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Reinforcing gut integrity: A systematic review and meta-analysis of clinical trials assessing probiotics, synbiotics, and prebiotics on intestinal permeability markers

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ABSTRACT

Background: Given the magnitude and variety of chronic metabolic disease linked to increased intestinal permeability, appropriate strategies to reinforce gut barrier function are urgently needed.
Methods: This systematic review and meta-analysis explores the effects of pro- and synbiotic, or prebiotic administration, on various intestinal permeability markers. Systematic searches across the Medline and Scopus databases were performed from 1961 to January 2023. The review included data from 46 published studies on pro- and synbiotics, and 22 studies on prebiotics. 46 The meta-analysis calculated standardized mean differences (SMD) along with 95 % confidence intervals (95 %CIs) using a random-effects model to evaluate the average effect sizes (ES). To analyze heterogeneity, we employed Galbraith plots and performed the Cochrane Chi-squared test.
Results: The analysis on 24 trials (28 ES, n = 1603) revealed a significant reduction in lipopolysaccharide levels following pro- and synbiotics consumption with high heterogeneity and very low certainty of evidence (SMD (95 %CI) = -0.54 (-1.01, −0.07); I^2 (%) = 94.4). Synthesis of 13 trials showed zonulin levels were significantly lowered after pro- and synbiotics consumption with high heterogeneity and moderate certainty of evidence (15 ES, *n*=778) (SMD (95 %CI) = -0.49 (-0.79, −0.18); I^2 (%) = 74.9). Following prebiotics supplementation, a significant reduction in lipopolysaccharide levels was observed, with high heterogeneity identified from data including 16 RCTs (n = 792; SMD (95 %CI) = -0.88 (-1.28, −0.47); P < 0.001; high certainty of evidence; I^2 (%) = 85.7; P-heterogeneity< 0.001).
Conclusion: This meta-analysis revealed promising findings regarding the efficacy of pro- and synbiotic and prebiotic supplements in alleviating "leaky gut".

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1. Introduction

The gut barrier is fundamental in regulating the selective influx of substances, such as antigens and microorganisms, from the intestinal lumen into the underlying mucosa [1]. This regulation occurs via two pathways: the paracellular route, which controls movement between epithelial cells, and the transcellular route, which allows substances to migrate through epithelial cells [1]. Tight junction proteins, including Zonula occludens, occludin, claudins, and junctional adhesion molecules, play a pivotal role in maintaining this selective permeability through paracellular spaces between enterocytes [2]. When these proteins are compromised, the gut barrier's integrity diminishes, a condition often referred to as "leaky gut" [3,4]. This allows harmful substances, including bacterial antigens like lipopolysaccharide (LPS), to enter the bloodstream, triggering low-grade inflammation, oxidative stress, and metabolic dysfunction [3,5]. Dysbiosis, or an imbalance in gut microbiota from commensal toward harmful gut bacteria, further exacerbates this condition by altering tight junction protein expression and generating toxic metabolites [5].

Although direct causality remains elusive, increasing evidence implicates gut barrier dysfunction in the onset and progression of chronic diseases, including obesity, cardiometabolic disorders, and gastrointestinal conditions [5]. Intestinal permeability, therefore, serves as a valuable marker for assessing gut integrity and the extent of mucosal damage in disorders like Crohn's disease and celiac disease [1]. Biomarkers such as serum LPS, zonulin, lipopolysaccharide-binding protein (LBP), and fecal calprotectin are commonly used to evaluate intestinal permeability [6]. Elevated levels of LPS and zonulin are associated with compromised gut barrier function, while LBP and calprotectin reflect acute-phase responses and inflammation, respectively [6].

Given the widespread implications of leaky gut in chronic diseases, there is a pressing need for strategies to restore gut barrier integrity. Dietary interventions, particularly probiotics, synbiotics, and prebiotics, have shown promise in addressing gut dysbiosis and reinforcing the gut barrier [7]. Probiotics and synbiotics are known to modulate tight junction protein expression, reduce inflammation, and improve metabolic health, although their efficacy in human trials remains inconsistent [7–11]. Prebiotics, on the other hand, are non-digestible compounds that stimulate the growth of beneficial gut bacteria. Derived from plant-based sources such as inulin, resistant starches, and fructooligosaccharides, prebiotics undergo fermentation in the colon, producing short-chain fatty acids that support gut health [12].

Despite the potential benefits of these interventions, existing systematic reviews and meta-analyses are limited in scope [7–11]. Most studies focus on specific populations, such as individuals with obesity or colorectal cancer, or narrow their analysis to particular markers like LPS or zonulin. A comprehensive evaluation of the effects of probiotics, synbiotics, and prebiotics on gut permeability across diverse populations and markers remains lacking.

To address this gap, our systematic review and meta-analysis synthesize findings from 67 randomized controlled trials (RCTs) that investigated the impact of probiotics, synbiotics, and prebiotics on intestinal permeability biomarkers, including serum/plasma LPS, LBP, and zonulin, as well as fecal calprotectin and zonulin. The analysis of prebiotics (n = 22) was separated from probiotics and synbiotics analysis (n = 46) to delineate their distinct effects. Additionally, we explore the influence of dosage, intervention type, study duration, and participants' health status on the outcomes.

Our primary objective is to provide a comprehensive understanding of how these interventions affect gut barrier function. By consolidating evidence from a broad range of clinical trials, this study aims to clarify the role of probiotics, synbiotics, and prebiotics in managing intestinal permeability and their potential to mitigate chronic disease progression.

2. Methods

This systematic review and meta-analysis report adheres to the PRISMA 2020 guidelines. The study's protocol was registered in the PROSPERO database at https://www.crd.york.ac.uk/prospero/, under the registration number CRD42022358668 (Supplementary Material 1, Supplementary Files 1)

2.1. Search strategy

An exhaustive literature review integrated unstructured keywords, Medical Subject Headings (MeSH), and systematic searches across the Medline (PubMed) and Scopus databases. To investigate the effects of probiotics, prebiotics, and synbiotics on intestinal health, particularly intestinal permeability, and related biomarkers, a systematic search was conducted across two major databases: SCOPUS and PubMed. The search was designed using a comprehensive array of keywords to capture a broad spectrum of relevant studies. The search strategy, as detailed in Supplementary Material 1, Supplementary File 1, included variations such as "probio*", "synbio*", "symbio*", and "prebiot*", terms related to probiotics specific bacterial genera (e.g., *Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus*), prebiotics (e.g., "oligosaccharid*", fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), inulin, resistant starch, fiber), and synbiotics (e.g., combinations of probiotics and prebiotics). To evaluate intestinal integrity and permeability, these key terms were combined with terms related to intestinal permeability, barrier function, and biomarkers (e.g., tight junctions, intestinal epithelial cells, intestinal permeability, mucosal barrier, leaky gut, lipopolysaccharide (LPS), zonulin, calprotectin, occludin, claudin, trimethylamine oxide (TMAO), soluble CD14, I-FABP, flagellin, toll-like receptors (TLRs)).The search further encompassed clinical trial terminologies, such as randomized, placebo, double-blind, single-blind, and controlled trial. This strategy allowed for the retrieval of relevant studies from their inception in 1961 up to January 2023. Our initial search parameters were limited to human studies published in English. Additionally, we conducted manual searches and reviewed bibliographic references to ensure the inclusion of all relevant studies. However, this process did not yield any additional studies beyond those identified in the systematic search. The precise search methods and keyword strategies used are comprehensively outlined in (Supplementary Material 1, Supplementary File 2.).

2.2. Study selection

The research framework was established using the PICOS criteria ("Participants, Intervention, Comparison, Outcomes, Study design"), as detailed in Table 1. We focused on RCTs that examined the effects of pro or synbiotic intake, in food or supplement form, on the serum and fecal levels of key gut permeability markers (such as serum/plasma LPS, zonulin, LBP, trimethylamine (TMA)/ TMAO), and calprotectin, alongside fecal calprotectin, and zonulin, fecal LPS). Inclusion criteria for studies were stringent, requiring reported baseline/end-of-study values or the variation of these markers during the trial for both the intervention and control groups, as shown in Table 1. Among these, serum/plasma LPS, zonulin, LBP, and fecal calprotectin and zonulin levels were consistently reported across studies, allowing for a robust meta-analysis of these particular markers.

Reviews, meta-analyses, in vitro studies, observational or experimental study designs, book chapters and supplementary materials were excluded to focus on primary research. Animal models (e.g., rodents, mice, pigs, chickens, zebrafish) were excluded. The exclusion criteria removed RCTs where participants were undergoing bariatric surgery or in advanced stages of illness. This encompassed individuals with acute infectious or inflammatory diseases, including but not limited to patients requiring hemodialysis, critically ill subjects, or those suffering from severe neurological dysfunctions, spinal cord injuries, or chronic

Table 1
PICOS criteria for inclusion of studies.

Parameter	Criterion
Population	All adult subjects (healthy and unhealthy aged more than 18 years old) (except for those with autoimmune, or infectious disorders or those with a history of cancer or neoplasm sepsis gestational-diabetes pregnancy bariatric surgery acute infectious critically ill hemodialysis spinal cord injury)
Intervention	Probiotics (single strain or multi-strain) or synbiotic foods or supplements in form of a capsule, powder, sachet, tablet, liquid vial, milk, yogurt, drink, or soy milk, administered for at least 4 weeks Prebiotics (fructooligosaccharide, FOS, galactooligosaccharide, GOS, inulin, dietary fiber, resistant starch, etc) foods or supplements in form of a capsule, powder, sachet, tablet, liquid vial, or drink, administered for at least 4 weeks.
Comparison	Placebo supplements. / No intervention /
Outcomes	Plasma/serum/fecal levels of at least one of the intestinal permeability related markers including lipopolysaccharide, LPS, lipopolysaccharide binding protein (LBP), trimethylamine, TMA), trimethylamine oxide (TMAo), zonulin, occluding, claudin calprotectin, defensin, soluble adhesion molecule, soluble CD14, soluble CD163, sCD163, intestinal fatty acid, I-FABP, citrulline, Reg3A, or toll-like receptor(TLRs)
Study design	Cross-over or Parallel randomized, controlled trials.

illnesses such as HIV/AIDS or cancer. Furthermore, we excluded studies that involved participants with gestational diabetes and those focusing on populations of pregnant or lactating women, as well as children and adolescents. Trials were also omitted if the pro- and synbiotics intervention lasted less than six weeks, if the trial lacked a control group, if it utilized an experimental or uncontrolled design, or if the publications lacked adequate data to assess changes in the relevant variables during the trial. Studies were excluded if dietary supplements were given alongside specific medications or enteral nutrition.

Following initial literature searches the selection process for eligible studies comprised two distinct phases. Two researchers independently screened articles by title, abstract and keywords and then by full text (NSh and KT). Any disagreements during this process were addressed through discussions with collaborating researchers, leading to consensus resolution.

2.3. Data extraction

Data extraction was completed by researchers NSh, KT, and ZGh, and rechecked by ZGh, MN, SKh, and AB. Information including publication details such as the lead author's name, year of publication, and the study's geographic location was extracted alongside the characteristics of the trials and results on a predetermined spreadsheet. Information extracted including trial design, the health status and demographic details of the subjects, the nature of the intervention (whether probiotic, synbiotic, or prebiotic), the types of supplements used (like fortified foods, fermented products, capsules or powders), the specific bacterial strains involved, the dosages administered, the duration of the trial, the body mass index (BMI), and the number of participants in both the intervention and control groups. They also analyzed the mean values and standard deviations (SD) of the serum or plasma levels of the targeted variables at the start and end of the trial or the mean and SD of the changes observed. In cases where RCTs measured the outcomes of interest at several points, only data from the latest time point were included in the meta-analysis. Each arm was treated as an individual study for studies with multiple arms where different interventions were tested against a control group. To prevent the same participants from being counted more than once in the meta-analysis, the control group's sample size was halved in such instances.

Three researchers (NSh, ZGh, and KT) independently assessed each paper for data extraction and quality evaluation. In instances of disagreement, a third-party (AK or SKF) discussion was initiated to reach a unanimous decision.

2.4. Risk of bias assessment

The Cochrane Risk of Bias Tool for Randomized Controlled Trials was utilized. This assesses various potential bias factors, including random sequence generation, the concealment of allocation, the blinding of participants and researchers, the completeness of outcome data, the blinding of outcome assessment, and the selective disclosure of study variables. The included studies were independently evaluated by two authors (NSh and ZGh), who categorized the risk of bias as unclear, low, or high, following the Cochrane Collaboration's established guidelines. In instances of disagreement, a third reviewer (AK or SFK) was consulted for resolution. Subsequently, each RCT was assigned a quality rating of poor, fair, or good.(Fig. 1)

2.5. Statistical analysis

The meta-analyses were conducted using the STATA 16 software (StataCorp LC, Texas, USA). The outcome measure for each group was calculated as the difference in mean values from the baseline and endpoint of the study. Group mean differences were then estimated by normalizing these differences against the mean (SD) of intergroup changes. When needed, the mean and SD for the pre-and-post differences of the outcomes of interest were deduced from graphical data via the Web Plot Digitizer application. A heterogeneity assessment was conducted employing the Cochrane Chi-squared test and depicted with Galbraith plots. An I^2 statistic of 50 % or higher was indicative of notable heterogeneity. Mixed-effect models were used to ascertain the average effect sizes, considering heterogeneity and characteristics of the trials (such as participant age, gender, and health status). These effect sizes were expressed as standardized mean differences (SMD) and illustrated with 95 % confidence intervals (CIs) in forest plots (refer to Figs. 2–6). A P-value threshold of 0.05 was established for statistical significance.

In instances in which initial and concluding mean values for the desired outcomes were unavailable, the standard deviations (SDs) of the means for each group were computed using the following formula:

$SD_{change} = \text{square root}\ (SD^2_{baseline} + SD^2_{final} - (2 \times r \times SD_{baseline} \times SD_{final}))$, assuming a correlation coefficient (r) ≅ 0.8.

It is presumed that the correlation coefficient (r) is 0.8.

2.5.1. Subgroup analyses of pro- and synbiotics effects on permeability factors

Subgroup analyses were performed based on the following criteria:

1. *Health Status of Participants*: For serum/plasma LPS, the trials were categorized into groups comprising individuals with conditions such as type 2 diabetes mellitus (T2DM), metabolic syndrome (MetSyn), polycystic ovary syndrome (PCOS), or coronary artery disease (CAD), vs. patients with gastrointestinal (GI) or liver disorders, contrasted with groups of healthy individuals, or those with other diseases. For serum/plasma zonulin, the subgroup analysis focused on two groups only: unhealthy vs. healthy subjects. The serum/plasma LBP analysis focused on different health conditions, particularly looking at patients who are overweight or obese vs. patients with T2DM or MetSyn vs. those with other conditions or healthy subjects. Finally, the subgroup analysis for fecal calprotectin primarily compared patients with GI disorders vs. healthy subjects.

