms. Using the pooled estimates from a random-effects model, it was determined that the decrease in IL-1β levels after synbiotic supplementation was not statistically significant (SMD: -0.25, 95% CI: -0.56 to 0.07, $P = 0.13$) while the heterogeneity among the studies was significant ($I^2 = 73.5\%$, $P \leq 0.001$) (Fig. 2B). Subgroup analysis highlighted the role of continents (P -between = 0.03), age (P -between ≤ 0.001), and quality of studies (P -between ≤ 0.001) as potential determinants of the observed heterogeneity. Also, considering subgroup analysis, significant reductions were noted in studies conducted in Asia ($P = 0.02$), fair quality of studies ($P \leq 0.001$), and among participants with a normal BMI ($P = 0.01$) (Table S3).

Effect of synbiotic supplementation on IL-6

A total of 30 studies, encompassing 31 treatment arms, assessed the effects of synbiotic supplementation on IL-6 levels. According to the results of the random-effects model, supplementation with synbiotics significantly reduced IL-6 levels (SMD: -0.33, 95% CI: -0.61 to -0.05, $P = 0.02$), though there was considerable heterogeneity among studies ($I^2 = 85.2\%$, $P < 0.001$) (Fig. 2C). Subgroup analysis of synbiotic supplementation on IL-6 is shown in Table S3. Based on subgroup analysis, significant reductions were observed in studies conducted in Asia ($P \leq 0.001$), participants aged < 50 years ($P = 0.049$), and other probiotic types ($P = 0.045$), in populations including both sexes ($P = 0.02$), and among participants with a normal BMI ($P = 0.04$) (Table S3).

Effect of synbiotic supplementation on IL-8

IL-8 data were collected from six studies, which included seven treatment arms. Using a random-effects model, the meta-analysis determined that IL-8 levels were significantly

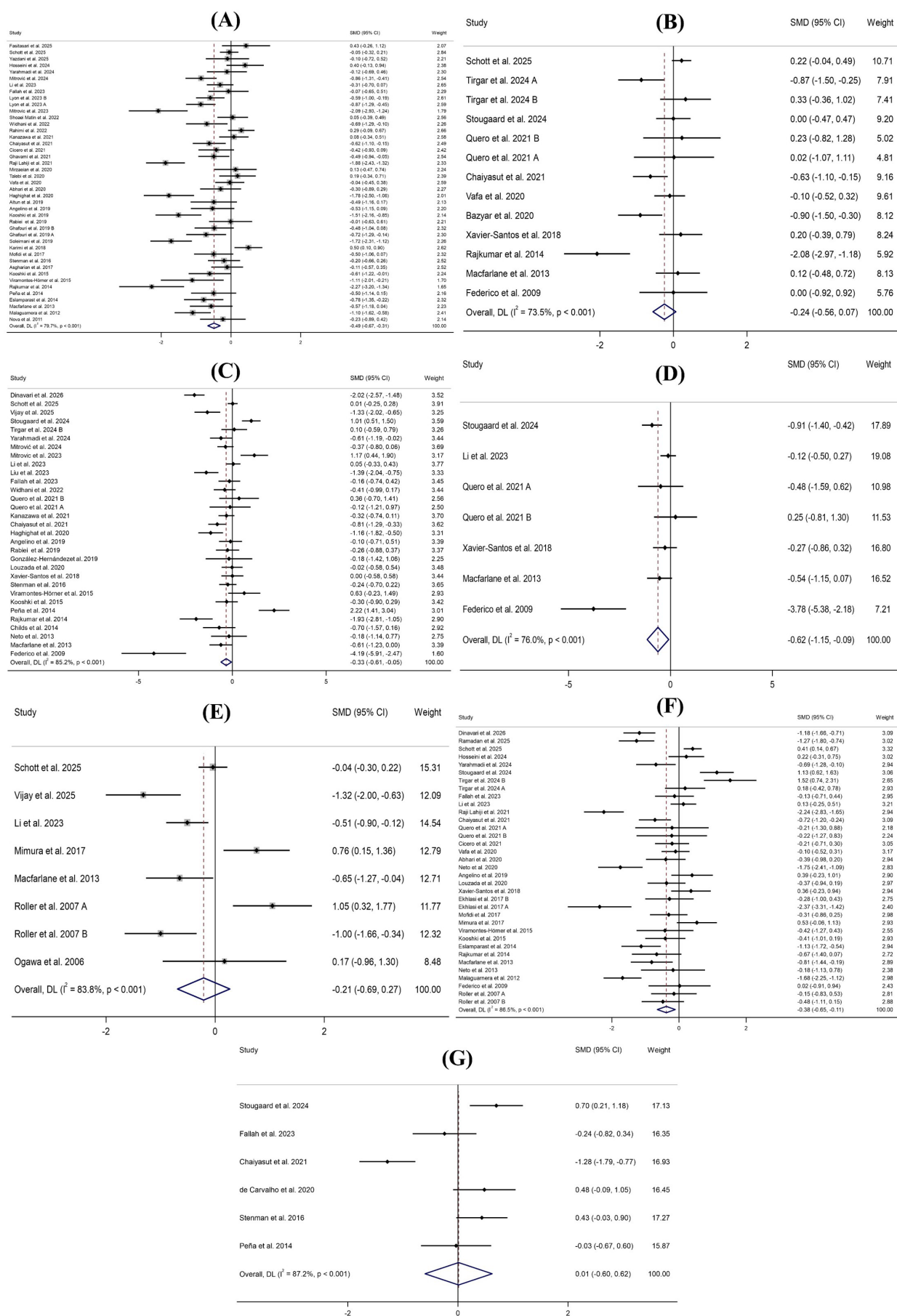


Fig. 2. Forest plots showing the effect of synbiotic supplementation on inflammatory markers in adults: A. C-reactive protein (CRP), B. Interleukin-1β (IL-1β), C. Interleukin-6 (IL-6), D. Interleukin-8 (IL-8), E. Interferon-gamma (IFN-γ), F. Tumor necrosis factor-alpha (TNF-α), G. Lipopolysaccharide (LPS). Results are expressed as standardized mean differences between intervention and control groups.

reduced following the consumption of synbiotics (SMD: -0.62; 95% CI: -1.15 to -0.09; $P=0.02$). However, considerable heterogeneity was detected among the studies ($I^2=76.0\%$, $P\leq 0.001$) (Fig. 2D). Subgroup analysis highlighted the role of quality of studies ($P\text{-between}\leq 0.001$) as a potential determinant of the observed heterogeneity. In Table S3, a subgroup analysis of the effects of synbiotic supplementation on IL-8 is presented. Based on subgroup analysis, significant reductions were observed in studies conducted in Europe ($P=0.03$), among individuals aged > 50 years ($P\leq 0.001$), other probiotic types ($P=0.03$), among unhealthy participants ($P=0.03$), among participants with overweight ($P\leq 0.001$), good ($P=0.02$) and poor ($P\leq 0.001$) quality of studies, and in populations including both sexes ($P=0.02$) (Table S3).

Effect of synbiotic supplementation on IFN- γ

IFN- γ data were collected from seven studies, which included eight treatment arms. Using the random effects model, it was determined that synbiotic supplementation did not result in a statistically significant reduction in IFN- γ levels (SMD: -0.21, 95% CI: -0.69 to 0.27, $P=0.39$) while the heterogeneity among the studies was significant ($I^2=83.8\%$, $P<0.001$) (Fig. 2E). Subgroup analysis highlighted the role of continents ($P\text{-between}=0.03$), type of prebiotics ($P\text{-between}=0.02$), and type of colony ($P\text{-between}=0.01$) as potential determinants of the observed heterogeneity. More pronounced effects were observed among studies conducted in South America ($P=0.01$), trials with intervention durations of <12 weeks ($P=0.005$), healthy individuals ($P=0.04$), specific probiotic strains such as *L. paracasei*, *L. rhamnosus*, *L. acidophilus*, and *B. lactis* ($P=0.01$), as well as *B. longum* alone ($P=0.04$), use of inulin as a type of prebiotic ($P\leq 0.001$), and those with a BMI classified as normal ($P=0.01$) (Table S3).