2. *Type of intervention*, which was divided into those receiving probiotic vs. synbiotic supplementation.

3. *Follow-up duration*, segmented into studies lasting less than 12 weeks and those lasting 12 weeks or more.

4. *Daily dosage of probiotics*, classified into a lower dosage (< 1 ×10^10 colony-forming units (CFU)/day) and a higher dosage (> 1 ×10^10 CFU/day).

5. *Risk of bias in the included RCTs*, subdivided into studies with a high risk of bias (poor) and those with a lower risk of bias (good/or fair).

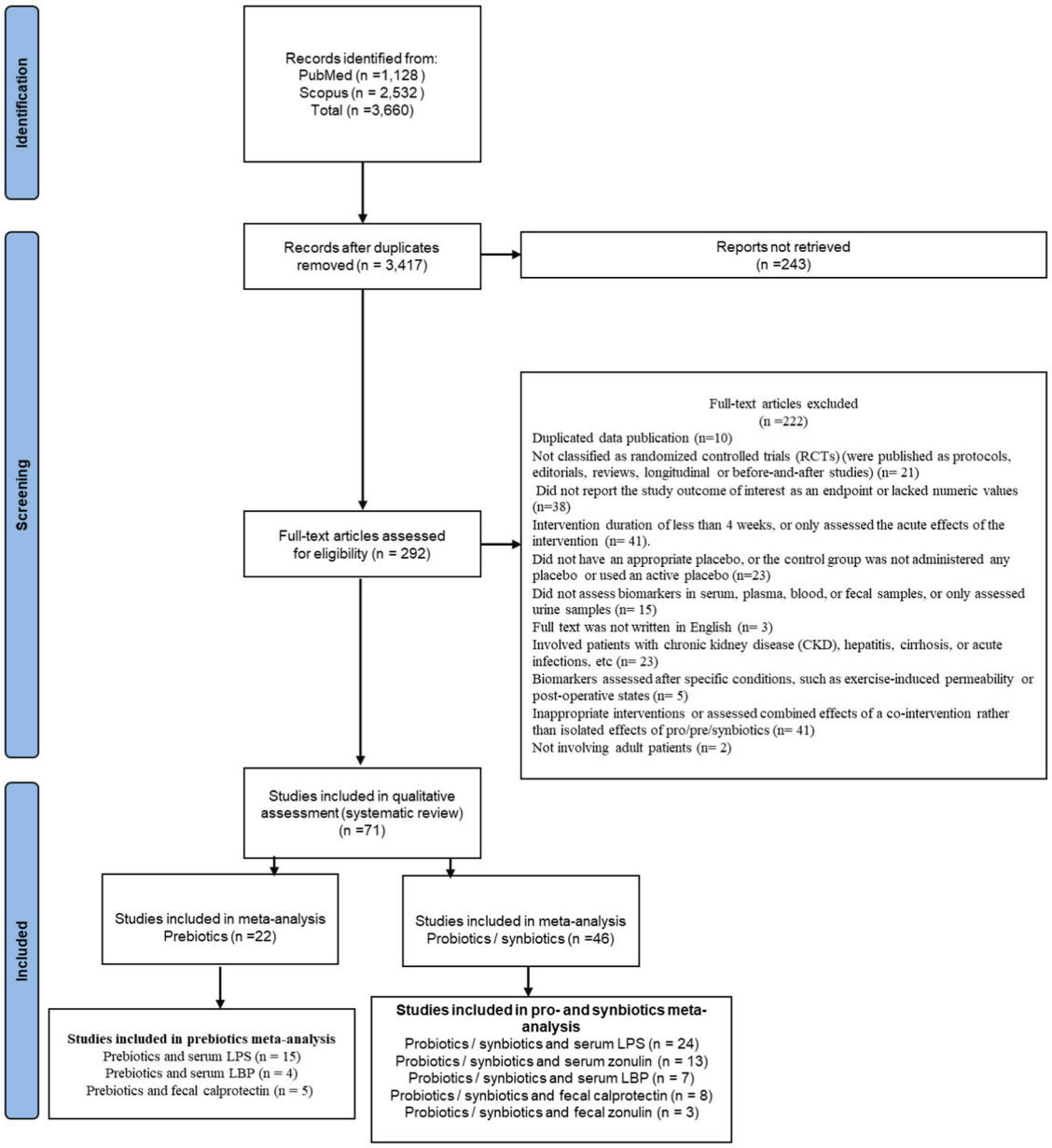

Fig. 1. Meta-analysis flow diagram.

2.5.2. Subgroup analyses of prebiotic effects on permeability factors

This investigation stratified subjects into three major subgroups based on distinct parameters:

1) *Participants' Health Status*: Each outcome was analyzed across different trials, categorizing them according to the health status of the participants. For prebiotic effects on serum/plasma LPS, the trials were categorized similarly to those of pro- and synbiotics. For the subgroup analysis for fecal calprotectin, the included trials' participants were primarily divided into two groups: those with overweight, obesity, or MetSyn vs. those with other conditions.

2) *Intervention duration*: Subjects were segmented into those with follow-up periods of less than two months and those with durations extending beyond two months.

3) *Risk of Bias*: The included RCTs were categorized into studies with a high risk of bias (poor) and those with a low risk of bias (good/or fair).

2.5.3. Meta-regression

An analysis applying a random-effects model was conducted to investigate the role of age and body mass index (BMI) as moderating variables and to estimate the overall changes in gut permeability factors (specifically serum zonulin and LPS for pro- and synbiotics and serum/plasma LPS and fecal calprotectin levels for prebiotics). This was achieved by employing the unrestricted maximum likelihood estimation technique.

2.5.4. Publication bias

To assess the likelihood of publication bias for the outcomes with $\geq$ 10 studies, Egger's regression test, which is weighted, and a visual examination of the symmetry in funnel plots was completed. In instances where publication bias was detected, the non-parametric trim-and-fill method, as proposed by Duval & Tweedie, was implemented to adjust for the bias's effect (Supplementary Material 2: Supplementary File 2.1., Supplementary Figures 2.1 (a. to c.); and Supplementary Material 3: Supplementary File 3.1.).

2.5.5. Sensitivity/influence analysis

A leave-one-out sensitivity analysis was performed to determine the contribution of each trial to the overall effect size calculation. An

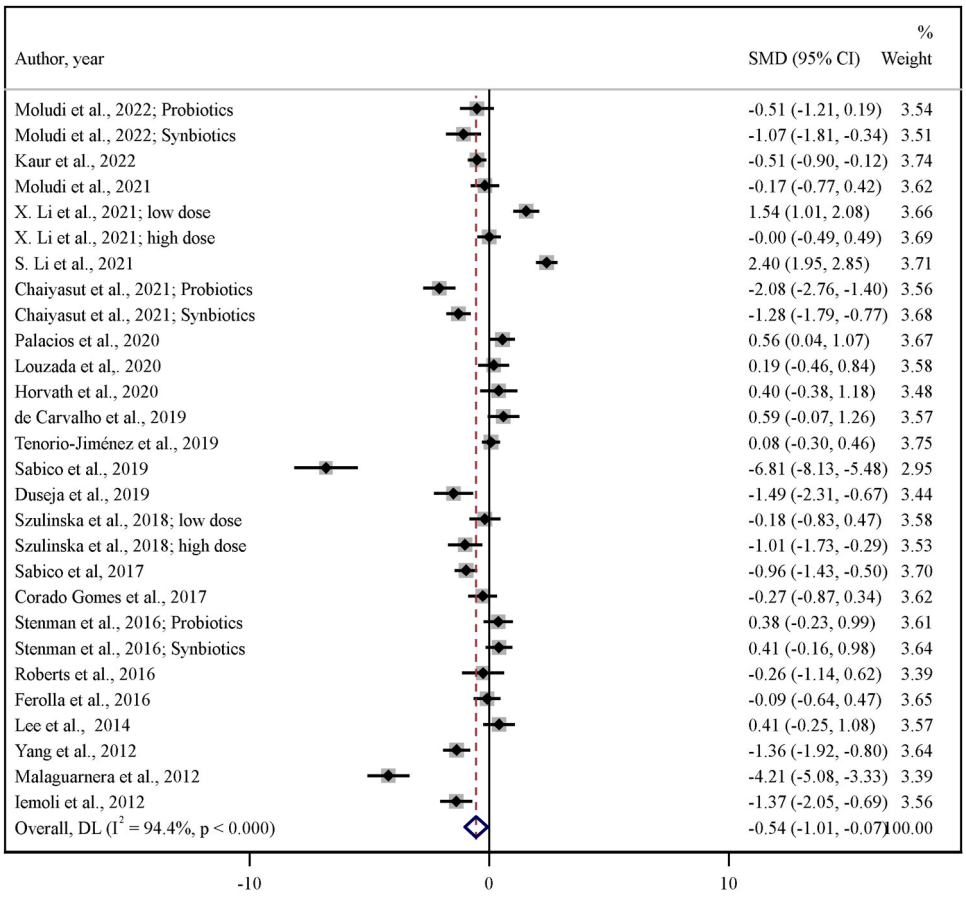

Fig. 2. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of probiotics and synbiotics on serum/plasma lipopolysaccharide (LPS) levels.

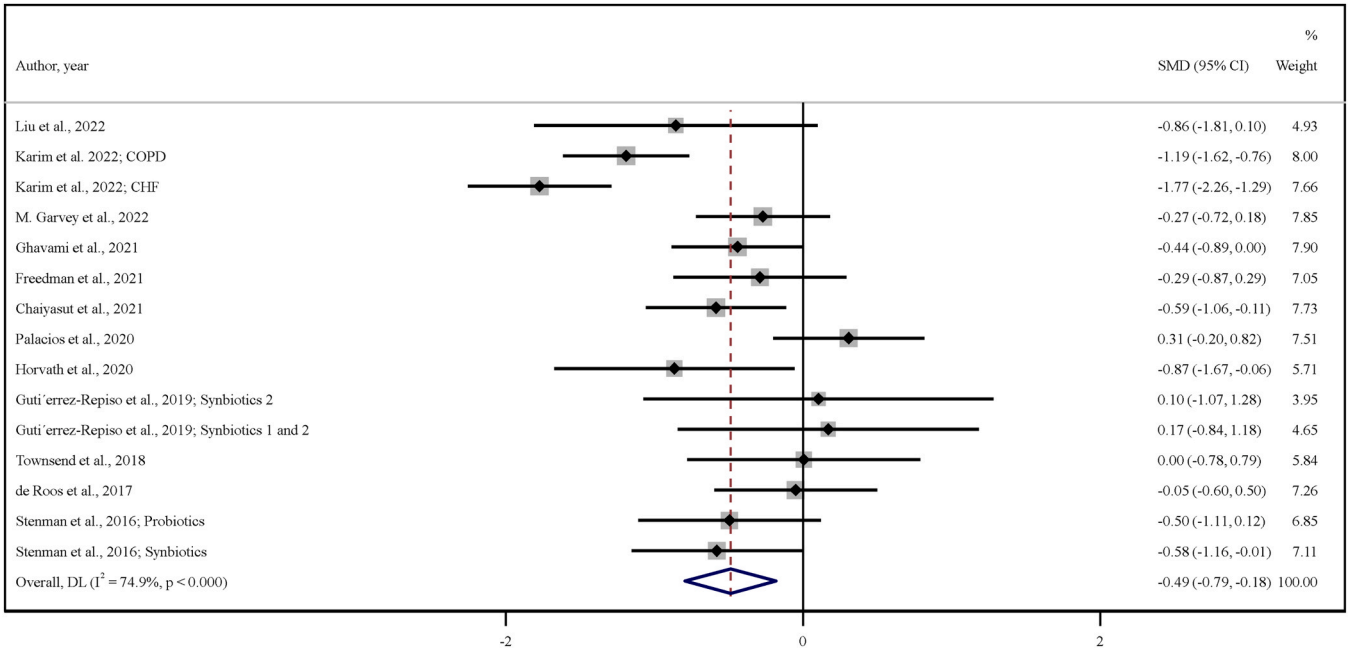

Fig. 3. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of probiotics and synbiotics on serum/plasma zonulin levels.

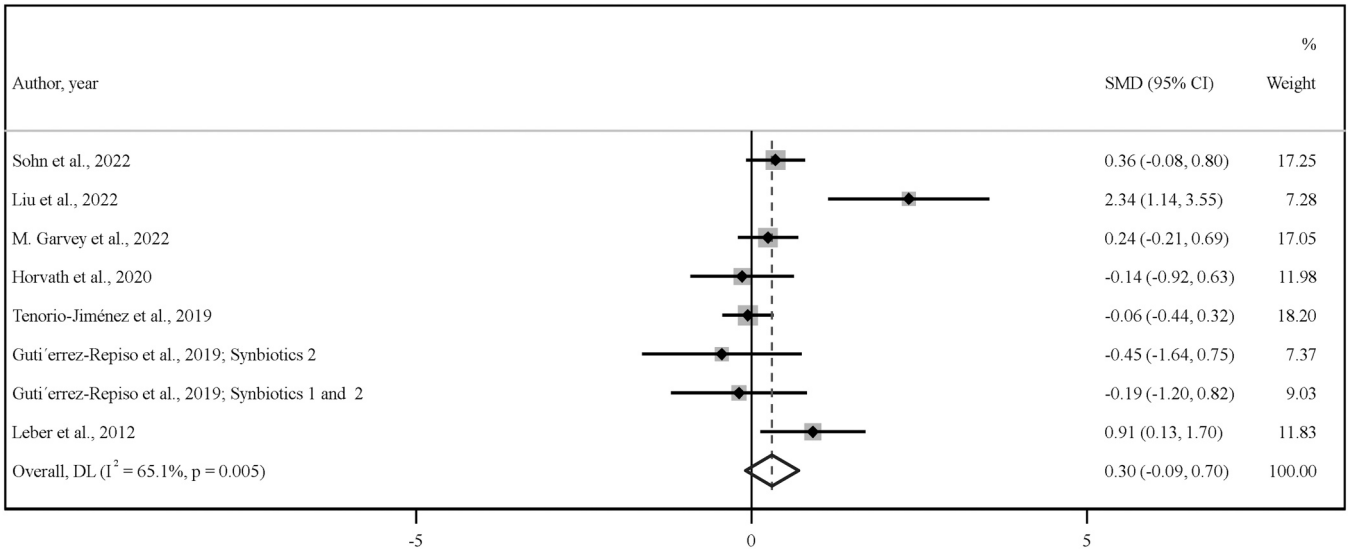

Fig. 4. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of probiotics and synbiotics on serum/plasma lipopolysaccharide-binding protein (LBP) levels.

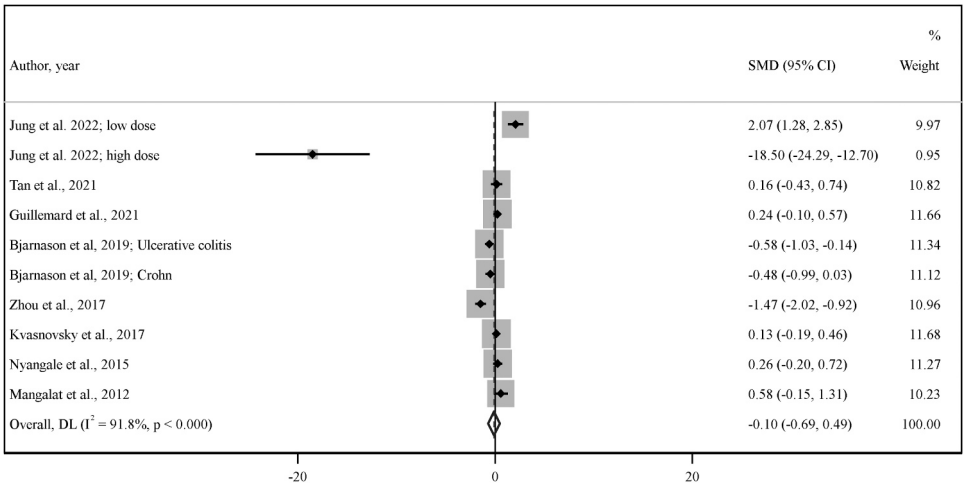

Fig. 5. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of probiotics and synbiotics on fecal calprotectin levels.

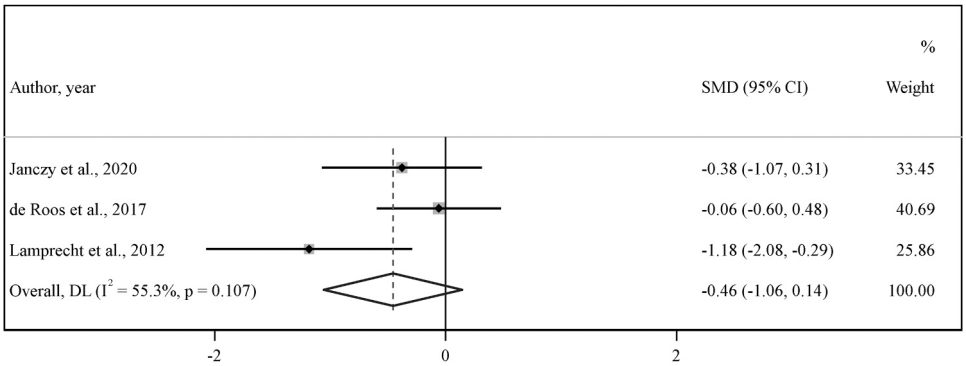

Fig. 6. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of probiotics and synbiotics on fecal zonulin levels.

additional sensitivity analysis was conducted to confirm the impact of study quality on the results by removing RCTs that were deemed to have a high risk of bias (Supplementary Material 2: Supplementary File 2.2, Figures 2.2 (a. to e.), and Supplementary Material 3: Supplementary File 3.2, Figures 3.2 (a to c)).

2.5.6. Certainty of evidence

Evidence certainty was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [13]. Initially, randomized controlled trials (RCTs) are considered to provide a high level of evidence but may be subject to downgrading for several reasons: risk of bias, inconsistency (notable heterogeneity with no clear explanation, I^2 > 50 %; $p < 0.05$), indirectness (factors that reduce the applicability of the study results), imprecision (broad 95 % confidence intervals for the effect size or a sample size smaller than 400), and signs of publication bias. The GRADE methodology categorizes the quality of evidence into four levels: high, moderate, low, and very low (Supplementary Material 2: Supplementary file 2.3; Supplementary Material 3: Supplementary file 3.3).

3. Results

Following the initial search, 3660 records were identified, with 1128 from PubMed and 2532 from SCOPUS. After removing duplicates, 3417 unique records were screened for eligibility. Full text screening was then performed on 292 articles based on predefined inclusion and exclusion criteria. Exclusions were made for various reasons, including not being RCTs (n = 21 studies), lacking relevant outcome measures (n = 38), intervention durations of less than four weeks (n = 41), and absence of appropriate control groups (n = 23). Additional exclusions included studies not assessing prebiotic/probiotic-related biomarkers (n = 15), articles not written in English (n = 3), and studies involving specific patient populations such as children or those with chronic diseases (n = 23). Ultimately, this rigorous screening process led to the exclusion of 222 full-text articles. The final selection comprised 71 studies, with 67 studies contributing to the quantitative meta-analysis. Following a full-text assessment of the retrieved articles, 49 papers were included in the systematic review of probiotics and synbiotics, of which three studies [14–16] investigated trimethylamine and trimethylamine-N-oxide did not reach the minimum number of articles necessary for conducting meta-analysis on these outcomes. Our main goal was to clarify the specific impacts of prebiotics, probiotics, and synbiotics on intestinal permeability. As a result, we chose to analyze prebiotics (n = 22) separately from probiotics and synbiotics (n = 46). Thus, 46 papers on on probiotics and synbiotics were selected for the final quantitative analysis (meta-analysis). Among these, 24 RCTs explored the effects of pro- and synbiotics on serum LPS, 13 RCTs on serum zonulin, 7 RCTs on serum LBP, 8 RCTs on fecal calprotectin, and 3 RCTs on fecal zonulin). Among the 22 studies retrieved for searches on prebiotics, effects on serum LPS were reported in 15 studies, serum LBP in 4 studies, and fecal calprotectin in 5 studies. Fig. 1 depicts this meta-analysis search flow.

The search flow of the current meta-analysis is depicted in Fig. 1.

3.1. Characteristics of included studies on pro- and synbiotics effects on permeability factors

The current systematic review and meta-analysis incorporates data from 46 published papers detailing 52 RCTs. To conduct the meta-analysis, the comparison of each intervention arm with the controls was treated as a single study. A number of the included studies [17–22] presented multiple intervention groups compared to a placebo, resulting in a higher trial count than the number of articles. In total, 52 RCTs enrolled 3208 subjects who were randomly assigned to the control group (n total = 1492; with an average age and BMI of 49 years, and 28 kg/m2, respectively) or intervention consuming either probiotic (in n = 39 studies) or synbiotic supplements (in n = 12 studies). The intervention groups included 1716 subjects, with an average age and BMI of 50 years and 28 kg/m2, respectively. The administered probiotic bacteria primarily included *Lactobacillus* and *Bifidobacterium* bacterial genera. Fructooligosaccharides (FOS), maltodextrin, and inulin were the main ingredients added as prebiotic agents of the administered synbiotic supplements. Almost all trials administered the pro- and synbiotics in the form of capsules. Among the remaining trials, 15 RCTs employed the supplements as powder. The majority of trials applied placebo for the controls, while three trials used no intervention approach. No serious adverse effects were detected in any of the trials.

The characteristics of the included RCTs are demonstrated in Table 2. The research articles were published from 2012 to 2022. Among them, five trials were conducted in China, 5 in the USA, 4 in the UK, 4 in Brazil, 4 in Iran, 3 in Austria, 3 in Korea, 2 in Thailand, 2 in Poland, 2 in Saudi Arabia, 2 in Spain, 2 in India, and 2 in Italy and one each in Japan, Australia, Netherlands , Finland, Germany, Malaysia, UAE, and Pakistan.The trials recruited 13–143 subjects, predominantly patients suffering from obesity and/or overweight (n = 9), followed by liver disorders (n = 5), GI disorders (n = 9), T2DM (n = 4), CAD (n = 3), and MetSyn (n = 3). The intervention duration of the trials varied between 4 weeks to 12 months. Almost all trials applied a parallel design, except for Nyangale et al., 2015 and Tenorio-Jiménez et al., 2019, which were cross-over trials [23,24].

3.2. Characteristics of included studies on prebiotic effects on permeability factors

The meta-analysis encompassed 22 papers (23 trials), with 579 participants in the intervention group and 547 subjects in the control arms (n=1126 in total). Overall, the mean age and BMI of the subjects in the intervention and control groups were estimated to be about 44 years and 30 kg/m2, respectively.

The included RCTs conducted across various countries, with the majority originating from Iran (10 studies), followed by Canada (3 studies), Netherlands (2 studies), Belgium (2 studies), France (1 study), Finland (1 study), Germany (1 study), Japan (1 study), and the UK (1 study).

All included studies focused on prebiotic interventions, with a variety of specific prebiotic substances being administered, including inulin, resistant starch, galacto- or oligooligosaccharides, and arabinoxylan. The health conditions addressed by these studies predominantly included obesity or overweight (n = 9), T2DM (n = 6), NAFLD (n = 3), alongside healthy individuals (n = 3), and other conditions. The age of participants in the intervention groups ranged from 20.1 years in the study by Lecerf et al. [25] to 59.2 years in the study by Canfora et al. [26]. The BMI of participants in the intervention groups varied, with the lowest reported mean BMI being 20.9 in the study by Lecerf et al. [25] and the highest being 36.1 in the study by Dewulf et al. [27]. The duration of the interventions spanned from 28 days to 180 days. Most studies administered the prebiotic intervention daily, with frequencies ranging from once to three times per day. The doses of prebiotics varied considerably, from as low as 5 g per administration to as high as 35 g per day, depending on the study design and specific prebiotic used (Table 3).

3.3. Risk of bias assessment of included studies on pro- and synbiotics effects on permeability factors

Twenty-six RCTs out of 46 trials were ranked as having an overall low risk of bias, 13 RCTs were found to be at high risk of bias, having at least two or more bias domains that were assessed to be of high risk, and/or unclear or inadequate information regarding the domains (predominantly random sequence generation and allocation concealment domains, and/or selective reporting). The remaining seven trials, were assessed as fair quality.

Table 4 demonstrates a detailed overview of domains considered in the risk of bias assessment of each included RCT based on the Cochrane

Table 2
Included studies characteristics in a systematic review and meta-analysis of clinical trials assessing pro- and synbiotics effects on permeability factors.

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
Iemoli, Trabattoni et al. 2012	Italy	RDBPC	AD patients	F/M	Sachet/probiotic	*L. salivarius LS01, B. breve BR03*	2	2 × 10^9 CFU/ strain/day	12 wks	32.4 / 30.9	31 / 15	-
Lamprecht, Bogner et al. 2012	Austria	RDBPC	Trained male athletes	M	Sachet/probiotic	*B. bifidum W23, B. lactis W51, E. faecium W54, L. acidophilus W22, L. brevis W63, L. lactis W58*	2	10^10 CFU/day	14 wks	37.6 / 38.2	11 / 12	23.7 / 23.9
Leber, Tripolt et al. 2012	Austria	Open-label, RCT	MetS	F/M	Bottle/probiotic	*L. casei Shirota*	3	6.5 × 10^9 CFU/day	12 wks	51.5 / 54.5	13 / 15	35.4 / 31.6
Malaguarnera, Vacante et al. 2012	Italy	RDBPC	NASH	F/M	Sachet/synbiotic (FOS)	*B. longum*	1	2.5 g/day	24 wks	46.9 / 46.7	34 / 32	27.3 / 27.2
Mangalat, Liu et al. 2012	USA	DBPC	Healthy adults	F/M	Drops/probiotic	*L. reuteri DSM 17938*	5 drops per day	5 × 10^8 CFU/ day	8 wks	34.6 / 32.9	30 / 10	28.3 / 27.7
Yang, Guo et al. 2012	China	RCT	NASH	F/M	Capsules/probiotic	*B. subtilis, E. faecium*	-	-	4 wks	-	30 / 30	-
Lee, Bose et al. 2014	Korea	RDBPC	Obesity (BMI >25)	F	Capsules/probiotic	*S. thermophilus, L. plantarum, L. acidophilus, L. rhamnosus, B. lactis, B. longum, B. breve*	2	10^10 CFU/day	8 wks	-	25 / 25	28.3 / 28.5
Boutagy, Neilson et al. 2015	USA	RDBP-Cross	Healthy, non-obese males	M	Sachet/probiotic	*L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii, B. longum, B. breve, B. infantis, S. thermophilus*	1	1.125 × 10^11 CFU/day	4 wks	22.8	10	23.3
Nyangale, Farmer et al. 2015	United Kingdom	DBPC-Cross	Healthy adults (65–80 yrs)	F/M	Capsules/probiotic	*B. coagulans GBI−30, 6086 (BC30)*	1	1 × 10^9 CFU/ day	28 days with 21-day washout	65–80	36	18–31
Ferolla, Couto et al. 2016	Brazil	RCT	NASH	F/M	Synbiotic (guar gum, inulin)	*L. reuteri*	2	10^9 CFU/dose (5 g)	12 wks	57.3	27 / 23	32.5 / 32.5
Roberts, Suckling et al. 2016	United Kingdom	RDBPC	Healthy, active individuals	F/M	Capsules/probiotic	*L. acidophilus CUL−60, L. acidophilus CUL−21, B. bifidum CUL−20, B. lactis CUL−34*	1	3 × 10^10 CFU/day	12 wks	-	30	-
Stenman, Lehtinen et al. 2016	Finland	RDBPC	Overweight and obese adults (BMI 28–34.9 kg/m^2)	F/M	Sachets/probiotic	*B. animalis ssp. lactis 420 (B420)*	1	1 × 10^10 CFU/day	24 wks	50.6 / 49.9	48 / 56	31.5 / 31.2
					Synbiotic (LU)	-		12 g + 10^10 CFU/d		47 / 49.9	52 / 56	31.3 / 31.2
de Roos, van Hemert et al. 2017	Netherlands	RDBPC	Migraine patients	F/M	Sachet/probiotic	*B. bifidum W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L.*	1	5 × 10^9 CFU/ day	12 wks	42 / 38	31 / 29	24.2 / 25.6