Effect of synbiotic supplementation on TNF- α

Across 31 studies including 35 treatment arms, the effects of synbiotic supplementation on TNF- α levels were systematically evaluated. According to the pooled estimates from the random-effects model, synbiotic supplementation demonstrated a significant effect on reducing TNF- α levels (SMD: -0.38, 95% CI: -0.65 to -0.11, $P=0.005$). However, substantial heterogeneity was detected among the studies ($I^2=86.5\%$, $P<0.001$) (Fig. 2F). Subgroup analysis revealed that the type of colony ($P\text{-between}=0.03$) and continents ($P\text{-between}=0.02$) might serve as a potential source of heterogeneity. As presented in Table S3, significant reductions in TNF- α levels were observed in studies conducted in Asia ($P=0.009$) and Africa ($P\leq 0.001$), and in trials with durations of <12 weeks ($P=0.009$). Notable effects were also associated with the use of FOS ($P=0.04$) and inulin ($P=0.02$) as prebiotics, specific probiotic strains such as *L. casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. longum*, and *L. bulgaricus* ($P=0.001$), as well as *B. longum* alone ($P=0.004$). Furthermore, significant reductions were observed among unhealthy individuals ($P=0.03$), in both sexes ($P=0.001$), participants classified as normal weight ($P=0.03$), and good ($P=0.03$) and fair ($P=0.02$) quality of studies.

Effect of synbiotic supplementation on LPS

Across six studies involving six treatment arms, changes in LPS levels following synbiotic supplementation were evaluated. Results from the random-effects model showed that synbiotic supplementation had no significant impact on LPS levels (SMD: -0.01, 95% CI: -0.60 to 0.62, $P=0.97$) with significant heterogeneity among the studies ($I^2=87.2\%$, $P<0.001$) (Fig. 2G). Subgroup analysis revealed that type of prebiotics ($P\text{-between}\leq 0.001$) and continents ($P\text{-between}=0.04$) might serve as a potential source of heterogeneity. Based on the subgroup analysis, a significant increase was observed in studies conducted in Europe ($P=0.001$), with the use of Inulin + FOS as prebiotics ($P\leq 0.001$), and among unhealthy individuals ($P\leq 0.001$) (Table S3).

Findings from the meta-analysis of synbiotic supplementation on Anti-inflammatory markers

Effect of synbiotic supplementation on IL-10

Changes in IL-10 levels after synbiotic supplementation were evaluated in 15 studies comprising 18 treatment arms. The results of the random-effects model showed that supplementing with synbiotics resulted in a statistically significant increase in the level of IL-10 (SMD: 0.30, 95% CI: 0.002 to 0.59, $P=0.048$) and heterogeneity among the studies was significant ($I^2=76.1\%$, $P<0.001$) (Fig. 3A). Based on the subgroup analysis, a significant increase was observed in studies conducted in Asia ($P=0.01$), trials with durations of ≥ 12 weeks ($P=0.046$), with the use of FOS as a type of prebiotic ($P=0.03$), good ($P=0.02$) quality of studies, and among individuals with a normal BMI ($P=0.008$) (Table S3).

Effect of synbiotic supplementation on adiponectin

Three studies, comprising three treatment arms, measured the changes in adiponectin levels following synbiotic supplementation. According to the pooled results from the random-effects model, synbiotic supplementation had a non-significant effect on the adiponectin levels (SMD: 1.17, 95% CI: -0.44 to 2.78, $P=0.15$) with significant heterogeneity among the studies ($I^2=96.3\%$, $P<0.001$) (Fig. 3B).

Sensitivity analysis

Based on the sensitivity analysis, the pooled estimates for adiponectin, LPS, TNF- α , IFN- γ , CRP, and IL-1 β were robust, as no single study materially changed the overall effect sizes. In contrast, the results for IL-6 were influenced by the exclusion of Federico et al.⁴⁸ and the findings for IL-8 were sensitive to the removal of Stougaard et al.⁹⁵ The pooled effect for IL-10 was also affected by the exclusion of several individual studies, including Salamat et al.,⁹³ Tirgar et al.,⁹⁷ Fallah et al.,⁸⁹ Li et al.,⁸⁸ Chaiyasut et al.,⁷⁸ Quero et al.,⁸² Saneei Totmaj et al.,⁸³ Angelino et al.,⁶⁹ Louzada et al.,⁶¹ Xavier-Santos et al.,⁶² Mimura et al.,⁶⁰ and Roller et al.⁴⁷ Overall, these findings suggest that most outcomes were stable, although IL-6, IL-8, and IL-10 showed some degree of sensitivity to individual studies.

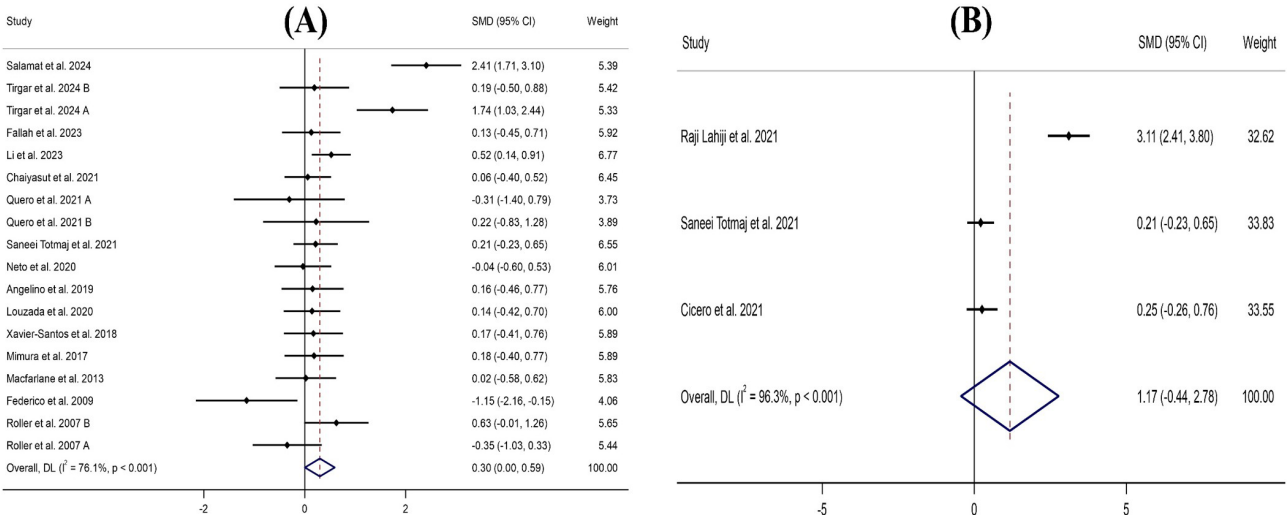


Fig. 3. Forest plots showing the effect of synbiotic supplementation on anti-inflammatory markers in adults: A. Interleukin-10 (IL-10), B. Adiponectin. Results are expressed as standardized mean differences between intervention and control groups

Publication bias

Egger's linear regression test indicated potential publication bias for CRP (Egger's test: $P=0.001$). Due to the significant publication bias observed in studies assessing the effect of synbiotic supplementation on CRP levels, a trim-and-fill analysis was subsequently performed, which showed that no missing studies needed to be imputed (number of imputed studies = 0, observed and adjusted effect size = -0.492, 95% CI: -0.681, -0.303).

Conversely, no significant publication bias was detected for the other biomarkers, as Egger's test yielded non-significant P values for adiponectin ($P=0.20$), LPS ($P=0.74$), TNF- α ($P=0.10$), IFN- γ ($P=0.92$), IL-1 β ($P=0.18$), IL-6 ($P=0.37$), IL-8 ($P=0.26$), and IL-10 ($P=0.82$). The results of the funnel plots are provided in Fig. S1.

Discussion

This meta-analysis is, to our knowledge, the most comprehensive assessment of randomized controlled trials investigating the effects of synbiotics on inflammatory and anti-inflammatory markers. Systemic inflammation is linked to the onset and advancement of various chronic health issues. This encompasses some of the top causes of death globally, including cancer, dementia, ischemic heart disease, cerebrovascular disorders, and chronic lower respiratory conditions.^{104,105} These conditions are characterised by persistent immune activation and the production of pro-inflammatory mediators, including CRP, TNF- α , IL-1 β , and IL-6.¹⁰⁶

This systematic review and meta-analysis of RCTs suggests that synbiotic supplementation may reduce selected pro-inflammatory markers, including CRP, IL-6, IL-8, and TNF- α , while increasing the anti-inflammatory marker IL-10. However, no significant effects were observed for IL-1 β , IFN- γ , LPS, or adiponectin. The CRP finding should be interpreted with caution because of potential publication bias and the low certainty of evidence.