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
						lactis W19, L. lactis W58						
Gomes, de Sousa et al. 2017	Brazil	DB	Women with excess weight or obesity	F	Sachet/probiotic	*L. acidophilus, L. casei, L. lactis, B. bifidum, B. lactis*	4	2 × 10^10 CFU/day	8 wks	-	21 / 22	24.9–40
Kvasnovsky, Bjarnason et al. 2017	United Kingdom	RDBPC	SUDD	F/M	Symprove/ probiotic	*L. rhamnosus, L. plantarum, L. acidophilus, E. faecium*	1	10^9 CFU/mL	12 wks	60 / 63.5	71 / 72	27.7 / 29.5
Matsumoto, Kitado et al. 2017	Japan	DBPC-PG	Healthy adults	F/M	Powder stick/ probiotic	*B. animalis subsp. lactis LKM512*	1	6 × 10^9 CFU/ day	12 wks	47.1 / 47.1	17 / 10	25.3 / 26.9
Sabico, Al-Mashharawi et al. 2017	Saudi Arabia	RDBPC	T2DM, medication-naïve	F/M	Sachets/probiotic	*B. bifidum W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W19, L. lactis W58*	2	5 × 10^9 CFU/ day	12 wks	48 / 46.6	39 / 39	29.4 / 30.1
Zhou 2017	-	RCT	Active UC	-	Powder/probiotic	*S. boulardii*	-	-	6 wks	-	33 / 32	-
Szulińska, Łoniewski et al. 2018	Poland	RDBPC	Obese postmenopausal women with MetS risk	F	Sachets/probiotic	*B. bifidum W23, B. lactis W51, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W19, L. lactis W58*	2	Low: 2.5 × 10^9 CFU/day, High: 10^10 CFU/day	12 wks	56.38 / 58.72 (Low), 55.16 / 58.72 (High)	24 / 24 (Low), 23 / 24 (High)	36.0 / 36.1 (Low), 36.57 / 36.1 (High)
Townsend, Bender et al. 2018	USA	RDBPC	Division I male baseball athletes, healthy	M	Capsules/probiotic	*B. subtilis DE111*	1	10^10 CFU/day	12 wks	20.1 ± 1.5 yrs	13 / 12	-
Bjarnason, Sission, Hayee 2019	United Kingdom	RDBPC	Asymptomatic UC Asymptomatic CD	F/M	Symprove /probiotic	*L. rhamnosus NCIMB 30174, L. plantarum NCIMB 30173, L. acidophilus NCIMB 30175, E. faecium NCIMB 30176*	1	10^10 CFU/day	4 wks	47.3 / 43.4 41.2 / 39	40 / 41 33 / 29	-
Duseja, Acharya et al. 2019	India	RDBPC	NAFLD	F/M	Capsules/probiotic	*L. paracasei, L. plantarum, L. acidophilus, L. delbrueckii, B. longum, B. infantis, B. breve, S. thermophilus*	6 capsules daily (2 capsules 3x/ day)	675 × 10^9 CFU/day	48 wks	38 / 33	19 / 20	26 / 27
Gutiérrez-Repiso et al. 2019	Spain	RSC	Obesity	F/M	Phase 1 (VLCKD+Synbiotic 1 capsule (prebiotic fiber)	*B. lactis, L. rhamnosus, B. longum ES1*	1	-	VLCKD 2 months, LCD 2 months	48.7 Synbiotic1 + 2 group/ 47 Placebo+Synbiotic2 group/38.2control	15 Synbiotic1 + 2 group/ 9 Placebo+Synbiotic2 group/9 control	32.82 Synbiotic1 + 2 group/ 33 Placebo+Synbiotic2 group/33.1control

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
					Phase 2 (LCD+Synbiotic 2 capsule(prebiotic fiber))	*B. animalis subsp. lactis*						
Sabico, Al-Mashharawi et al. 2019	Saudi Arabia	RDBPC	T2DM	F/M	Sachets/probiotic	*B. bifidum W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W19, L. lactis W58*	2	5 × 10^9 CFU/ day	24 weeks	48 / 46.6	31 / 30	29.4 / 30.1
Tenorio-Jiménez, Martínez -Ramírez et al. 2019	Spain	RCP-SC	MetS	F/M	Capsule/probiotic	*L. reuteri* V3401	1	5 × 10^9 CFU/ day	12 weeks	-	53	-
de Carvalho, Luzia et al. 2019	Brazil	RDBPC-P	Pre-frail elderly, community-dwelling	F/M	Substance/ synbiotic (FOS)	*L. paracasei LPC−31, L. rhamnosus HN001, L. acidophilus NCFM, B. lactis HN019*	2	12 g/day (10^8–10^9 CFU/strain)	24 weeks	76.4 / 79.5	21 / 16	-
Horvath, Leber et al. 2020	Austria	RDBPC-Pilot	Diabesity (Obesity + T2DM)	F/M	Sachets/synbiotic (Omnilogic Plus)	*B. bifidum W23, B. lactis W51 & W52, L. acidophilus W37, L. casei W56, L. brevis W63, L. salivarius W24, L. lactis W58 & W19*	1	1.5 × 10^10 CFU/day + 10 g/day of prebiotics	24 weeks	61 / 59	12 / 14	33 / 34
Janczy, Aleksandrowicz-Wrona et al. 2020	Poland	PRSB	Overweight and obese (BMI ≥ 25 kg/ m^2)	F/M	Capsule/synbiotic (FOS, inulin)	*B. lactis W51, W52, L. acidophilus W22, L. paracasei W20, L. plantarum W21, L. salivarius W24, L. lactis W19*	2–4 capsules/ day	10^9 CFU/g	12 weeks	42.8 / 37.1	36 / 20	33.4 / 34.4
Louzada, Ribeiro ET AL. 2020	Brazil	RDBPC	Elderly with brain disorder symptoms	F/M	Synbiotic (FOS)	*L. paracasei, L. rhamnosus, L.* acidophilus, B. lactis	2	10^9 CFU/ strain/dose + 6 g/dose of prebiotics	24 weeks	77.2 / 77.0	25 / 24	-
Palacios, Vitetta et al. 2020	Australia	RCPS	Prediabetes and early T2DM	F/M	Capsule/probiotic	*L. plantarum, L. bulgaricus, L. gasseri, B. breve, B. animalis sbsp. lactis, B. bifidum, S. thermophilus, and S. boulardii*	4	2 × 10^11 CFU/day	12 weeks	61.4/56.1	30/30	35.5/36.3
Chaiyasut,Tirawat et al. 2021	Thailand	RDBPC	Moderate hypercholesterolemia	F/M	Sachet/ probiotic	*L. paracasei HII01*	1	1.25 × 10^{10} CFU/day	12 weeks	50.8// 54.2	26/26	27.2/ 27.4

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
Chaiyasut, Sivamaruthi et al. 2021	Thailand	RDBPC	Obese adults (BMI $\geq$ 25 kg/m^2, according to Asia-Pacific criteria)	F/M	Sachet/Synbiotic (FOS, inulin)	*L. paracasei, B. longum, B. breve*	1	5 × 10^10 CFU probiotics + 10 g prebiotics/day		54.8/58.9	36/36	28.97/30.01
Chen, Jian et al. 2021	China	DBRCT	Healthy males	M	Sachet/probiotic	*L. acidophilus, L. rhamnosus GG, B. animalis, B. longum*	1	1.32 × 10^11 CFU/day	4 weeks	20–25	20 / 19	18.5–24.0
Freedman, Hill et al. 2021	USA	RDBPC	Healthy (normal weight to mildly obese)	F/M	Capsule/probiotic	*B. subtilis DE111*	1	10^9 CFU/day	4 weeks	36.9 / 34.4	25 / 21	24.9 / 24.7
Ghavami, Khorvash et al. 2021	Iran	MCRPDB	Women with migraines	F	Capsule/symbiotic (FOS)	*L. casei, L. acidophilus, L. rhamnosus, L. helveticus, L. bulgaricus, L. plantarum, L. gasseri, B. breve, B. longum, B. lactis, B. bifidum,* S. *thermophilus*	1	500 mg/ capsule	12 weeks	38.05 / 37.62	40 / 40	27.74 / 27.38
Guillemard, Poirel et al. 2021	Germany	RDBC	H. pylori infection undergoing eradication	F/M	Bottle/probiotic	L. paracasei CNCM I−1518, L. paracasei CNCM I−3689, and L. rhamnosus CNCM I−3690	2	100 g/ bottle	28 DAYS	42.1 / 42.6	68/68	24.8 / 25.0
Li, Yin et al. 2021	China	RDBPC	UC	F/M	Capsule/probiotic	*E. faecalis, L. acidophilus, B. longum*	3	420 mg per capsule	8 weeks	40.83 / 40.79	65/65	23.67 / 23.66
Li, Liu et al. 2021	China	RDBPC	Alcoholic liver injury	M	Bottle/probiotic	*L. casei Shirota (LcS))*	1 2	10^10 CFU/day 2 × 10^10 CFU/day	60 days	51.1/52.6 49.6/ 52.6	58/46 54/46	26.63/25.05 26.76/ 25.06
Moludi, Kafil et al. 2021	Iran	DBRCT	CAD	F/M	Capsule/probiotic	*L. rhamnosus GG (LGG)*	1	1.6 × 10^9 CFU/capsule	12 weeks	56.7 / 57.1	22 / 22	25–35
Tan, Lim et al. 2021	Malaysia	RDBPC	Parkinson's disease with constipation	F/M	Capsule/probiotic	*L. acidophilus, L. reuteri, L. gasseri, L. rhamnosus, B. bifidum, B. longum, E. faecalis, E. faecium*	1	10^10 CFU/day	4 weeks	70.9 / 68.6	34 / 38	-
Garvey, Mah et al. 2022	USA	RDBPC	Healthy adults with mild GI symptoms	F/M	Capsule/probiotic	*B. subtilis BS50*	1	2 × 10^9 CFU/ day	6 weeks	50.4 / 50.5	38 / 38	25.8 / 25.8
Jung, Jung et al. 2022	South Korea	RDBPC	Functional diarrhea with high fecal calprotectin levels	F/M	Powder/probiotic	*Lactiplantibacillus plantarum CJLP243*	1	10^10 CFU/day	8 weeks	51.8 / 50.2	10 / 12	26.4 / 25.2
Jung, Kim et al. 2022	South Korea	RDBPC	Functional diarrhea with high fecal calprotectin levels	F/M	Sachet/synbiotic (FOS)	*L. acidophilus La−14, L. plantarum Lp−115, B. animalis subsp. lactis CBG-C10*	2	$\geq$ 1 × 10^8 CFU/day	8 weeks	49.8 / 46.3	19 / 20	26.0 / 26.1

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Table 2 (*continued*)

Author, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Specific strains	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
Karim, Muhammad et al. 2021	UAE, Pakistan	RCT	Chronic heart failure (CHF)	M	Capsule/probiotic	*B. longum DSM 24736, B. breve DSM 24732, L.* D*SM 24735, S. thermophilus DSM 24731*	1	112 × 10^9 CFU/day	12 weeks	67.6 / 65.5	44 / 48	23.08 / 23.66
Karim, Muhammad et al. 2022	Pakistan	RDBPC	COPD with sarcopenia	M	Capsule/probiotic	*S. thermophilus, B. longum, B. breve, L. acidophilus, L. helveticus, L. paracasei, L. delbrueckii subsp. bulgar*icus	1	112 × 10^9 CFU/day	16 weeks	66.9 / 68.3	47 / 53	23.18 / 24.15
Kaur, Suri et al. 2022	India	RDBPC	PCOS	F	Capsule/probiotic	*L. acidophilus UBLA−34, L. rhamnosus UBLR−58, L. reuteri UBLRu−87, L. plantarum UBLP−40, L. casei UBLC−42, L. fermentum UBLF−31, B. bifidum UBBB−55, and FOS*	Initially 1 capsule/day for 2 months, then 2 capsules/day for the next 4 months	10^10 CFU/day	24 weeks	23.6 / 24.4	52 / 52	26.5 / 27.8
Liu, Chen et al. 2022	China	RSBC	Elderly people	F/M	Probiotic	*Clostridium butyricum*	after each meal	3.5 × 10^5–3.5 × 10^8 CFU	12 weeks	81.64 / 85.38	11 / 8	19.64/21.18
Moludi, Khedmatgozar et al. 2021	Iran	DB−4PC	CAD	F/M	Capsule/probiotic	*L. rhamnosus GG* -	1	1.9 × 10^9 CFU/day	8 weeks	51.25 / 51.82	24 / 24	28.55 / 26.84
					Sachet/synbiotic (inulin)		1	+ 15 g of inulin/day		49.12 / 51.82	24 / 24	27.59 / 26.84
Sohn, Na et al. 2021	South Korea	RDBPC	Obesity (BMI 25–30 kg/m^2)	F/M	Capsule/probiotic	*L. plantarum K50*	2	4 × 10^9 CFU/ day	12 weeks	47.8 / 45.5	35 / 36	27.1 / 27.3

RDBPC: Randomized Double-Blind Placebo-Controlled, RDBPC-Pilot: Randomized Double-Blind Placebo-Controlled Pilot Study, DBPC: Double-Blind Placebo-Controlled, DB: Double-Blind, RCT: Randomized Controlled Trial, RCPS: Randomized Controlled Parallel Study, RSC: Randomized Single-Controlled, DBRCT: Double-Blind Randomized Controlled Trial, RDBP-Cross: Randomized Double-Blind Placebo-Controlled Crossover Study, DBPC-Cross: Double-Blind Placebo-Controlled Crossover Study, RDBPC-P: Randomized Double-Blind Placebo-Controlled with Parallel Groups, PRSB: Prospective Randomized Single-Blind, RCP-SC: Randomized Controlled Parallel-Single Control, RSBC: Randomized Single Blind-Controlled, DB-4PC: Double-Blind, Four-Parallel-Controlled, AD: Atopic Dermatitis, CAD: Coronary Artery Disease, T2DM: Type 2 Diabetes Mellitus, NASH: Non-Alcoholic Steatohepatitis, MetS: Metabolic Syndrome, SUDD: Symptomatic Uncomplicated Diverticular Disease, UC: Ulcerative Colitis, COPD: Chronic Obstructive Pulmonary Disease, PCOS: Polycystic Ovary Syndrome, FOS: Fructooligosaccharides, CFU: Colony-Forming Units, VLCKD: Very-Low-Calorie Ketogenic Diet, LCD: Low-Calorie Diet, F: Female, M: Male, Lactobacillus (L.), Bifidobacterium (B.)

Table 3
Included studies characteristics in a systematic review and meta-analysis of clinical trials assessing prebiotics effects on permeability factors.

Authors, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
Lecerf, Dépeint et al. 2012	France	RDBPC	Healthy volunteers	F/M	XOS	1	6.64 g/day for XOS group	4 weeks	20.1/20	20/20	20.9–21.6
					INU	1	6.64 g/day for INU–XOS group		20.1/20	20/20	21.4/21.6
Dewulf, Cani et al. 2013	Belgium	RDBPC CT	Obese women	F	ITF	2	16 g/day (8 g twice daily)	3 months	47 / 48	15 / 15	36.1 / 35.6
Vulevic, Juric et al. 2013	UK	DBPCCO	Overweight adults with MetS	F/M	B-GOS	1	5.5 g/day	12 weeks (+ 4w WO)	42.8 (M) / 46.4 (F)	45 completed	30.7 (M) / 32.1 (F)
Dehghan, Gargari et al. 2014	Iran	TBRCT	T2DM	F	INU	1	10 g/day	8 weeks	47.8 / 48.7	24 / 25	31.6 / 29.9
Aliasgharzadeh, Dehghan et al. 2015	Iran	TBRCT	T2DM	F	RD	1	10 g/day	8 weeks	49.2 / 49.6	30 / 25	31.8 / 30.8
Clarke, Green-Johnson et al. 2016	Canada	RDBPCCO	Healthy adults	F/M	β2–1 fructan	3	5 g/dose (15 g/ day)	Two 28-day phases + 14d WO	28.1	30	24.2
Karimi, Farhangi et al. 2015	Iran	RTBPC	T2DM	F	RS2	1	10 g/day	8 weeks	49.5 / 48.6	28 / 28	31.5 / 31.0
Stenman, Lehtinen et al. 2016	Finland	RDBPC CT	Overweight and obese adults (BMI 28–34.9 kg/m^2)	F/M	LU	1	12 g/day of LU	6 months	48.8 / 49.9	53 / 56	31.2 / 31.2
Canfora, van der Beek et al. 2017	Netherlands	RDBPC	Overweight or obese prediabetic individuals	F/M	GOS	3	15 g/day of GOS (5 g per dose)	12 weeks	59.2 / 58.4	21 / 23	33.3 / 32.3
Gonai, Shigehisa et al. 2017	Japan	DBCT	T2DM patients and healthy controls	F/M	GOS	1	10 g/day	4 weeks	55 / 54	27 / 25	27.9 / 27.2
Parnell, Klancic and Reimer 2017	Canada	RDBPC	Adults with overweight and obesity	F/M	oligofructose	3	7 g/dose (21 g/ day)	12 weeks	-	20 / 17	30.4 / 29.5
Farhangi, Javid et al. 2017	Iran	RTBPC CT	T2DM	F	Nutriose®06 (resistant dextrin)	1	10 g/day	8 weeks	49.2 / 49.6	30 / 25	31.8 / 30.8
Farhangi, Dehghan and Namazi 2020	Iran	TBPRCT	NAFLD	F/M	RDCSO	2	10 g resistant dextrin + ~20 g Camelina sativa oil/day	12 weeks	43.72 / 42.17	18 / 18	33.74 / 35.39
Müller, Hermes et al. 2020	Netherlands	RPCDB	Healthy adults with slow gut transit	F/M	AXOS	3	15 g/day	12 weeks	36.1 / 35.7	24 / 24	24.7 / 24.2
Kavyani, Saleh-Ghadimi et al. 2021	Iran	RDBPC CT	NAFLD	F/M	CSO + resistant dextrin	1	20 g CSO + 10 g resistant dextrin/ day	12 weeks	43.72 / 42.17	18 / 18	33.74 / 35.39
Neyrinck, Rodriguez et al. 2021	Belgium	RPCT	Obesity	F/M	Inulin-type fructans	1	16 g/day	3 months	-	12 / 12	-
Becker, Schmartz et al. 2022	Germany	MOLCT	Parkinson's disease	F/M	RS	2	10 g/day	8 weeks	64.5 / 61.5	32 / 30	-
Deehan, Zhang et al. 2022	Canada	RCT-Exploratory	Adults with excess weight (BMI: 25–35 kg/m^2)	F/M	AX	1	F: 25 g/day; M: 35 g/day	6 weeks	32.9 across groups	15 / 16	28.7 kg/m^2 across groups
Farhangi, Dehghan et al. 2022	Iran	RTBPC	NAFLD	F/M	RDCSO	2	10 g resistant dextrin + CSO/ day	12 weeks	42.17 / 43.72	18 / 18	33.74 / 35.39

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Table 3 (*continued*)

Authors, year	Geographical location	Study design	participants health conditions	Gender	Type of intervention	Number of supplements per day	Dosage	Intervention duration	Mean age, in intervention/ control	N intervention/ control	Mean BMI, in intervention/ control
Moludi, Khedmatgozar et al. 2021	Iran	RDB4ACT	CAD with depression and inflammation	F/M	INU	1	15 g/day	8 weeks	52.18	24 / 24	27.64 / 26.84
Saleh-Ghadimi, Dehghan et al. 2022	Iran	RCCT	T2DM in obese women	F	RD	1	10 g/day	8 weeks	47.3 / 46.6	33 / 30	35.8 / 34.8
Vaghef-Mehrabani, Harouni et al. 2022	Iran	DBPRCT	Obesity and MDD	F	INU	1	10 g/day	8 weeks	38.55 / 40.96	22 / 23	34.49 / 33.57

Abbreviations: RDBPC: Randomized Double-Blind Placebo-Controlled, RDBPC CT: Randomized Double-Blind Placebo-Controlled Clinical Trial, DBPCCO: Double-Blind Placebo-Controlled Crossover, TBRCT: Triple-Blind Randomized Controlled Trial, RDBPCCO: Randomized Double-Blind Placebo-Controlled Crossover, RTBPC: Randomized Triple-Blind Placebo-Controlled, DBCT: Double-Blind Controlled Trial, TBPRCT: Triple-Blind Placebo Randomized Controlled Trial, RPCDB: Randomized Placebo-Controlled Double-Blind, RPCT: Randomized Placebo-Controlled Trial, MOLCT: Multi-Observational Longitudinal Clinical Trial, RCT-Exploratory: Randomized Controlled Trial - Exploratory, RDB4ACT: Randomized Double-Blind 4-Arm Controlled Trial, RCCT: Randomized Controlled Clinical Trial, DBPRCT: Double-Blind Placebo Randomized Controlled Trial, CO: Crossover, WO: Washout, F: Female, M: Male, INU: Inulin, XOS: Xylo-oligosaccharide, ITF: Inulin-type Fructan, B-GOS: Galactooligosaccharide, RD: Resistant Dextrin, RS2: Resistant Starch, RS: Resistant Starch, AX: Arabinoxylan, AXOS: Arabinoxylan-Oligosaccharides, LU: Litesse® Ultra polydextrose, GOS: Galacto-oligosaccharides, CSO: Camelina sativa oil, RDCSO: Resistant Dextrin and Camelina sativa oil, T2DM: Type 2 Diabetes Mellitus, NAFLD: Non-alcoholic Fatty Liver Disease, CAD: Coronary artery diseasMetS: Metabolic Syndrome, MDD: Major Depressive Disorder.

Risk of Bias Tool for Randomized Controlled Trials I. Over half of the studies provided details on the specific method used for random sequence generation. The majority of the studies were assessed as having a low risk of bias for allocation concealment, mostly low risk for blinding of participants and personnel, followed by selective reporting. All the studies were evaluated as having a low risk of bias concerning the blinding of outcome assessors, as the authors determined that the outcome measurements were not likely to be affected by the absence of blinding. Most studies also demonstrated a low risk of bias for incomplete outcome data and other biases.

3.4. Risk of bias assessment of included studies on prebiotic effects on permeability factors

The evaluation of trial quality in the reviewed RCTs indicated that among the 22 trials assessed, 10 were classified as exhibiting a low risk of bias, seven were considered fair quality, and five were judged to have a high risk of bias. While most trials adequately addressed major sources of bias, such as blinding and selective reporting, many did not sufficiently control for baseline variables or potential confounders in their statistical analyses of study outcomes. Additionally, several RCTs lacked comprehensive descriptions of their methods for random sequence generation and allocation concealment. Further details regarding these quality assessments are presented in Table 5' which delineates the various domains evaluated using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Table 5).

3.5. Quantitative data synthesis of included studies on pro- and synbiotics effects on permeability factors

3.5.1. Pro- and synbiotics and serum LPS

Random-effect meta-analysis on 24 RCTs (with 28 effect sizes) exploring the effects of pro- and synbiotics on serum/plasma LPS revealed a significant reduction in the intervention arm with high heterogeneity (SMD (95 %CI) = -0.54 (-1.01, −0.07); P-value = 0.025; 24 trials (28 effect sizes); 1603 participants). There was a high level of heterogeneity (I^2 (%)= 94.4; $p < 0.001$) and a low evidence certainty according to GRADE scoring (Table 6 and Fig. 2).

According to the subgroup analysis based on the studied subjects' health condition (patients with overweight or obesity, vs. T2DM, or MetSyn, vs. those with other conditions or healthy subjects), the intervention type (RCTs administered probiotics vs. synbiotics agents), or probiotics daily dosage (RCTs administered low-dose vs. high-dose probiotic bacteria), no significant differences were observed between the trials. However, the intervention duration (< 12 weeks vs. ≥ 12 weeks) may have contributed to heterogeneity. The RCTs that administered pro- and synbiotic supplements for at least 12 weeks significantly lowered LPS levels (SMD (95 % CI) = -0.81 (-1.32, −0.30); P = 0.002; 20 effect sizes; $I^2 = 93.0$; P for heterogeneity < 0.001), whereas studies using the supplements for less than this duration did not show significant changes

The decrease in LPS level remained significant when only lower risk of bias trials was considered in the analysis (SMD (95 %CI) = -0.60 (-1.09–0.10); P-value = 0.019; 21 effect sizes; I2 (%) = 93.4; P heterogeneity< 0.001) (Table 4 and Supplementary Material 2, Supplementary file 2.4., Supplementary Figures 2.4 (a-e)).

Meta-regression for age and BMI failed to show any significant findings (Table 8, Supplementary Material 2, Supplementary file 2.5., Supplementary Figures 2.5. (a-b)).

3.5.2. Pro- and synbiotics and serum zonulin

A significant effect of pro- and synbiotics administration on lowering serum/plasma concentrations of zonulin was detected by random effect meta-analysis with high heterogeneity (SMD (95 %CI) = -0.49 (-0.79, −0.18); P-value = 0.002; 13 trials (15 effect sizes); 778 participants). There was a high level of heterogeneity (I^2 (%)= 74.9; $p < 0.001$) and

Table 4
Quality assessment of the studies using the Cochrane Risk of Bias Tool for Randomized controlled trials assessing pro- and synbiotics effects on permeability factors.

Author, date Ref. No.	Quality	Random sequence generation	Allocation concealment	Selective reporting bias	Blinding of participants	Incomplete outcome data	Outcome assessor blinding	Other bias
(Karim, Muhammad et al. 2022) [28]	Fair	U	L	U	L	L	L	L
(Jung, Kim et al. 2022) [29]	Good	L	L	L	L	L	L	L
(Karim, Muhammad et al. 2022) [28]	Good	L	L	U	L	L	L	L
(Kaur, Suri et al. 2022) [30]	Good	L	L	L	L	L	L	L
(Jung, Jung et al. 2022) [31]	Poor	U	L	L	L	L	L	H
(Moludi, Khedmatgozar et al. 2022) [20]	Poor	L	H	L	H	L	L	L
(Liu, Chen et al. 2022) [32]	Poor	U	H	U	L	H	L	L
(Garvey, Mah et al. 2022) [33]	Good	L	L	L	L	L	L	L
(Freedman, Hill et al. 2021) [34]	Poor	U	L	U	L	L	L	H
(Ghavami, Khorvash et al. 2021) [35]	Good	L	L	L	L	L	L	L
(Chaiyasut, Sivamaruthi et al. 2021) [36]	Good	L	L	U	L	L	L	L
(Chaiyasut, Tirawat et al. 2021) [37]	Good	L	L	U	L	L	L	L
(Guillemard, Poirel et al. 2021) [38]	Good	L	L	L	L	L	L	L
(Li, Yin et al. 2021) [39]	Poor	U	U	U	H	L	L	L
(Moludi, Kafil et al. 2021) [40]	Good	L	L	L	L	L	L	L
(Li, Liu et al. 2021) [19]	Good	L	L	U	L	L	L	L
(Sohn, Na et al. 2021) [41]	Poor	U	L	U	L	U	L	L
(Tan, Lim et al. 2021) [42]	Good	L	L	U	L	L	L	L
(Louzada and Ribeiro 2020) [43]	Good	L	L	U	L	L	L	L
(Palacios, Vitetta et al. 2020) [44]	Good	L	L	L	L	L	L	L
(Horvath, Leber et al. 2020) [45]	Fair	L	L	L	L	H	L	L
(Janczy, Aleksandrowicz-Wrona et al. 2020) [46]	Poor	U	U	U	L	H	L	L
(Bjarnason, Sission and Hayee 2019) [17]	Good	L	L	U	L	L	L	L
(Gutiérrez-Repiso, Hernández-García et al. 2019) [18]	Poor	L	L	L	L	U	L	H
(de Carvalho, Luzia et al. 2019) [47]	Good	L	L	U	L	L	L	L
(Duseja, Acharya et al. 2019) [48]	Fair	L	L	L	L	H	L	L
(Tenorio-Jiménez, Martínez-Ramírez et al. 2019) [24]	Good	U	L	L	L	L	L	L
(Sabico, Al-Mashharawi et al. 2019) [49]	Fair	L	L	L	L	H	L	L
(Townsend, Bender et al. 2018) [50]	Fair	U	L	U	L	L	L	L
(Szulińska, Łoniewski et al. 2018) [22]	Good	L	U	L	L	L	L	L
(de Roos, van Hemert et al. 2017) [51]	Fair	L	L	L	L	H	L	L
(Gomes, de Sousa et al. 2017) [52]	Good	U	L	L	L	L	L	L
(Sabico, Al-Mashharawi et al. 2017) [53]	Good	L	L	L	L	U	L	L
(Kvasnovsky, Bjarnason et al. 2017) [54]	Good	L	L	L	L	L	L	L
(Ferolla, Couto et al. 2016) [55]	Poor	U	H	U	H	L	L	L
(Zhou 2017) [56]	Poor	U	U	U	U	L	L	U
(Roberts, Suckling et al. 2016) [57]	Good	L	L	U	L	L	L	L
(Nyangale, Farmer et al. 2015) [23]	Fair	U	L	U	L	L	L	L
(Stenman, Lehtinen et al. 2016) [21]	Good	L	L	L	L	L	L	L
(Lee, Bose et al. 2014) [58]	Good	U	L	L	L	L	L	L

(continued on next page)

Table 4 (*continued*)

Author, date Ref. No.	Quality	Random sequence generation	Allocation concealment	Selective reporting bias	Blinding of participants	Incomplete outcome data	Outcome assessor blinding	Other bias
(Iemoli, Trabattoni et al. 2012) [59]	Poor	U	L	U	L	L	L	H
(Lamprecht, Bogner et al. 2012) [60]	Good	L	L	U	L	L	L	L
(Malaguarnera, Vacante et al. 2012) [61]	Good	L	L	U	L	L	L	L
(Mangalat, Liu et al. 2012) [62]	Good	L	L	L	L	L	L	L
(Yang, Guo et al. 2012) [63]	Poor	U	U	U	U	L	L	U
(Leber, Tripolt et al. 2012) [64]	Poor	L	H	U	H	L	L	L

Low risk of bias (L, possible bias unlikely to seriously alter the trial findings).
High risk of bias (H, possible bias that seriously weakens confidence in the trial findings).
Unclear risk of bias (U, possible bias that raises some doubt about the trial findings).

Table 5
Quality assessment of the studies using the Cochrane Risk of Bias Tool for Randomized controlled trials assessing prebiotics effects on permeability factors.