Earlier meta-analyses that looked into the effects of

synbiotics on these markers primarily concentrated on probiotic strains and lacked thorough subgroup analysis for prebiotics. Additionally, unlike previous analyses, more recent relevant studies were incorporated.¹⁶ Numerous meta-analyses have been performed in this area, mainly focusing on specific disease states. In contrast, the current meta-analysis takes into account both healthy and unhealthy conditions.

According to the present meta-analysis, CRP levels showed a decrease in both healthy and unhealthy individuals, which aligns with another meta-analysis examining the effects of probiotic and synbiotic supplementation on inflammatory markers, which reported that CRP decreased in healthy individuals, and in patients with IBD, arthritis, metabolic disorders, and critically ill patients, but not in renal failure patients. Additionally, IL-1 β levels remained unchanged in healthy individuals and those with arthritis, as the results of the present study showed that IL-1 β levels did not change significantly according to the health status subgroup analysis. Additionally, IL-6 levels did not change based on health status subgroup analysis in the present study. Kazemi et al,¹⁶ reported that IL-6 levels did not vary in healthy participants, metabolic disorders, or arthritis. Healthy individuals, fatty liver patients, those with IBD, and those with cirrhosis performed better in the study, while diabetes, metabolic syndrome, polycystic ovary syndrome, and arthritis participants did not perform as well.¹⁶

Kazemi et al. found that probiotic and synbiotic supplements had no impact on inflammatory markers in their study, but their results are inconclusive and cannot be used to make any clinical conclusions due to the fact that each inflammatory marker was evaluated according to a specific disease.¹⁶ Therefore, we examined the included studies within both healthy and unhealthy subgroups in the present study. In the current study that the decrement in IL-6 levels was significant in Asians, participants aged <50 years, and normal-weight individuals. Similarly, the reduction in TNF- α was significant in Asian and African participants, intervention durations of <12 weeks, specific

types of prebiotic and probiotic, unhealthy subjects, and normal weight individuals.

Moreover, the findings of the present study were consistent with those of another meta-analysis, which indicated that probiotic consumption by colorectal cancer patients post-surgery significantly reduced CRP levels, although it did not affect IL-6 levels.¹⁰⁴ Additionally, studies involving patients with diabetes have reported that the intake of probiotics and synbiotics led to a decrease in inflammatory markers.^{26,107,108}

The reduction of CRP in many disease conditions could possibly be attributed to its higher serum levels compared to cytokines, which can more accurately indicate changes in systemic inflammation.¹⁰⁹ In hepatic cells, the primary pro-inflammatory cytokines that stimulate CRP production are IL-1 β , IL-6, and IL-17.¹¹⁰ Thus, the notable decrease in CRP, even in the absence of changes in IL-1 β , may be driven by IL-6 and IL-17.

According to the results of the present study, supplementing with synbiotics significantly increased the level of IL-10, which was observed in studies conducted in Asia, trials with durations of ≥ 12 weeks, with the use of FOS as a type of prebiotic, and among individuals with a normal BMI.

While the mechanism of anti-inflammatory actions of probiotics and synbiotics has yet to be fully understood, it has been proposed that SCFAs produced by these compounds may play a significant role in lowering inflammation.^{111,112} Despite the fact that prebiotic and synbiotic supplementation may produce anti-inflammatory properties, other mechanisms may also play a role. SCFAs may help reduce the inflammatory and oxidative stress response by inhibiting hepatic CRP production enzymatically.¹¹³ It is reported that after eight weeks of probiotic supplementation in patients with ulcerative colitis, inflammation was reduced through lower levels of IL-6 and decreased levels of gene expression of tumor necrosis factor- α and nuclear factor kappa B (NF- κ B). Reduced NF- κ B levels could lead to a decline in various inflammatory markers.¹¹⁴

A combination of prebiotics and synbiotics has been found to promote colon health by growing beneficial bacteria. It has been shown that certain bacteria, including *Lactobacillus* species, play an indirect role in regulating inflammation by repairing and maintaining epithelial barriers, which in turn reduces the effects of pro-inflammatory stimuli such as LPS.¹¹⁵ Additionally, commensal bacteria can enhance the production of antimicrobial peptides that are crucial for resolving inflammation. In addition, certain bacterial species and their metabolic byproducts directly influence pro-inflammatory signaling pathways, including nuclear factor-kappa B, by acting as ligands for receptors of the innate immune system, such as Toll-like receptors.¹¹⁶ There is another potential mechanism for the anti-inflammatory action of gut bacteria, which involves their influence on dendritic cells, which enhances the production of cytokines such as IL-10 by influencing their differentiation and function.^{117,118}

The theoretical benefits of combining prebiotics and probiotics in a single product may be greater than using them separately, and their synergistic effects could account for the findings of subgroup analyses in this meta-analysis. Varying strains or species and dosages of prebiotics may operate through different mechanisms and produce inconsistent results, but the impact of these variations on inflammatory markers has not yet been fully explored.

It is important to emphasize the pooled findings represent an average effect across heterogeneous synbiotic interventions and should not be extrapolated to any specific formulation or commercial product. While the present meta-analysis demonstrates beneficial effects of synbiotic supplementation on inflammatory and anti-inflammatory markers, such effects should be attributed to the synbiotic class as a whole rather than to any individual product, brand, or formulation. This approach is based on the premise that heterogeneous synbiotic formulations, comprising different probiotic strains, prebiotic substrates, dosages, and delivery formats, may exert overlapping biological effects through partially shared mechanisms of action, thereby allowing estimation of a potential class-level effect. Nevertheless, such an inference does not imply therapeutic equivalence across formulations, nor should it be taken to suggest that all commercially available synbiotic products are interchangeable or equally effective.

While the findings of the present study indicated that synbiotics had significant effects compared to the control groups, there was statistically significant heterogeneity in the pooled results from the studies examining circulating levels of IL-6, CRP, IL-8, IL-10, and TNF- α . We performed subgroup analyses based on BMI, health status, duration of intervention, and treatment dose. The diversity in probiotics and prebiotics, along with variations in dosage and duration of use, made it challenging to offer clear therapeutic recommendations for clinicians, and it is important to interpret the final results with caution.

However, despite the small number of studies with high bias risks, the level of certainty of evidence varied across different outcomes: CRP was rated with very low certainty, and IL-1 β , IL-6, IL-8, IL-10, TNF- α were rated as low certainty, mainly due to high heterogeneity and significant inconsistencies and limitations in precision. Consequently, the predominantly low and very low certainty of evidence for key outcomes dictates that these aggregated effect sizes cannot easily be translated into definitive clinical guidelines. The inconsistency, risk of bias, and imprecision observed across trials underscore a critical gap in the current literature.

In this study, no significant effects of synbiotic supplementation on other inflammatory markers such as IL-1 β , IFN- γ , and LPS were observed. These non-significant findings could possibly be attributed to the limited number of studies included and the high level of heterogeneity in the results. Further research is required to clarify this effect, which aligns with findings from previous meta-analyses.^{16,119,120} Also, no significant effects were observed on anti-inflammatory marker adiponectin

following synbiotic supplementation in this study.

Strengths and Limitations

The present study has several important strengths. First, to provide a comprehensive and balanced perspective on immune modulation, we systematically analyzed both pro-inflammatory and anti-inflammatory markers wherever data were available. Second, our robust methodology ensured the inclusion of the most contemporary and relevant literature, while rigorously identifying and excluding retracted studies to maintain the highest level of data integrity and reliability. Third, unlike previous meta-analyses that primarily focused on probiotic strains, our study incorporated detailed subgroup analyses for both prebiotics and probiotics, categorizing them by specific types and strains whenever possible. Finally, we employed the GRADE approach to rigorously assess the certainty of our findings, and we conducted leave-one-out sensitivity analyses to evaluate the influence of individual studies on the pooled estimates.

Several limitations also complicate the interpretation of the findings of the present study. Firstly, intervention details varied widely across the included studies, encompassing a broad range of probiotic strains, prebiotic types, colony dosages, and intervention durations. As a result, this considerable combinatorial diversity complicates the attribution of the observed anti-inflammatory effects to any specific synbiotic component or optimal dosage.

Secondly, some of the included trials had limitations in design, execution, or data analysis. There was also significant heterogeneity among the studies in terms of supplement formulation, health status, study duration, participants' nationality, and BMI, which may have affected the results. Thirdly, some asymmetry was observed in the funnel plot for CRP, suggesting that the estimated effect size may be slightly susceptible to overestimation. While the broader evidence from other inflammatory markers remains encouraging, we adopted a conservative approach in interpreting the CRP findings, acknowledging that the actual clinical impact may be more modest than the current statistical estimate implies.