		Quality	Random sequence generation	Allocation concealment	Selective reporting bias	Blinding of participants	Incomplete outcome data	Outcome assessor blinding	Other bias
(Deehan, Zhang et al. 2022)	[65]	Fair	L	L	L	H	L	L	L
(Becker, Schmartz et al. 2022)	[66]	Poor	H	H	L	H	L	L	H
(Farhangi, Dehghan et al. 2022)	[67]	Good	L	L	L	L	L	L	L
(Moludi, Khedmatgozar et al. 2021)	[20]	Poor	L	H	L	H	L	L	L
(Vaghef-Mehrabani, Harouni et al. 2022)	[68]	Fair	L	L	L	L	H	L	L
(Saleh-Ghadimi, Dehghan et al. 2022)	[69]	Good	L	U	L	L	L	L	L
(Neyrinck, Rodriguez et al. 2021)	[70]	Fair	U	U	L	L	L	L	L
(Kavyani, Saleh-Ghadimi et al. 2021)	[71]	Good	L	L	L	L	L	L	L
(Müller, Hermes et al. 2020)	[72]	Fair	L	L	L	L	L	L	H
(Farhangi, Dehghan and Namazi 2020)	[73]	Good	L	L	L	L	L	L	L
(Farhangi, Javid et al. 2017)	[74]	Good	L	L	L	L	L	L	L
(Canfora, van der Beek et al. 2017)	[75]	Fair	L	L	L	L	L	L	H
(Gonai, Shigehisa et al. 2017)	[76]	Fair	L	L	L	L	L	L	H
(Parnell, Klancic and Reimer 2017)	[77]	Fair	L	L	H	L	L	L	L
(Stenman, Lehtinen et al. 2016)	[21]	Good	L	L	L	L	L	L	L
(Karimi, Farhangi et al. 2015)	[78]	Good	L	L	L	L	L	L	L
(Clarke, Green-Johnson et al. 2016)	[79]	Good	L	L	U	L	L	L	L
(Aliasgharzadeh, Dehghan et al. 2015)	[80]	Good	L	L	L	L	L	L	L
(Dehghan, Gargari et al. 2014)	[81]	Good	L	L	L	L	L	L	L
(Dewulf, Cani et al. 2013)	[27]	Poor	U	L	L	L	H	L	U
(Vulevic, Juric et al. 2013)	[82]	Poor	U	U	U	L	L	L	L
(Lecerf, Dépeint et al. 2012)	[25]	Poor	U	L	L	L	L	L	H

Low risk of bias (L, possible bias unlikely to seriously alter the trial findings).
High risk of bias (H, possible bias that seriously weakens confidence in the trial findings).
Unclear risk of bias (U, possible bias that raises some doubt about the trial findings).

moderate evidence certainty according to GRADE scoring (Table 6 and Fig. 3).

The form of intervention administered in the trials, the applied dosage for the intervention, age, and BMI of the studied populations seemed to be the main sources of heterogeneity according to the subgroup and the meta-regression analyses conducted. The administration of both probiotics and synbiotics resulted in significant reductions in zonulin concentrations. However, pooling the results of the trials using synbiotic agents showed a non-significant result with very low heterogeneity (for probiotics supplements: SMD (95 %CI) = -0.52

Table 6
Subgroup analysis of trials assessing the effects of pro- and synbiotics on permeability factors, categorized by participants' health conditions, type of intervention, follow-up duration, total daily dose of probiotic bacteria, and form of intervention.

	N (effect sizes)	SMD (95 %CI)*	P value	I^2 (%)	P heterogeneity	P between
Plasma/ serum lipopolysaccharide (LPS)						
All included trials (24 trials)	28	−0.54 (−1.01, −0.07)	0.025	94.4	< 0.001	
Health conditions						
Patients with T2DM, MetSyn, PCOS, or CAD	9	−0.85 (−1.58, −0.11)	0.024	93.5	< 0.001	0.728
Patients with GI or liver disorders	7	−0.43 (−1.87, 1.00)	0.554	97.7	< 0.001	
Patients with overweight, obesity, or hypercholesterolemia	8	−0.45 (−1.08, 0.18)	0.164	88.0	< 0.001	
Those with other conditions or Healthy subjects	4	−0.21 (−1.09, 0.67)	0.641	83.6	< 0.001	
Form of intervention						
Probiotics	18	−0.54 (−1.17, 0.11)	0.098	95.3	< 0.001	0.955
Synbiotics	10	−0.56 (−1.25, −0.13)	0.111	92.0	< 0.001	
Intervention duration						
< 12 weeks	8	0.15 (−0.81, 1.12)	0.754	95.6	< 0.001	0.084
≥ 12 weeks	20	−0.81 (−1.32, −0.30)	0.002	93.0	< 0.001	
Probiotics daily dosage**						
Low dose	11	−0.81 (−1.46, −0.15)	0.016	92.1	< 0.001	0.157
High dose	14	−0.22 (−0.71, 0.28)	0.390	89.7	< 0.001	
Risk of bias assessment						
Poor	6	−0.32 (−1.69, 1.04)	0.642	96.8	< 0.001	0.716
Good/Fair	21	−0.60 (−1.09–0.10)	0.019	93.4	< 0.001	
Plasma/ serum zonulin						
All included trials (13 trials)	15	−0.49 (−0.79, −0.18)	0.002	74.9	< 0.001	
Health conditions						
Unhealthy	12	−0.56 (−0.93, −0.19)	0.004	78.3 %	< 0.001	0.221
Healthy	3	−0.23 (−0.55, 0.10)	0.167	0.00	0.812	
Form of intervention						
Probiotics	9	−0.52 (−0.99, −0.04)	0.032	84.5	< 0.001	0.910
Synbiotics	6	−0.49 (−0.74, −0.24)	< 0.001	0.00	0.588	
Intervention duration						
< 12 weeks	3	−0.25 (−0.59, 0.10)	0.159	0.00	0.830	0.231
≥ 12 weeks	12	−0.55 (−0.92, −0.19)	0.003	78.7	< 0.001	
Probiotics daily dosage**						
Low dose	6	−0.29 (−0.52, −0.06)	0.013	0.00	0.687	0.116
High dose	7	−0.75 (−1.26, −0.23)	0.005	84.7	< 0.001	
Risk of bias assessment						
Poor	4	−0.27 (−0.69, 0.15)	0.203	0.00	0.464	0.324
Good/ fair	11	−0.55 (−0.91, −0.19)	0.003	80.5	< 0.001	
*Plasma/ serum lipopolysaccharide-binding protein (LBP)****						
All included trials (7 trials)	8	0.30 (−0.09, 0.70)	0.134	65.1	0.005	
Health conditions						
Patients with overweight, or obesity	3	0.17 (−0.26, 0.60)	0.451	8.5	0.335	0.616
Patients with T2DM, or MetSyn	3	0.19 (−0.40, 0.77)	0.531	61.3	0.076	
Those with other conditions or Healthy subjects	2	1.21 (−0.84, 3.27)	0.245	90. 2	0.001	
Form of intervention						
Probiotics	4	0.67 (−0.05, 1.39)	0.067	82.2	< 0.001	0.183

(*continued on next page*)

Table 6 (*continued*)

	N (effect sizes)	SMD (95 %CI)*	P value	I^2 (%)	P heterogeneity	P between
Synbiotics	4	0.13 (−0.21, 0.47)	0.456	0.0	0.426	
Probiotics daily dosage**						
Low dose	4	0.47 (−0.10,1.04)	0.105	79.1	0.002	0.885
High dose	2	0.38 (−0.653, 1.42)	0.469	71.8	0.060	
Risk of bias assessment						
Poor	5	0.57 (−0.17, 1.31)	0.130	72.7	0.005	0.188
Good/Fair	3	0.04 (−0.23, 0.31)	0.762	0.0	0.538	
*Fecal calprotectin****						
All included trials (8 trials)	10	−0.10 (−0.69, 0.49)	0.733	91.8	< 0.001	
Health conditions						
Patients with GI disorders	8	−0.28 (−1.00, 0.45)	0.453	93.3 %	< 0.001	0.134
Healthy subjects	2	0.35 (−0.04, 0.74)	0.077	0.00	0.470	
Probiotics daily dosage						
Low dose	4	0.69 (0.00, 1.39)	0.051	85.3	< 0.001	0.017
High dose	4	−1.10 (−2.39, 0.20)	0.097	92.8	< 0.001	
Risk of bias assessment¥						
Fecal zonulin						
All included trials	3	−0.46 (−1.06, 0.14)	0.136	55.3	0.107	

NAFLD: non alcoholic fatty live disease; MetSyn: metabolic syndrome; T2DM: type 2 diabetes mellitus ' CAD: coronary artery disease; PCOS: Polycystic Ovary Syndrome; GI: gastrointestinal.

* Standardized Mean Differences (SMD) with 95 % Confidence Intervals (95 % CI).

** Note 1: Some studies did not provide sufficient information for this subgroup analysis.

*** Note 2: Other subgroup analysis were not applicable.

¥ Note 3: Subgroup analysis based on the risk of bias assessment was not applicable, as only one study remained in the subgroup.

(-0.99, −0.04); P-value = 0.032; 9 effect sizes; I2 (%) = 84.5; P heterogeneity< 0.001; for synbiotics supplements: SMD (95 %CI) = -0.49 (-0.74, −0.24); P-value < 0.001; 6 effect sizes; I2 (%) = 0.00; P heterogeneity= 0.588). Besides, both RCTs administering low-dose and high-dose probiotic bacteria significantly reduced zonulin levels (for low-dose probiotics: SMD (95 %CI) = -0.29 (-0.52, −0.06); P-value = 0.013; 6 trials; I2 (%) = 0.00; P heterogeneity= 0.687; for high-dose probiotics: SMD (95 %CI) = -0.75 (-1.26, −0.23); P-value = 0.005; 7 trials; I2 (%) = 84.7; P heterogeneity< 0.001), indicating negligible heterogeneity for the low-dose group. Subgroup analyses based on participants' health conditions (unhealthy vs. healthy subjects) and intervention duration (< 12 weeks vs. ≥12 weeks) revealed no significant differences. When only lower risk of bias trials was considered in the analysis, the decrease in zonulin levels following pro-and synbiotics supplementation remained significant with high heterogeneity (SMD (95 %CI) = -0.55 (-0.91, −0.19); P-value = 0.003; 11 effect sizes; I^2 (%) = 80.5; P heterogeneity< 0.001) (Table 6, Supplementary Material 2, Supplementary file 2.6, and Supplementary Figure 2.6 (a-e)).

In the present meta-analysis, meta-regression findings revealed that a significant, though weak, relationships exist between serum /plasma zonulin changes and the studied subjects' mean age and BMI. Age significantly moderates the effect of probiotics on serum zonulin (P-value = 0.025). BMI also significantly moderates the effect of probiotics on serum zonulin (P-value = 0.048). Specifically, older individuals with lower BMI exhibited reduced effect sizes of serum/plasma zonulin following pro- and synbiotics supplementation (Table 8, Supplementary Material 2, Supplementary file 2.7., Supplementary Figures 2.7. (a-b)).

3.5.3. Pro- and synbiotics and serum LBP

Our random effect meta-analysis of 8 RCTs also indicated no significant changes in serum/plasma LBP levels following consuming pro-and synbiotic supplements (SMD (95 % CI) = 0.30 (-0.09, 0.70); P-value = 0.134; 7 trials (8 effect sizes); 369 participants). There was a moderate level of heterogeneity (I^2 (%)= 65.1; p = 0.005) and moderate evidence certainty according to GRADE scoring (Table 6, Fig. 4).

No significant differences between the trials were noted for subgroup analysis based on the studied subjects' health condition (patients with overweight or obesity, vs. T2DM, or MetSyn, vs. those with other conditions or healthy subjects), the intervention type (RCTs administered probiotics vs. synbiotics agents), the intervention duration (< 12 weeks vs. ≥12 weeks), or probiotics daily dosage (RCTs administered low-dose vs. high-dose probiotic bacteria). After excluding the high risk of bias RCTs, the same non-significant findings were also observed with very low heterogeneity (Table 6 and Supplementary Material 2, Supplementary file 2.8., Supplementary figure 2.8 (a-d)).

Meta-regression for age and BMI failed to find any significant relationships (Table 8, Supplementary Material 2, Supplementary file 2.9., Supplementary Figures 2.9. (a-b)).

3.5.4. Pro- and synbiotics and fecal calprotectin

According to the random effect meta-analysis, pro-and synbiotic administration had no significant effects on fecal calprotectin levels with high heterogeneity (SMD (95 %CI) = -0.10 (-0.69, 0.49); P-value = 0.733; 8 trials (10 effect sizes); 705 participants). There was a high level of heterogeneity (I2 (%) = 91.8; P heterogeneity< 0.001) and very low evidence certainty according to GRADE scoring (Table 6, Fig. 5).

The subgroup analysis showed the administered dosage of intervention was an effective factor for the high heterogeneity, such that supplementation with low-dose bacterial agents resulted in a marginal increment in levels of fecal calprotectin levels (SMD (95 %CI) = 0.69 (0.00, 1.39); P-value = 0.051; 4 effect sizes; I2 (%) = 85.3; P heterogeneity< 0.001), whereas no significant changes were noted in the RCTs administering high-dose bacteria. However, no significant changes were identified in serum fecal calprotectin levels when performing the

Table 7
Subgroup analysis of trials assessing the effects of prebiotics on permeability factors, categorized by participants' health conditions, intervention duration, and quality of the trials.

	N (effect sizes)	SMD (95 %CI)*	P value	I^2 (%)	P heterogeneity	P between
Serum/Plasma *lipopolysaccharide (LPS)*						
All included trials (15 effect sizes)	16	−0.88 (−1.28, −0.47)	< 0.001	85.7	< 0.001	
Health conditions						
Patients with overweight, or obesity	4	−0.25 (−0.67, 0.18)	0.252	52.9	0.095	< 0.001
T2DM, NAFLD, or CVD	9	−1.40 (−1.80, −0.996)	< 0.001	73.1	< 0.001	
Healthy subjects	3	−0.01 (−0.49, 0.48)	0.979	35.8	0.211	
Intervention duration						
< 2 months	3	−0.01 (−0.49, 0.48)	0.979	35.8	0.211	0.001
≥ 2 months	13	−1.06 (−1.49, −0.63)	< 0.001	85.2	< 0.001	
Risk of bias assessment						
Poor	4	−0.20 (−0.54, 0.15)	0.259	0.0	0.755	0.003
Good/Fair	12	−1.09 (−1.58, −0.60)	< 0.001	88.0	< 0.001	
Serum/Plasma lipopolysaccharide-binding protein (LBP)						
All included trials	4	0.26 (−0.04, 0.56)	0.091	0.0	0.926	
Risk of bias assessment**						
Fecal calprotectin: Studies included						
All included trials	5	- 1.08 (−2.96, 0.80)	0.258	97.2	< 0.001	
Health conditions						
Patients with overweight, obesity, or MetSyn	3	−1.81 (−5.88, 2.25)	0.382	98.5	< 0.001	0.398
Other conditions	2	−0.05 (−0.44, 0.33)	0.796	0.00	0.590	
Risk of bias assessment						
Poor	2	−3.14 (−9.04, 2.76)	0.296	99.9	< 0.001	0.261
Fair	3	0.26 (−0.40, 0.92)	0.435	59.9	0.083	

NAFLD: non-alcoholic fatty live disease; MetSyn: metabolic syndrome; T2DM: type 2 diabetes mellitus; CVD: Cardiovascular disease;
* Standardized Mean Differences (SMD) with 95 % Confidence Intervals (95 % CI).
** Note 1: Subgroup analysis based on the risk of bias assessment was not applicable, as all studies were ranked fair.