Most notably, our inclusion criteria encompassed both healthy individuals and patients with a wide range of pathologies, including NAFLD, diabetes, cancer, and hemodialysis. This introduced substantial clinical heterogeneity, as the underlying pathophysiological mechanisms of systemic inflammation differ markedly across these conditions. Although we attempted to address this through subgroup analyses based on general health status, i.e., healthy versus unhealthy, we acknowledge that this approach only partially accounts for clinical variability and may obscure disease-specific responses to synbiotics. Importantly, even after extensive subgroup analyses, substantial heterogeneity ($I^2 > 80\%$) persisted across several pooled estimates. This unresolved heterogeneity suggests that the aggregated effect sizes should be interpreted with caution, particularly with respect to their precise clinical magnitude. The persistent variance is likely driven by

complex, unmeasured factors inherent to microbiome research, such as individual differences in baseline gut microbiota profiles, genetic host–microbe interactions, and highly strain-specific biological responses that meta-regression techniques cannot fully isolate.

Moreover, background dietary nutrient intake may influence systemic inflammatory biomarkers, thereby complicating the attribution of observed effects to supplementation alone. This factor should be considered in the design of future studies; therefore, measuring background dietary intake in future research is essential. A formal dose-response analysis could not be performed because the synbiotic formulations were too heterogeneous to be placed on a single dose-response continuum. Consequently, the present findings cannot determine whether higher doses or specific combinations of prebiotics and probiotics produce greater anti-inflammatory effects. Future studies using standardized formulations and dose-ranging designs are needed to clarify whether a dose-response relationship exists and to identify the optimal synbiotic composition for reducing inflammatory markers.

Conclusion

This systematic review and meta-analysis provides evidence that synbiotic supplementation can significantly reduce key inflammatory markers, including CRP, IL-6, IL-8, and TNF- α , and increase IL-10 levels. However, no significant effects were observed for other pro-inflammatory markers, including IL-1 β , IFN- γ , and LPS, or for the anti-inflammatory marker adiponectin. The substantial and persistent heterogeneity across studies, driven by variations in synbiotic formulations, dosages, participant baseline characteristics, and host-microbiome interactions, limits confidence in the precise magnitude of the pooled effects. In addition, the CRP finding should be interpreted with caution because of potential publication bias. Consequently, although the overall trend suggests an anti-inflammatory benefit, these findings do not allow definitive conclusions regarding optimal intervention strategies. Future research should prioritize well-defined synbiotic formulations with clear reporting of probiotic strains, prebiotic types, and dosages. Standardization of study design and rigorous methodological quality are essential to improve the reliability and comparability of findings. Larger, longer-term, and high-quality RCTs are needed to clarify the therapeutic potential of synbiotics in managing systemic inflammation.

Authors' Contribution

Conceptualization: Mohammad Vesal Bideshki.

Data curation: Behrad Sadeghi, Zahra Asadi, Tohid Salehi, Hannane Jozi, Mehrdad Behzadi.

Formal analysis: Hossein Bahari, Seyed Fazel Zinat Motlagh.

Investigation: Mohammad Vesal Bideshki, Ali Rashidinejad.

Methodology: Mohammad Vesal Bideshki, Zahra Sohrabi, Ali Rashidinejad.

Project administration: Mohammad Vesal Bideshki, Zahra Sohrabi, Ali Rashidinejad.

Supervision: Zahra Sohrabi, Ali Rashidinejad.

Writing-original draft: Mohammad Vesal Bideshki, Naimeh Mesri

Alamdari, Behrad Sadeghi, Hannane Jozi, Mehrdad Behzadi, Seyed Fazel Zinat Motlagh, Zahra Sohrabi.

Writing-review & editing: Mohammad Vesal Bideshki, Zahra Sohrabi, Ali Rashidinejad.

Competing Interests

The authors report there are no competing interests to declare.

Data Availability Statement

Data described in the manuscript will be made available upon request, pending application and approval.

Ethical Approval

Not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary files

Supplementary file 1 contains Figure S1 (A–I, assessment of publication bias), Table S1 (characteristics of included studies), Table S2 (risk-of-bias assessment), and Table S3 (subgroup analyses).

References

- Sivamaruthi BS, Kesika P, Suganthi N, Chaiyasut C. A review on role of microbiome in obesity and antiobesity properties of probiotic supplements. *Biomed Res Int* **2019**; 2019: 3291367. doi:10.1155/2019/3291367
- Sivamaruthi BS, Prasanth MI, Kesika P, Chaiyasut C. Probiotics in human mental health and diseases-a minireview. *Trop J Pharm Res* **2019**; 18: 889-95. doi:10.4314/tjpr.v18i4.29
- Sivamaruthi BS, Suganthi N, Kesika P, Chaiyasut C. The role of microbiome, dietary supplements, and probiotics in autism spectrum disorder. *Int J Environ Res Public Health* **2020**; 17: 2647. doi:10.3390/ijerph17082647
- Sivamaruthi BS, Kesika P, Chaiyasut C. The role of probiotics in colorectal cancer management. *Evid Based Complement Alternat Med* **2020**; 2020: 3535982. doi:10.1155/2020/3535982