Table 8
Meta-Regression Analysis of Potential Moderators in Trials Assessing the Effects of Pro- and Synbiotics on Permeability Factors *.

	Coefficient (95 % CI)	P value	Residual heterogeneity: I2 (%)	R-squared (%)
Probiotics and serum LPS				
Age	0.04 (−0.05, 0.13)	0.378	94.60	−1.14
BMI	0.02 (−0.09, 0.13)	0.737	94.84	−4.38
Probiotics and serum zonulin				
Age	−0.02 (−0.04, −0.003)	0.025	63.57	37.79
BMI	0.07 (0.00, 0.14)	0.048	66.04	32.12
Probiotics and serum LBP				
Age	0.22 (−0.06, 0.49)	0.101	55.10	41.35
BMI	−0.08 (−.19, 0.02)	0.087	55.53	32.31
Probiotic and fecal calprotectin**				
Age	−0.26 (−1.68, 1.16)	0.683	92.18	−24.79

* Age and body mass index (BMI).
** Note 1: Some studies did not provide sufficient information for this analysis.

subgroup analysis based on the subject's health conditions (patients with GI disorders vs. healthy subjects). These non-significant changes were obtained when only high-quality RCTs were analyzed (Table 6 and Supplementary Material 2, Supplementary file 2.10., Supplementary Figure 2.10 (a-c)).

Meta-regression for mean age and BMI did not show significant findings (Table 8, Supplementary Material 2, Supplementary file 2.11., Supplementary Figures 2.11. a).

3.5.5. *Pro- and synbiotics and fecal zonulin*

The random-effect meta-analysis conducted on 3 RCTs enrolled 91 subjects showed that pro-and synbiotic supplementation had no significant effects on fecal zonulin levels with moderate heterogeneity (SMD (95 %CI) = -0.46 (-1.06, 0.14); P-value = 0.136; 3 trials; 91 participants; very low certainty of evidence; I2 (%) = 55.3; P heterogeneity= 0.107) (Table 6, and Fig. 6).

3.6. *Quantitative data synthesis of included studies on prebiotic effects on permeability factors*

3.6.1. *Prebiotics, serum/plasma LPS, and LBP*

A significant reduction in serum/plasma LPS levels was detected following supplementation with prebiotics with high heterogeneity, according to the random-effect meta-analysis on data from 15 RCTs (16

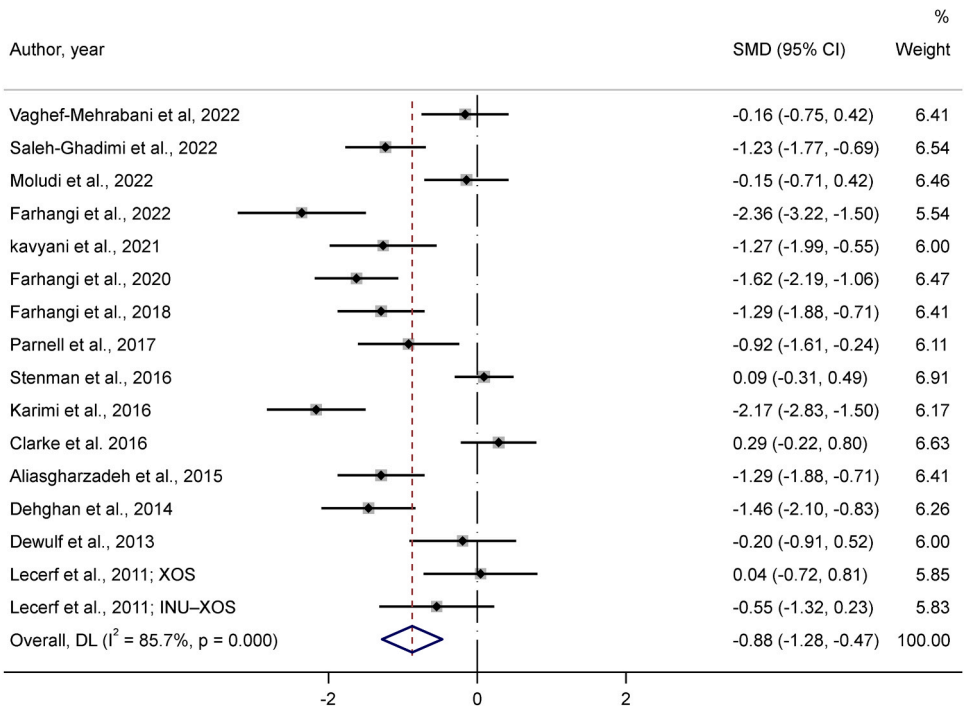

Fig. 7. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of prebiotic administration on serum/plasma lipopolysaccharide (LPS) levels.

effect sizes) with 792 subjects (SMD (95 %CI) = -0.88 (-1.28, −0.47); P-value < 0.001). There was a high level of heterogeneity (I^2 (%)= 85.7; p < 0.001) and a high evidence certainty according to GRADE scoring (Table 7 and Fig. 7).

The studied participants' health condition as well as intervention duration were identified as probable sources for heterogeneity. According to the results of subgroup analysis based on the studied subjects' health conditions, in comparison with the RCTs involving overweight or obese individuals and healthy subjects, the RCTs on patients suffering from T2DM, NAFLD, or CVDs were found to show a significant reduction in LPS concentrations (SMD (95 %CI) = -1.40 (-1.80, −1.00); P-value < 0.001; 9 effect sizes; I2 (%) = 73.1; P heterogeneity< 0.001). However, the reduction in LPS levels did not achieve statistical significance when the subgroup analysis was conducted on RCTs involving overweight or obese vs. healthy individuals. Moreover, the RCTs that administered prebiotic supplements for at least 2 months significantly reduced LPS levels (SMD (95 %CI) = −1.06 (−1.49, −0.63); P-value = <0.001; 13 effect sizes; I2 (%) = 85.2; P heterogeneity< 0.001). In contrast, studies that used the supplements for less than 2 months did not show significant changes.

The significant findings were also repeated when excluding the RCTs, which were at high risk of bias (SMD (95 %CI) = −1.09(−1.58, −0.60); P-value < 0.001; 12 effect sizes; I2 (%) = 88.0; P heterogeneity< 0.001) (Table 7 and Supplementary Material 3, Supplementary file 3.4., Supplementary figure 3.4 (a-c)).

Furthermore, in our random effect meta-analysis of 4 RCTs with 175 participants, prebiotic supplementation failed to significantly affect serum/plasma LBP levels. No significant heterogeneity was detected (I^2 (%)= 0.00; p = 0.926), and a low evidence certainty was noted according to GRADE scoring (Table 7, Fig. 8).

Meta-regression for BMI and age did not find significant effects of these variables on the studied outcomes (Table 9 and Supplementary Material 3, Supplementary file 3.5., Supplementary figure 3.5 (a-b)).

3.6.2. *Prebiotics and fecal calprotectin*

Prebiotic supplementation did not significantly change the fecal

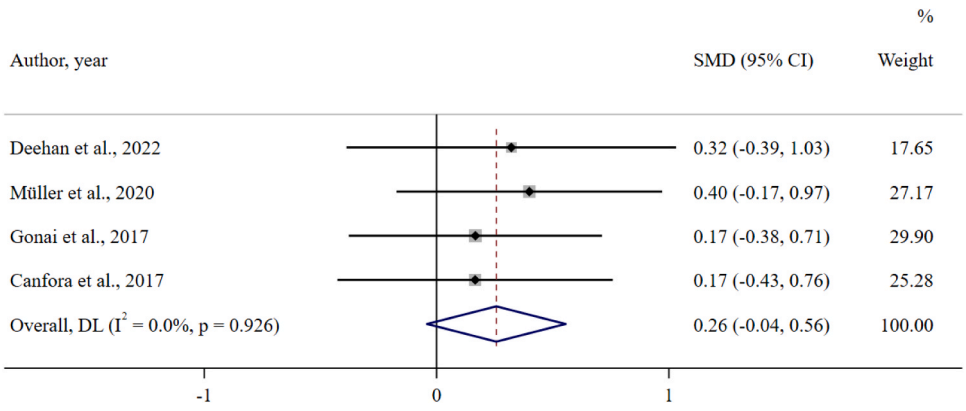

Fig. 8. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of prebiotic administration on serum/plasma lipopolysaccharide-binding protein (LBP) levels.

Table 9
Meta-Regression Analysis of Potential Moderators in Trials Assessing the Effects of Prebiotics on Permeability Factors*.

	Coefficient (95 % CI)	P value	Residual heterogeneity: I2 (%)	R-squared (%)
Prebiotics and serum LPS				
Age	−0.04 (−0.08, 0.01)	0.103	84.55	13.95
BMI	−0.08 (−0.17, 0.01)	0.074	83.52	17.99
Prebiotic and fecal calprotectin				
Age	−0.03 (−0.70, 0.65)	0.881	98.59	−49.57
BMI **				

* Age and body mass index (BMI).
** Note 1: Some studies did not provide sufficient information for this analysis.

calprotectin levels, according to the results of random effect meta-analysis on data from 5 RCTS with 246 participants. There was a high level of heterogeneity (I^2 (%)= 97.2; $p < 0.001$) and very low certainty of evidence according to GRADE scoring (Table 7 and Fig. 9).

Based on the subgroup analysis performed according to the study population's health status, no significant differences were identified between RCTs enrolling patients with MetSyn or overweight/obesity vs. those with other disorders. These non-significant results were also repeated when excluding the RCTs, which were at high risk of bias (Table 7 and Supplementary Material 3, Supplementary file 3.6.; Supplementary Figure 3.6 (a-b)).

The results of the performed meta-regression for age and BMI did not show any significant findings (Table 9 and Supplementary Material 3, Supplementary file 3.7.; Supplementary file 3.7.a).

5. Publication bias of included studies on pro- and synbiotics effects on permeability factors

The Egger's test found no evidence of potential publication bias regarding the effects of probiotic and synbiotic supplementation on the explored outcomes, apart from serum LPS. Consequently, the trim-and-fill analysis was conducted. No new studies were imputed which indicated no publication bias may be present in the data on probiotic and synbiotic administration on serum LPS (Supplementary Material 2, Supplementary File 2.1, Supplementary Figure 2.1 (a)).

Notably, although the funnel plot for zonulin appears asymmetrical, Egger's test did not detect any publication bias (Supplementary Material 2, Supplementary File 2.1, Supplementary Figure 2.1.b).

3.7. Publication bias of included studies on prebiotic effects on permeability factors

We conducted the publication bias only for LPS since the number of studies for the other two outcomes was less than 10. No significant asymmetry in effect sizes was observed, suggesting minimal risk of publication bias. Additionally, Egger's linear regression test did not provide evidence of publication bias (Supplementary Material 3, Supplementary File 3.1, Supplementary Figure 3.1).

3.8. Influence/Sensitivity analysis of included studies on pro- and synbiotics effects on permeability factors

According to the influence analysis conducted, the summary SMD on plasma/serum zonulin, LPS, and LBP levels, alongside fecal calprotectin and zonulin levels, was robust and remained unchanged when each trial was sequentially excluded from the main meta-analysis (Supplementary Material 2, Supplementary File 2.2, Supplementary Figure 2.2 (a-e)).

3.9. Influence/Sensitivity analysis of included studies on prebiotic effects on permeability factors

The summary SMD on serum/plasma LPS and LBP, as well as fecal calprotectin levels, seemed robust and did not change when each study was sequentially eliminated from the main meta-analysis (Supplementary Material 3, Supplementary File 3.2, Supplementary Figure 3.2 (a-c)).

4. Discussion

This meta-analysis revealed promising findings regarding the efficacy of pro- and synbiotic supplements on alleviating "leaky gut", as reflected by lowering some of the key markers of intestinal permeability including LPS and zonulin, when compared to controls. On other hand, the ameliorating effects of prebiotic administration on leaky gut syndrome was mainly attributed to reducing serum/plasma LPS levels (endotoxemia).

Specifically, the current meta-analysis reveal a significant reduction in LPS levels following pro-, pre-, and synbiotic supplementation, supported by a relatively large number of studies, though with high heterogeneity and very low certainty of evidence. These findings showed moderate certainty of evidence. Interestingly, when only lower risk of bias trials were considered in the analysis, the observed decreases in LPS levels remained significant, though with high heterogeneity. According to subgroup analysis, the effects of pre-, pro- and synbiotics seem to be more prominent when the supplements were administered for longer durations (e.g., more than 8–12 weeks). The effects of prebiotics on LPS

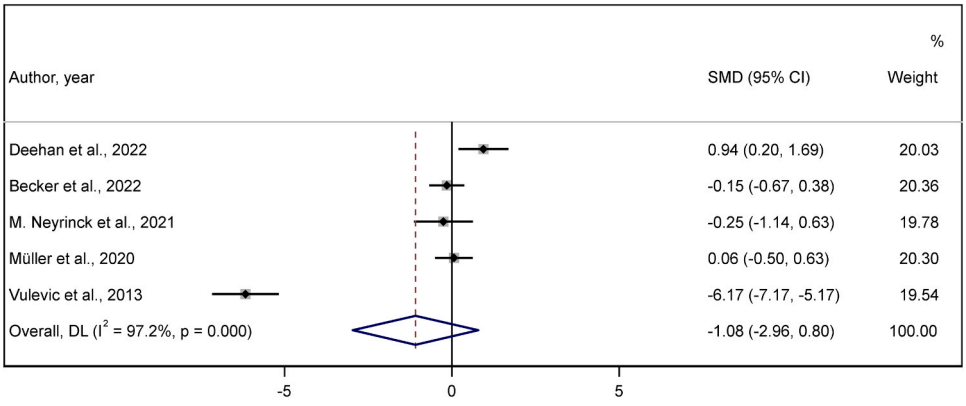

Fig. 9. Forest plot illustrating standardized mean differences (SMD) and 95 % confidence intervals (CI) for the effect of prebiotic administration on fecal calprotectin levels.

levels were also more pronounced among individuals with conditions such as T2DM, NAFLD, and CVDs. These results contrast with the effects of pro- and synbiotics on serum zonulin, where fewer trials showed a significant reduction but with moderate certainty and slightly lower heterogeneity. A large proportion of RCTs included in the meta-analysis on pro- and synbiotic supplementation (24 RCTs (28 effect sizes) recruiting 1603 subjects) as well as prebiotics (15 RCTs (16 effect sizes) involving 769 individuals) employed serum/plasma LPS levels measurement as an indicator of intestinal permeability. It can be speculated that the difference in outcomes may stem from the fact that LPS is a direct microbial product, making it a more specific marker for microbiome-related interventions. Since LPS originates from Gram-negative bacteria, changes in its levels likely reflect shifts in microbial composition or reduced bacterial translocation due to improved gut barrier function. In contrast, zonulin is a host-derived protein influenced by multiple factors beyond the microbiome, such as inflammation, diet, and stress, introducing additional variability that may obscure intervention effects [6,19,83]. Another key consideration is study design. LPS-focused trials which tend to use lower dosages of probiotics bacteria had also longer durations, hence, they may achieve more stable and physiologically relevant microbiome changes, enhancing the likelihood of detecting significant effects. Lower dosages could improve tolerability and adherence, while extended intervention periods allow sufficient time for microbial modulation and downstream effects on LPS.