- de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. *Adv Biochem Eng Biotechnol* **2008**; 111: 1-66. doi:10.1007/10_2008_097
- Konstantinov SR, Smidt H, de Vos WM, Bruijns SC, Singh SK, Valence F, et al. S-layer protein A of *Lactobacillus acidophilus* NCFM regulates immature dendritic cell and T cell functions. *Proc Natl Acad Sci U S A* **2008**; 105: 19474-9. doi:10.1073/pnas.0810305105
- Ouwehand AC, Tiihonen K, Saarinen M, Putaala H, Rautonen N. Influence of a combination of *Lactobacillus acidophilus* NCFM and lactitol on healthy elderly: intestinal and immune parameters. *Br J Nutr* **2009**; 101: 367-75. doi:10.1017/s0007114508003097
- Wiciński M, Gębalski J, Gołębiowski J, Malinowski B. Probiotics for the treatment of overweight and obesity in humans-a review of clinical trials. *Microorganisms* **2020**; 8: 1148. doi:10.3390/microorganisms8081148
- Hadi A, Mohammadi H, Miraghajani M, Ghaedi E. Efficacy of synbiotic supplementation in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials: synbiotic supplementation and NAFLD. *Crit Rev Food Sci Nutr* **2019**; 59: 2494-505. doi:10.1080/10408398.2018.1458021
- Ferrarese R, Ceresola ER, Preti A, Canducci F. Probiotics, prebiotics and synbiotics for weight loss and metabolic syndrome in the microbiome era. *Eur Rev Med Pharmacol Sci* **2018**; 22: 7588-605. doi:10.26355/eurrev_201811_16301
- Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int* **2013**; 83: 1010-6. doi:10.1038/ki.2012.440
- Viramontes-Hörner D, Márquez-Sandoval F, Martín-del-Campo F, Vizmanos-Lamotte B, Sandoval-Rodríguez A, Armendáriz-Borunda J, et al. Effect of a symbiotic gel (*Lactobacillus acidophilus* + *Bifidobacterium lactis* + inulin) on presence and severity of gastrointestinal symptoms in hemodialysis patients. *J Ren Nutr* **2015**; 25: 284-91. doi:10.1053/j.jrn.2014.09.008
- Voltolini C, Battersby S, Etherington SL, Petraglia F, Norman JE, Jabbour HN. A novel anti-inflammatory role for the short-chain fatty acids in human labor. *Endocrinology* **2012**; 153: 395-403. doi:10.1210/en.2011-1457
- Kalina U, Koyama N, Hosoda T, Nuernberger H, Sato K, Hoelzer D, et al. Enhanced production of IL-18 in butyrate-treated intestinal epithelium by stimulation of the proximal promoter region. *Eur J Immunol* **2002**; 32: 2635-43. doi:10.1002/1521-4141(200209)32:9<2635::Aid-immu2635>3.0.Co;2-n
- Vitali B, Ndagijimana M, Cruciani F, Carnevali P, Candela M, Guerzoni ME, et al. Impact of a synbiotic food on the gut microbial ecology and metabolic profiles. *BMC Microbiol* **2010**; 10: 4. doi:10.1186/1471-2180-10-4
- Kazemi A, Soltani S, Ghorabi S, Keshtkar A, Daneshzad E, Nasri F, et al. Effect of probiotic and synbiotic supplementation on inflammatory markers in health and disease status: a systematic review and meta-analysis of clinical trials. *Clin Nutr* **2020**; 39: 789-819. doi:10.1016/j.clnu.2019.04.004
- Naseri K, Saadati S, Ghaemi F, Ashtary-Larky D, Asbaghi O, Sadeghi A, et al. The effects of probiotic and synbiotic supplementation on inflammation, oxidative stress, and circulating adiponectin and leptin concentration in subjects with prediabetes and type 2 diabetes mellitus: a GRADE-assessed systematic review, meta-analysis, and meta-regression of randomized clinical trials. *Eur J Nutr* **2023**; 62: 543-61. doi:10.1007/s00394-022-03012-9
- Cosier DJ, Lambert K, Neale EP, Probst Y, Charlton K. The effect of oral synbiotics on the gut microbiota and inflammatory biomarkers in healthy adults: a systematic review and meta-analysis. *Nutr Rev* **2025**; 83: e4-24. doi:10.1093/nutrit/nuae002
- Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* **2021**; 372: n160. doi:10.1136/bmj.n160
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **2008**; 336: 924-6. doi:10.1136/bmj.39489.470347.AD
- Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; **2008**.
- Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* **2019**; 10: ED000142. doi:10.1002/14651858.Ed000142
- Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **2000**; 56: 455-63. doi:10.1111/j.0006-341x.2000.00455.x
- Karamali M, Nasiri N, Taghavi Shavazi N, Jamilian M, Bahmani F, Tajabadi-Ebrahimi M, et al. The effects of synbiotic supplementation on pregnancy outcomes in gestational diabetes. *Probiotics Antimicrob Proteins* **2018**; 10: 496-503. doi:10.1007/s12602-017-9313-7
- Nasri K, Jamilian M, Rahmani E, Bahmani F, Tajabadi-Ebrahimi M, Asemi Z. The effects of synbiotic supplementation on hormonal status, biomarkers of inflammation and oxidative stress in subjects with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *BMC Endocr Disord* **2018**; 18: 21. doi:10.1186/s12902-018-0248-0
- Farrokhi A, Raygan F, Soltani A, Tajabadi-Ebrahimi M, Sharifi Esfahani M, Karami AA, et al. The effects of synbiotic supplementation on carotid intima-media thickness, biomarkers of inflammation, and oxidative stress in people with overweight, diabetes, and coronary heart disease: a randomized, double-blind, placebo-controlled trial. *Probiotics Antimicrob Proteins* **2019**; 11: 133-42. doi:10.1007/s12602-017-9343-1
- Asemi Z, Khorrami-Rad A, Alizadeh SA, Shakeri H, Esmailzadeh A. Retraction notice to "Effects of synbiotic food consumption on metabolic status of diabetic patients: a double-blind randomized cross-over controlled clinical trial" [Clin Nutr 33 (2014) 198-203]. *Clin Nutr* **2025**; 53: 284. doi:10.1016/j.clnu.2025.08.016
- Expression of concern. *Ann Nutr Metab* **2023**; 79: 108. doi:10.1159/000529288

29. Zamani B, Farshbaf S, Golkar HR, Bahmani F, Asemi Z. Synbiotic supplementation and the effects on clinical and metabolic responses in patients with rheumatoid arthritis: a randomised, double-blind, placebo-controlled trial - expression of concern. *Br J Nutr* **2022**; 127: 156. doi:10.1017/s0007114521002051
30. Arteaga-Henríquez G, Ramos-Sayalero C, Ibañez-Jimenez P, Karina Rosales-Ortiz S, Kilencz T, Schiweck C, et al. Efficacy of a synbiotic in the management of adults with Attention-Deficit and Hyperactivity Disorder and/or Borderline Personality Disorder and high levels of irritability: results from a multicenter, randomized, placebo-controlled, "basket" trial. *Brain Behav Immun* **2024**; 120: 360-71. doi:10.1016/j.bbi.2024.06.012
31. Hütt P, Andreson H, Kullisaar T, Vihalemm T, Unt E, Kals J, et al. Effects of a synbiotic product on blood antioxidant activity in subjects colonized with *Helicobacter pylori*. *Lett Appl Microbiol* **2009**; 48: 797-800. doi:10.1111/j.1472-765X.2009.02607.x
32. Mehrabani S, Khorvash F, Heidari Z, Tajabadi-Ebrahimi M, Amani R. The effects of synbiotic supplementation on oxidative stress markers, mental status, and quality of life in patients with Parkinson's disease: a double-blind, placebo-controlled, randomized controlled trial. *J Funct Foods* **2023**; 100: 105397. doi:10.1016/j.jff.2022.105397
33. Zolghadripour MA, Jowshan MR, Heidari Seyedmahalleh M, Imani H, Karimpour F, Asghari S. Consumption of a new developed synbiotic yogurt improves oxidative stress status in adults with metabolic syndrome: a randomized controlled clinical trial. *Sci Rep* **2024**; 14: 20333. doi:10.1038/s41598-024-71264-y
34. Giamarellos-Bourboulis EJ, Bengmark S, Kanellakopoulou K, Kotzampassi K. Pro- and synbiotics to control inflammation and infection in patients with multiple injuries. *J Trauma* **2009**; 67: 815-21. doi:10.1097/TA.0b013e31819d979e
35. Fernandes R, Beserra BT, Mocellin MC, Kuntz MG, da Rosa JS, de Miranda RC, et al. Effects of prebiotic and synbiotic supplementation on inflammatory markers and anthropometric indices after Roux-en-Y gastric bypass: a randomized, triple-blind, placebo-controlled pilot study. *J Clin Gastroenterol* **2016**; 50: 208-17. doi:10.1097/mcg.0000000000000328
36. Seifi N, Sedaghat A, Nematy M, Khadem-Rezaian M, Shirazinezhad R, Ranjbar G, et al. Effects of synbiotic supplementation on the serum endotoxin level, inflammatory status, and clinical outcomes of adult patients with critical illness: a randomized controlled trial. *Nutr Clin Pract* **2022**; 37: 451-8. doi:10.1002/ncp.10758
37. Zhang L, Xiao H, Zhao L, Liu Z, Chen L, Liu C. Comparison of the effects of prebiotics and synbiotics supplementation on the immune function of male university football players. *Nutrients* **2023**; 15: 1158. doi:10.3390/nu15051158
38. Rossi M, Johnson DW, Morrison M, Pascoe EM, Coombes JS, Forbes JM, et al. Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. *Clin J Am Soc Nephrol* **2016**; 11: 223-31. doi:10.2215/cjn.05240515
39. Hinchado MD, Quero-Calero CD, Otero E, Gálvez I, Ortega E. Synbiotic supplementation improves quality of life and immunoneuroendocrine response in patients with fibromyalgia: influence of codiagnosis with chronic fatigue syndrome. *Nutrients* **2023**; 15: 1591. doi:10.3390/nu15071591
40. Neyrinck AM, Rodriguez J, Taminiau B, Amadieu C, Herpin F, Allaert FA, et al. Improvement of gastrointestinal discomfort and inflammatory status by a synbiotic in middle-aged adults: a double-blind randomized placebo-controlled trial. *Sci Rep* **2021**; 11: 2627. doi:10.1038/s41598-020-80947-1
41. Nabhani Z, Clark CC, Goudarzi N, Hariri Far A, Razmpoosh E. The effect of synbiotic supplementation on atherogenic indices, hs-CRP, and malondialdehyde, as major CVD-related parameters, in women with gestational diabetes mellitus: a secondary data-analysis of a randomized double-blind, placebo-controlled study. *Diabetol Metab Syndr* **2022**; 14: 87. doi:10.1186/s13098-022-00858-1
42. Mofidi F, Poustchi H, Yari Z, Nourinayyer B, Merat S, Sharafkhan M, et al. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. *Br J Nutr* **2017**; 117: 662-8. doi:10.1017/s0007114517000204
43. Nova E, Viadel B, Wärnberg J, Carreres JE, Marcos A. Beneficial effects of a synbiotic supplement on self-perceived gastrointestinal well-being and immunoinflammatory status of healthy adults. *J Med Food* **2011**; 14: 79-85. doi:10.1089/jmf.2008.0328
44. Abhari K, Saadati S, Yari Z, Hosseini H, Hedayat M, Abhari S, et al. The effects of *Bacillus coagulans* supplementation in patients with non-alcoholic fatty liver disease: a randomized, placebo-controlled, clinical trial. *Clin Nutr ESPEN* **2020**; 39: 53-60. doi:10.1016/j.clnesp.2020.06.020
45. Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, et al. Bifidobacterium longum with fructo-oligosaccharides in patients with non-alcoholic steatohepatitis. *Dig Dis Sci* **2012**; 57: 545-53. doi:10.1007/s10620-011-1887-4
46. Ogawa T, Hashikawa S, Asai Y, Sakamoto H, Yasuda K, Makimura Y. A new synbiotic, *Lactobacillus casei* subsp. *casei* together with dextran, reduces murine and human allergic reaction. *FEMS Immunol Med Microbiol* **2006**; 46: 400-9. doi:10.1111/j.1574-695X.2006.00046.x
47. Roller M, Clune Y, Collins K, Rechkemmer G, Watzl B. Consumption of prebiotic inulin enriched with oligofructose in combination with the probiotics *Lactobacillus rhamnosus* and *Bifidobacterium lactis* has minor effects on selected immune parameters in polypectomised and colon cancer patients. *Br J Nutr* **2007**; 97: 676-84. doi:10.1017/s0007114507450292
48. Federico A, Tuccillo C, Grossi E, Abbiati R, Garbagna N, Romano M, et al. The effect of a new symbiotic formulation on plasma levels and peripheral blood mononuclear cell expression of some pro-inflammatory cytokines in patients with ulcerative colitis: a pilot study. *Eur Rev Med Pharmacol Sci* **2009**; 13: 285-93.
49. González-Hernández LA, Jave-Suarez LF, Fafutis-Morris M, Montes-Salcedo KE, Valle-Gutierrez LG, Campos-Loza AE, et al. Synbiotic therapy decreases microbial translocation and inflammation and improves immunological status in HIV-infected patients: a double-blind randomized controlled pilot trial. *Nutr J* **2012**; 11: 90. doi:10.1186/1475-2891-11-90
50. Macfarlane S, Cleary S, Bahrami B, Reynolds N, Macfarlane GT. Synbiotic consumption changes the metabolism and composition of the gut microbiota in older people and modifies inflammatory processes: a randomised, double-blind, placebo-controlled crossover study. *Aliment Pharmacol Ther* **2013**; 38: 804-16. doi:10.1111/apt.12453
51. Neto JV, de Melo CM, Ribeiro SM. Effects of three-month intake of synbiotic on inflammation and body composition in the elderly: a pilot study. *Nutrients* **2013**; 5: 1276-86. doi:10.3390/nu5041276
52. Childs CE, Róytö H, Alhoniemi E, Fekete AA, Forssten SD, Hudjec N, et al. Xylo-oligosaccharides alone or in synbiotic combination with *Bifidobacterium animalis* subsp. *lactis* induce bifidogenesis and modulate markers of immune function in healthy adults: a double-blind, placebo-controlled, randomised, factorial cross-over study. *Br J Nutr* **2014**; 111: 1945-56. doi:10.1017/s0007114513004261
53. Eslamparast T, Poustchi H, Zamani F, Sharafkhan M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Am J Clin Nutr* **2014**; 99: 535-42. doi:10.3945/ajcn.113.068890
54. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of probiotic *Lactobacillus salivarius* UBL S22 and prebiotic fructo-oligosaccharide on serum lipids, inflammatory markers, insulin sensitivity, and gut bacteria in healthy young volunteers: a randomized controlled single-blind pilot study. *J Cardiovasc Pharmacol Ther* **2015**; 20: 289-98. doi:10.1177/1074248414555004
55. Peña F, Mizgier ML, Morales P, Rios I, Carrasco-Pozo C, Diaz E, et al. Effect of the synbiotic (*B. animalis* spp. *lactis* Bb12+ oligofructose) in obese subjects. A randomized, double-blind, controlled clinical trial. *J Food Nutr Res* **2014**; 2: 491-8. doi:10.12691/jfnr-2-8-10
56. Kooshki A, Tofighian T, Rakhshani MH. Effects of synbiotics on inflammatory markers in patients with type 2 diabetes mellitus. *Glob J Health Sci* **2015**; 7: 1-5. doi:10.5539/gjhs.v7n7p1
57. Asgharian A, Askari G, Esmailzade A, Feizi A, Mohammadi V. The effect of symbiotic supplementation on liver enzymes, C-reactive protein and ultrasound findings in patients with non-alcoholic fatty liver disease: a clinical trial. *Int J Prev Med* **2016**; 7: 59. doi:10.4103/2008-7802.178533
58. Stenman LK, Lehtinen MJ, Meland N, Christensen JE, Yeung N,

- Saarinen MT, et al. Probiotic with or without fiber controls body fat mass, associated with serum zonulin, in overweight and obese adults-randomized controlled trial. *EBioMedicine* **2016**; 13: 190-200. doi:10.1016/j.ebiom.2016.10.036
59. Ekhlasi G, Zarrati M, Agah S, Hosseini AF, Hosseini S, Shidfar S, et al. Effects of symbiotic and vitamin E supplementation on blood pressure, nitric oxide and inflammatory factors in non-alcoholic fatty liver disease. *EXCLI J* **2017**; 16: 278-90. doi:10.17179/excli2016-846
 60. Mimura MA, Borra RC, Hirata CH, de Oliveira Penido N. Immune response of patients with recurrent aphthous stomatitis challenged with a symbiotic. *J Oral Pathol Med* **2017**; 46: 821-8. doi:10.1111/jop.12621
 61. Louzada ER, Ribeiro SM. Synbiotic supplementation, systemic inflammation, and symptoms of brain disorders in elders: a secondary study from a randomized clinical trial. *Nutr Neurosci* **2020**; 23: 93-100. doi:10.1080/1028415x.2018.1477349
 62. Xavier-Santos D, Lima ED, Simão AN, Bedani R, Saad SM. Effect of the consumption of a synbiotic diet mousse containing *Lactobacillus acidophilus* La-5 by individuals with metabolic syndrome: a randomized controlled trial. *J Funct Foods* **2018**; 41: 55-61. doi:10.1016/j.jff.2017.12.041
 63. Karimi E, Moini A, Yaseri M, Shirzad N, Sepidarkish M, Hossein-Boroujerdi M, et al. Effects of synbiotic supplementation on metabolic parameters and apelin in women with polycystic ovary syndrome: a randomised double-blind placebo-controlled trial. *Br J Nutr* **2018**; 119: 398-406. doi:10.1017/s0007114517003920
 64. Ghafouri A, Zarrati M, Shidfar F, Heydari I, Shokouhi Shoormasti R, Eslami O. Effect of synbiotic bread containing lactic acid on glycemic indicators, biomarkers of antioxidant status and inflammation in patients with type 2 diabetes: a randomized controlled trial. *Diabetol Metab Syndr* **2019**; 11: 103. doi:10.1186/s13098-019-0496-9
 65. Rabiei S, Hedayati M, Rashidkhani B, Saadat N, Shakerhossini R. The effects of synbiotic supplementation on body mass index, metabolic and inflammatory biomarkers, and appetite in patients with metabolic syndrome: a triple-blind randomized controlled trial. *J Diet Suppl* **2019**; 16: 294-306. doi:10.1080/19390211.2018.1455788
 66. Soleimani A, Motamedzadeh A, Zarrati Mojarrad M, Bahmani F, Amirani E, Ostadmohammadi V, et al. The effects of synbiotic supplementation on metabolic status in diabetic patients undergoing hemodialysis: a randomized, double-blinded, placebo-controlled trial. *Probiotics Antimicrob Proteins* **2019**; 11: 1248-56. doi:10.1007/s12602-018-9499-3
 67. Kooshki A, Tofighiyan T, Miri M. A synbiotic supplement for inflammation and oxidative stress and lipid abnormalities in hemodialysis patients. *Hemodial Int* **2019**; 23: 254-60. doi:10.1111/hdi.12748
 68. Kamarlı Altun H, Akal Yıldız E, Akin M. Effects of synbiotic therapy in mild-to-moderately active ulcerative colitis: a randomized placebo-controlled study. *Turk J Gastroenterol* **2019**; 30: 313-20. doi:10.5152/tjg.2019.18356
 69. Angelino D, Martina A, Rosi A, Veronesi L, Antonini M, Mennella I, et al. Glucose- and lipid-related biomarkers are affected in healthy obese or hyperglycemic adults consuming a whole-grain pasta enriched in prebiotics and probiotics: a 12-week randomized controlled trial. *J Nutr* **2019**; 149: 1714-23. doi:10.1093/jn/nxz071
 70. Haghighat N, Mohammadshahi M, Shayanpour S, Haghighizadeh MH. Effects of synbiotics and probiotics supplementation on serum levels of endotoxin, heat shock protein 70 antibodies and inflammatory markers in hemodialysis patients: a randomized double-blinded controlled trial. *Probiotics Antimicrob Proteins* **2020**; 12: 144-51. doi:10.1007/s12602-018-9509-5
 71. Bazayr H, Maghsoumi-Norouzabad L, Yarahmadi M, Gholinezhad H, Moradi L, Salehi P, et al. The impacts of synbiotic supplementation on periodontal indices and biomarkers of oxidative stress in type 2 diabetes mellitus patients with chronic periodontitis under non-surgical periodontal therapy. A double-blind, placebo-controlled trial. *Diabetes Metab Syndr Obes* **2020**; 13: 19-29. doi:10.2147/dms0.S230060
 72. de Carvalho CM, Luzia LA, Rondó PH, Ribeiro SM. Associations between vitamin D, systemic inflammation and synbiotic supplementation: secondary study from a randomized clinical trial. *Nutrire* **2019**; 45: 4. doi:10.1186/s41110-019-0104-7
 73. Mirzaeian S, Saraf-Bank S, Entezari MH, Hekmatdoost A, Feizi A, Atapour A. Effects of synbiotic supplementation on microbiota-derived protein-bound uremic toxins, systemic inflammation, and biochemical parameters in patients on hemodialysis: a double-blind, placebo-controlled, randomized clinical trial. *Nutrition* **2020**; 73: 110713. doi:10.1016/j.nut.2019.110713
 74. Talebi S, Karimifar M, Heidari Z, Mohammadi H, Askari G. The effects of synbiotic supplementation on thyroid function and inflammation in hypothyroid patients: a randomized, double-blind, placebo-controlled trial. *Complement Ther Med* **2020**; 48: 102234. doi:10.1016/j.ctim.2019.102234
 75. Valentini Neto J, Chella TP, Rudnik DP, Ribeiro SM. Effects of synbiotic supplementation on gut functioning and systemic inflammation of community-dwelling elders-secondary analyses from a randomized clinical trial. *Arq Gastroenterol* **2020**; 57: 24-30. doi:10.1590/s0004-2803.202000000-06
 76. Vafa S, Haghighat S, Janani L, Saneei Totmaj A, Navaei M, Amirinejad A, et al. The effects of synbiotic supplementation on serum inflammatory markers and edema volume in breast cancer survivors with lymphedema. *EXCLI J* **2020**; 19: 1-15. doi:10.17179/excli2019-1876
 77. Kanazawa A, Aida M, Yoshida Y, Kaga H, Katahira T, Suzuki L, et al. Effects of synbiotic supplementation on chronic inflammation and the gut microbiota in obese patients with type 2 diabetes mellitus: a randomized controlled study. *Nutrients* **2021**; 13: 558. doi:10.3390/nu13020558
 78. Chaiyasut C, Sivamaruthi BS, Kesika P, Khongtan S, Khampithum N, Thangaleela S, et al. Synbiotic supplementation improves obesity index and metabolic biomarkers in Thai obese adults: a randomized clinical trial. *Foods* **2021**; 10: 1580. doi:10.3390/foods10071580
 79. Cicero AFG, Fogacci F, Bove M, Giovannini M, Borghi C. Impact of a short-term synbiotic supplementation on metabolic syndrome and systemic inflammation in elderly patients: a randomized placebo-controlled clinical trial. *Eur J Nutr* **2021**; 60: 655-63. doi: 10.1007/s00394-020-02271-8.
 80. Raji Lahiji M, Najafi S, Janani L, Yazdani B, Razmpoosh E, Zarrati M. The effect of synbiotic on glycemic profile and sex hormones in overweight and obese breast cancer survivors following a weight-loss diet: a randomized, triple-blind, controlled trial. *Clin Nutr* **2021**; 40: 394-403. doi:10.1016/j.clnu.2020.05.043
 81. Ghavami A, Khorvash F, Heidari Z, Khalesi S, Askari G. Effect of synbiotic supplementation on migraine characteristics and inflammatory biomarkers in women with migraine: results of a randomized controlled trial. *Pharmacol Res* **2021**; 169: 105668. doi:10.1016/j.phrs.2021.105668
 82. Quero CD, Manonelles P, Fernández M, Abellán-Aynés O, López-Plaza D, Andreu-Caravaca L, et al. Differential health effects on inflammatory, immunological and stress parameters in professional soccer players and sedentary individuals after consuming a synbiotic. A triple-blinded, randomized, placebo-controlled pilot study. *Nutrients* **2021**; 13: 1321. doi:10.3390/nu13041321
 83. Saneei Totmaj A, Haghighat S, Jaberzadeh S, Navaei M, Vafa S, Janani L, et al. The effects of synbiotic supplementation on serum anti-inflammatory factors in the survivors of breast cancer with lymphedema following a low-calorie diet: a randomized, double-blind, clinical trial. *Nutr Cancer* **2022**; 74: 869-81. doi:10.1080/01635581.2021.1933096
 84. Rahimi F, Pasdar Y, Kaviani M, Abbasi S, Fry H, Hekmatdoost A, et al. Efficacy of the synbiotic supplementation on the metabolic factors in patients with metabolic syndrome: a randomized, triple-blind, placebo-controlled trial. *Int J Clin Pract* **2022**; 2022: 2967977. doi:10.1155/2022/2967977
 85. Widhani A, Djauzi S, Suyatna FD, Dewi BE. Changes in gut microbiota and systemic inflammation after synbiotic supplementation in patients with systemic lupus erythematosus: a randomized, double-blind, placebo-controlled trial. *Cells* **2022**; 11: 3419. doi:10.3390/cells11213419
 86. Shoaie Matin S, Shidfar F, Naderi N, Amin A, Hosseini-Baharanchi FS, Dehnad A. The effect of synbiotic consumption on serum NTProBNP, hsCRP and blood pressure in patients with chronic heart failure: a randomized, triple-blind, controlled trial. *Front Nutr*

- 2021; 8: 822498. doi:10.3389/fnut.2021.822498
87. Lyon J 3rd, Connell M, Chandrasekaran K, Srivastava S. Effect of synbiotics on weight loss and metabolic health in adults with overweight and obesity: a randomized controlled trial. *Obesity (Silver Spring)* **2023**; 31: 2009-20. doi:10.1002/oby.23801
 88. Li X, Hu S, Yin J, Peng X, King L, Li L, et al. Effect of synbiotic supplementation on immune parameters and gut microbiota in healthy adults: a double-blind randomized controlled trial. *Gut Microbes* **2023**; 15: 2247025. doi:10.1080/19490976.2023.2247025
 89. Fallah F, Mahdavi R. L-Carnitine and synbiotic co-supplementation: beneficial effects on metabolic-endotoxemia, meta-inflammation, and oxidative-stress biomarkers in obese patients: a double blind, randomized, controlled clinical trial. *Food Funct* **2023**; 14: 2172-87. doi:10.1039/d2fo03348h
 90. Liu M, Tandorost A, Moludi J, Dey P. Prebiotics plus probiotics may favorably impact on gut permeability, endocannabinoid receptors, and inflammatory biomarkers in patients with coronary artery diseases: a clinical trial. *Food Sci Nutr* **2024**; 12: 1207-17. doi:10.1002/fsn3.3835
 91. Mitrović M, Dobrosavljević A, Odanović O, Knežević-Ivanovski T, Kralj Đ, Erceg S, et al. The effects of synbiotics on the liver steatosis, inflammation, and gut microbiome of metabolic dysfunction-associated liver disease patients-randomized trial. *Rom J Intern Med* **2024**; 62: 184-93. doi:10.2478/rjim-2024-0004
 92. Mitrović M, Stanković-Popović V, Tolinački M, Golić N, Soković Bajić S, Veljović K, et al. The impact of synbiotic treatment on the levels of gut-derived uremic toxins, inflammation, and gut microbiome of chronic kidney disease patients-a randomized trial. *J Ren Nutr* **2023**; 33: 278-88. doi:10.1053/j.jrn.2022.07.008
 93. Salamat S, Jahan-Mihan A, Gharibvand L, Tabandeh MR, Mansoori A. Multi-species synbiotic supplementation increased fecal short chain fatty acids and anti-inflammatory cytokine interleukin-10 in adult men with dyslipidemia; a randomized, double-blind, clinical trial. *Cytokine* **2024**; 179: 156608. doi:10.1016/j.cyto.2024.156608
 94. Yarahmadi M, Zare Javid A, Bazayr H, Yousefimanesh H, Nejatian T, Gravand E, et al. The effects of synbiotic supplementation along with non-surgical periodontal therapy in improving the metabolic status and inflammatory markers in type 2 diabetes mellitus patients with periodontal disease: a double-blind randomized clinical trial. *J Educ Health Promot* **2024**; 13: 430. doi:10.4103/jehp.jehp_1382_23
 95. Stougaard EB, Tougaard NH, Sivalingam S, Hansen CS, Stirling J, Hansen TW, et al. Effects of probiotics and fibers on markers of nephropathy, inflammation, intestinal barrier dysfunction and endothelial dysfunction in individuals with type 1 diabetes and albuminuria. The ProFOS Study. *J Diabetes Complications* **2024**; 38: 108892. doi:10.1016/j.jdiacomp.2024.108892
 96. Hosseini F, Pourjam M, Mirzaeian S, Karimifard M, Feizi A, Entezari MH, et al. Appetite sensation improvement by synbiotic supplementation in patients with metabolic syndrome: a randomized controlled clinical trial. *Food Sci Nutr* **2024**; 12: 4772-82. doi:10.1002/fsn3.4124
 97. Tirgar A, Rezaei M, Ehsani M, Salmani Z, Rastegari A, Jafari E, et al. Exploring the synergistic effects of vitamin D and synbiotics on cytokines profile, and treatment response in breast cancer: a pilot randomized clinical trial. *Sci Rep* **2024**; 14: 21372. doi:10.1038/s41598-024-72172-x
 98. Yazdani A, Fattahi MR, Eftekhari MH, Ahmadi A, Soveid M, Zare M, et al. Effects of multi-strain synbiotic supplementation on liver enzymes, insulin resistance, anthropometric, and inflammatory indices in overweight and obese adults with fatty liver and diabetes: a randomized controlled trial. *J Diabetes Metab Disord* **2025**; 24: 120. doi:10.1007/s40200-025-01632-6
 99. Fasitasari M, Fatimah-Muis S, Prajoko YW, Maharani N, Antono D, Yusmawan W, et al. Efficacy of synbiotic maintenance dose on cancer cachexia in advanced nasopharyngeal cancer: a randomized controlled trial. *J Food Sci* **2025**; 90: e70482. doi:10.1111/1750-3841.70482
 100. Vijay A, Simpson L, Tooley M, Turley S, Kouraki A, Kelly A, et al. The anti-inflammatory effects of three different dietary supplement interventions. *J Transl Med* **2025**; 23: 1081. doi:10.1186/s12967-025-07167-x
 101. Schott EM, Charbonneau MR, Kiel DP, Bukata S, Zuscik MJ, Rosen C, et al. A randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy of the synbiotic medical food, SBD111, for the clinical dietary management of bone loss in menopausal women. *Osteoporos Int* **2025**; 36: 2019-30. doi:10.1007/s00198-025-07650-7
 102. Ramadan ME, Mostafa TM, Ghali AA, El-Afify DR. Randomized controlled trial evaluating synbiotic supplementation as an adjuvant therapy in the treatment of Parkinson's disease. *Inflammopharmacology* **2025**; 33: 3897-908. doi:10.1007/s10787-025-01752-8
 103. Faghieh Dinavari M, Abbasian S, Jabbaripour Sarmadian A, Vaezi T, Vaezi T, Nikniaz Z, et al. Multi-strain synbiotic and lifestyle modifications on patients with metabolic dysfunction-associated steatotic liver disease (MASLD): a randomized double-blinded placebo-controlled trial. *Eur J Med Res* **2026**; 31. doi:10.1186/s40001-026-03901-3
 104. Sin DD, Man SF. Systemic inflammation and mortality in chronic obstructive pulmonary disease. *Can J Physiol Pharmacol* **2007**; 85: 141-7. doi:10.1139/y06-093
 105. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS. Systemic inflammation predicts all-cause mortality: a Glasgow inflammation outcome study. *PLoS One* **2015**; 10: e0116206. doi:10.1371/journal.pone.0116206
 106. Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of inflammation. In: DeWitt JC, Rockwell CE, Bowman CC, eds. *Immunotoxicity Testing: Methods and Protocols*. New York: Springer; **2018**. p. 57-79. doi:10.1007/978-1-4939-8549-4_5
 107. Jafarnejad S, Saremi S, Jafarnejad F, Arab A. Effects of a multispecies probiotic mixture on glycemic control and inflammatory status in women with gestational diabetes: a randomized controlled clinical trial. *J Nutr Metab* **2016**; 2016: 5190846. doi:10.1155/2016/5190846
 108. Raygan F, Ostadmohammadi V, Bahmani F, Asemi Z. The effects of vitamin D and probiotic co-supplementation on mental health parameters and metabolic status in type 2 diabetic patients with coronary heart disease: a randomized, double-blind, placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* **2018**; 84: 50-5. doi:10.1016/j.pnpbp.2018.02.007
 109. Roshanravan N, Tarighat-Esfanjani A, Mesri Alamdari N, Kheirouri S, Mousavi R, Alizadeh M. The effects of zinc supplementation on inflammatory parameters in pregnant women with impaired glucose tolerance: a randomized placebo controlled clinical trial. *Prog Nutr* **2018**; 20: 330-6. doi:10.23751/pn.v20i1-S.5867
 110. Irandoost P, Mesri Alamdari N, Saidpour A, Shidfar F, Roshanravan N, Asghari Jafarabadi M, et al. The effects of royal jelly and tocotrienol-rich fraction on impaired glycemic control and inflammation through irisin in obese rats. *J Food Biochem* **2020**; 44: e13493. doi:10.1111/jfbc.13493
 111. Kim CH. Microbiota or short-chain fatty acids: which regulates diabetes? *Cell Mol Immunol* **2018**; 15: 88-91. doi:10.1038/cmi.2017.57
 112. McLoughlin RF, Berthon BS, Jensen ME, Baines KJ, Wood LG. Short-chain fatty acids, prebiotics, synbiotics, and systemic inflammation: a systematic review and meta-analysis. *Am J Clin Nutr* **2017**; 106: 930-45. doi:10.3945/ajcn.117.156265
 113. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. *Ann Surg Oncol* **2015**; 22: 803-10. doi:10.1245/s10434-014-4048-0
 114. Hegazy SK, El-Bedewy MM. Effect of probiotics on pro-inflammatory cytokines and NF-κB activation in ulcerative colitis. *World J Gastroenterol* **2010**; 16: 4145-51. doi:10.3748/wjg.v16.i33.4145
 115. Milajerdi A, Mousavi SM, Sadeghi A, Salari-Moghaddam A, Parohan M, Larijani B, et al. The effect of probiotics on inflammatory biomarkers: a meta-analysis of randomized clinical trials. *Eur J Nutr* **2020**; 59: 633-49. doi:10.1007/s00394-019-01931-8
 116. Oelschlaeger TA. Mechanisms of probiotic actions - a review. *Int J Med Microbiol* **2010**; 300: 57-62. doi:10.1016/j.ijmm.2009.08.005
 117. Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC. Mechanisms of action of probiotics: recent advances. *Inflamm Bowel Dis* **2009**; 15: 300-10. doi:10.1002/ibd.20602

-
118. Irandoost P, Lotfi Yagin N, Namazi N, Keshtkar A, Farsi F, Mesri Alamdari N, et al. The effect of capsaicinoids or capsinoids in red pepper on thermogenesis in healthy adults: a systematic review and meta-analysis. *Phytother Res* **2021**; 35: 1358-77. doi:10.1002/ptr.6897
119. Zheng HJ, Guo J, Jia Q, Huang YS, Huang WJ, Zhang W, et al. The effect of probiotic and synbiotic supplementation on biomarkers of inflammation and oxidative stress in diabetic patients: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* **2019**; 142: 303-13. doi:10.1016/j.phrs.2019.02.016
120. Tabrizi R, Ostadmohammadi V, Bagheri Lankarani K, Akbari M, Akbari H, Vakili S, et al. The effects of probiotic and synbiotic supplementation on inflammatory markers among patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pharmacol* **2019**; 852: 254-64. doi: <https://doi.org/10.1016/j.ejphar.2019.04.003>