To better understand and clarify the sources of this heterogeneity, subgroup analyses and meta-regression analyses were conducted. Intervention duration and dosage appears to be a significant contributor to heterogeneity, particularly for the effects of pro- and synbiotics on LPS and fecal calprotectin. Additionally, older age and lower BMI are likely sources of heterogeneity for the effects of pro- and synbiotics on serum zonulin. Regarding the effects of prebiotics, the primary source of heterogeneity for serum/plasma LPS was health conditions, intervention duration, and study quality. Despite these efforts to identify sources of heterogeneity, high heterogeneity persists within many subgroups. This suggests that other unmeasured factors—such as differences in study design, participant characteristics, or measurement methods—may also play a role. Variations in the composition and dosages of pre-, pro-, or synbiotics, participant characteristics, intervention protocols, adherence to interventions, or the sensitivity of assays used to measure outcomes could further contribute to the observed variability. These findings further emphasize that while LPS serves as a reliable biomarker for microbiome-targeted interventions due to its direct microbial origin, other markers like zonulin may still hold value but require more rigorous investigation. Future research should prioritize larger, longer-duration trials with standardized methodologies to better assess the effects of pre-, pro-, and synbiotics on gut permeability and systemic inflammation, accounting for the complex interplay between microbial and host factors. Addressing these factors in future research may help reduce heterogeneity and yield more consistent results.

Overall, the current findings support the evidence provided by some available meta-analyses showing that pro- and synbiotics administration could effectively improve gut permeability through lowering serum LPS or serum zonulin [84–86]. Nevertheless, the available systematic reviews and meta-analyses are constrained in their scope as they predominantly concentrate on specific conditions such as obesity [84], colorectal cancer patients [87] or narrow down their concentration to only particular permeability markers such as LPS or zonulin [84–87]. As a result, their findings cannot ascertain a definite conclusion. Moreover, the findings concerning the effects of prebiotics also align with previous systematic reviews and meta-analyses that demonstrate the ability of dietary fiber to enhance gut barrier function, as evidenced by improvements in the lactulose/rhamnose (L/R) ratio among critically ill patients [87].

While the exact mechanisms by which pro- and synbiotics, as well as prebiotics, maintain gut integrity remain unclear, several proposed pathways may contribute to these effects. In addition to low intake of probiotics bacteria in the diet, dysbiosis is also correlated with reduced dietary fiber intake, resulting in diminished production of short-chain fatty acids (SCFAs) in the colonic environment. This condition additionally activates the immune system, primarily due to endotoxemia arising from increased intestinal permeability and elevated absorption of LPS from Gram-negative bacteria (such as *Escherichia coli*). Subsequently, a chronic low-grade inflammation would be induced, creating a pathogenic environment conducive to the onset of metabolic diseases. Endotoxemia or heightened LPS levels plays a key role in this process [88–93]. Notable correlations have been revealed regarding LPS, and zonulin concentrations and metabolic disturbances, including insulin resistance alongside inflammatory markers, thereby boosting the risk of chronic disorders like obesity, T2DM, and complications associated with cardiovascular diseases [7,84,86,94–102]. On the other hand, pro- and synbiotics supplements, primarily containing the *Bifidobacteria* and *Lactobacillus* genera, are suggested to reduce intestinal permeability by altering gut microbial population and provoking diversity of bacteria, implicating their role in alleviating the severity and progression of chronic cardiometabolic disorders [7,84]. In clinical practice, the probiotic *Lacticaseibacillus (L.) casei* strain *Shirota* has been identified as a significant factor in decreasing gut bacterial translocation and modifying the gut microbiota in subjects with T2DM. Notably, both *L. reuteri* and *L. gasseri* were found in increased concentrations in the fecal samples of subjects receiving the probiotic treatment. This finding may account for the reduction in bacterial translocation, as these specific probiotic bacteria are believed to enhance gut barrier integrity by promoting mucus production and tighter junction formation and diminishing apoptotic cell death [103]. Moreover, findings from Horvath et al. suggest that a synbiotic supplement containing multispecies probiotic bacteria contributes to the fortification of intestinal barrier functionality, resulting in decreased serum levels of C-peptide, LPS, and bacterial DNA, which signals a reduced translocation of bacterial metabolites into the bloodstream [45]. Supplementation with *L. paracasei HII01* has been observed to improve inflammatory markers, such as LPS, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP). This reduction is believed to stem from the probiotic's positive modulation of gut microbiota, which subsequently leads to the amelioration of "leaky gut" and endotoxemia [104]. Notably, the lactic acid-producing metabolites synthesized by probiotic bacteria can interfere with the binding of LPS to CD14 receptors on immune cells, which may play a role in mitigating inflammation through NF-κB signaling inhibition [7,97,98,105,106–108]. Furthermore, resistant starches and fibers, which are indigestible in the healthy human gut, undergo fermentation by intestinal probiotic microbiota, particularly by genera such as *Lactobacilli* and *Bifidobacteria*. This fermentation process produces carbon dioxide, methane, hydrogen, and SCFAs, which subsequently result in enhanced growth of the commensal bacterial strains. Roughly one-third to two-thirds of resistant starches are absorbed in the large intestine, underlining their substantial prebiotic potential. Although the exact mechanisms by which prebiotics mitigate endotoxemia are not fully understood, SCFA-associated signalling pathways following prebiotic fermentation may play a role in reducing the translocation of LPS to the bloodstream. SCFAs may diffuse into the bloodstream through intestinal enterocytes, extending the beneficial effects of prebiotic bacterial fermentation beyond gut health and providing systemic advantages [88,89,91,93,109,80,110–112]. Particularly, butyrate and propionate among SCFAs have been implicated in upregulating anti-inflammatory regulatory T cells (Treg) and T helper 2 (TH2) cells, as well as enhancing intestinal epithelial development and barrier integrity. Ingesting prebiotics was revealed to diminish the activity of the key signalling pathway in the process of impaired permeability, referred to as TLR4-NF-κB-tight junction protein located on epithelial cell surfaces. This effect, combined with strengthened tight junctions, subsequently decreases the population of intestinal Gram-negative bacteria that produce LPS. Moreover, prebiotics are thought to enhance the growth of beneficial bacterial strains like

Lactobacillus and *bifidobacterium*, which help combat dysbiosis and endotoxemia [91,93,109,80,110–112]. Considering the role played by inflammation both as a cause and a consequence of altered intestinal permeability, the suppressing effects of pre-, pro- and synbiotics on this condition seem to be a crucial pathway related to the reinforcement of gut barrier integrity by these agents [7,106–108,113,114]. Consequently, administering probiotics bacteria along with prebiotic agents can reverse dysbiosis, promote a balanced microbial environment (rebiosis), enhance gut barrier integrity, and alleviate mild inflammatory conditions [91,93,98,109,80,110–112,115,116].

Yet, the use of probiotics and synbiotics did not significantly impact serum or plasma levels of LBP, as indicated by seven RCTs with eight effect sizes with moderate heterogeneity. This conclusion is made with moderate certainty of evidence. In a similar way, fecal calprotectin levels (evaluated in 8 trials (10 effect sizes) with a total of 705 participants) and fecal zonulin levels (analyzed in 3 trials with 91 participants) exhibited no significant alterations following the administration of probiotics and synbiotics with high and moderate heterogeneity, respectively. The certainty of these results is considered very low. Notably, the effects of prebiotics supplements on serum/plasma LBP and fecal calprotectin levels were not significant either, likely due to the limited number of RCTs and low to very low certainty of evidence ($n = 4$ for LBP and $n = 5$ for fecal calprotectin). The lack of significant alterations in these permeability markers may be attributed to the limited number of RCTs and small sample sizes, as seen in subgroup analyses of plasma/serum zonulin.

5. Strengths and limitations

To the best of our knowledge, this comprehensive systematic review and meta-analysis represent the initial attempt to elucidate the efficacy of either pro- and synbiotics or prebiotics supplementation in alleviating markers of intestinal permeability. Nevertheless, due to the diverse health conditions of study participants, their geographical region, and the varied types of bacterial strains or prebiotic agents utilized, our findings confronted substantial heterogeneity that may undermine the reliability of the findings. Despite efforts to conduct certain sub-group analyses based on health status, intervention duration, type and dosage of intervention, in addition to the risk of bias, and performing meta-regression according to age and BMI of the studied individuals, there may still be some concerns regarding the interpretation of results. Moreover, it should be noted that the certainty of evidence is low for the effects of pro- and synbiotics effects on LPS, and very low for fecal zonulin, and fecal calprotectin. In contrast, the certainty of evidence is moderate for serum LBP, and serum zonulin, which can be viewed as a strength. Results for the effects of prebiotics administration on LBP and zonulin should be also interpreted cautiously since the certainty of evidence was low and very low. Additionally, the constrained sample sizes and the shortage of RCTs exploring fecal zonulin, calprotectin, and serum/plasma levels of LBP pose challenges. This issue persists across various subgroup analyses based on intervention duration or risk of bias assessment for the studied outcomes. There is also a scarcity of research on additional factors in the bloodstream reflecting the status of intestinal permeability, such as TMA/TMAO and occuludin. These limitations restrict the ability of this meta-analysis to formulate firm conclusions regarding the effects of pro- and synbiotics or prebiotics supplements on gut permeability. As a result, it is advised to interpret these current findings cautiously, and they should be seen as preliminary. Hence, it underscores the necessity for further meticulously planned RCTs with adequate sample sizes, extended follow-up periods, and standardized measurements to enrich our knowledge of how these agents impact the leaky gut.

6. Conclusion

This meta-analysis revealed promising findings regarding the efficacy of either pro- and synbiotic or prebiotic supplements on alleviating "leaky gut". The effects of pro- and synbiotics were certainly reflected by lowering some of the key markers of intestinal permeability in the bloodstream, including LPS and zonulin following consumption of these supplements, as compared to controls. On the other hand, prebiotics were only shown to effectively decrease serum/plasma LPS levels.

Further well-designed randomized trials are warranted to elucidate the full potential of pro- and synbiotics, and prebiotics on other permeability factors, including LBP, zonulin, TMA/TMAO, and occludin. Moreover, future studies are suggested to compare the effect of these agents on gut permeability between individuals with T2DM, NAFLD, or CVDs and healthy subjects.

CRediT authorship contribution statement

Kate Taylor: Writing – review & editing, Resources, Investigation, Data curation. **Morvarid Noormohammadi:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Data curation. **Nargeskhatoon Shoaibinobarian:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Data curation. **Zeinab Ghorbani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kirke Forslund Sofia:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ulrike Löber:** Writing – review & editing, Resources, Investigation, Data curation. **Sara Khoshdooz:** Writing – review & editing, Resources, Investigation, Data curation. **Ali Bonyad:** Writing – review & editing, Resources, Investigation, Data curation. **Asma Kazemi:** Writing – review & editing, Resources, Investigation, Data curation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2025.107780.

Data availability

Data will be made available on request.

References

[1] E. Haroun, P.A. Kumar, L. Saba, J. Kassab, K. Ghimire, D. Dutta, S.H. Lim, Intestinal barrier functions in hematologic and oncologic diseases, J. Transl. Med. 21 (1) (2023) 233.

[2] A. Alizadeh, P. Akbari, J. Garssen, J. Fink-Gremmels, S. Braber, Epithelial integrity, junctional complexes, and biomarkers associated with intestinal functions, Tissue Barriers 10 (3) (2022) 1996830.
[3] B.E. Lacy, J.L. Wise, D.J. Cangemi, Leaky gut syndrome: myths and management, Gastroenterol. Hepatol. 20 (5) (2024) 264–272.
[4] M. Arzani, S.R. Jahromi, Z. Ghorbani, F. Vahabizad, P. Martelletti, A. Ghaemi, S. Sacco, M. Togha, Gut-brain Axis and migraine headache: a comprehensive review, J. Headache Pain. 21 (1) (2020) 15.
[5] S. Ghosh, C.S. Whitley, B. Haribabu, V.R. Jala, Regulation of intestinal barrier function by microbial metabolites, Cell. Mol. Gastroenterol. Hepatol. 11 (5) (2021) 1463–1482.
[6] B. Seethaler, M. Basrai, A.M. Neyrinck, J.-A. Nazare, J. Walter, N.M. Delzenne, S. C. Bischoff, Biomarkers for assessment of intestinal permeability in clinical practice, Am. J. Physiol. Gastrointest. Liver Physiol. 321 (1) (2021) G11–G17.
[7] M. Mahdavi-Roshan, A. Salari, J. Kheirkhah, Z. Ghorbani, The effects of probiotics on inflammation, endothelial dysfunction, and atherosclerosis progression: a mechanistic overview, Heart Lung Circ. 31 (5) (2022) e45–e71.
[8] Z. Ghorbani, A. Kazemi, U.P.B. T, F. Martami, M. Noormohammadi, A. Salari, U. Löber, H.A. Balou, K.F. S, M. Mahdavi-Roshan, The effect of probiotic and synbiotic supplementation on lipid parameters among patients with cardiometabolic risk factors: a systematic review and meta-analysis of clinical trials, Cardiovasc Res 119 (4) (2023) 933–956.
[9] A. Kazemi, S. Soltani, S. Ghorabi, A. Keshtkar, E. Daneshzad, F. Nasri, S. M. Mazloomi, 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. 39 (3) (2020) 789–819.
[10] A. Salari, M. Mahdavi-Roshan, J. Kheirkhah, Z. Ghorbani, Probiotics supplementation and cardiometabolic risk factors: a new insight into recent advances, potential mechanisms, and clinical implications, PharmaNutrition 16 (2021) 100261.
[11] M. Noormohammadi, Z. Ghorbani, U. Löber, M. Mahdavi-Roshan, T.U. P. Bartolomaeus, A. Kazemi, N. Shoaibinobarian, S.K. Forslund, The effect of probiotic and synbiotic supplementation on appetite-regulating hormones and desire to eat: a systematic review and meta-analysis of clinical trials, Pharmacol. Res. 187 (2023) 106614.
[12] D. Davani-Davari, M. Negahdaripour, I. Karimzadeh, M. Seifan, M. Mohkam, S. J. Masoumi, A. Berenjian, Y. Ghasemi, Prebiotics: definition, types, sources, mechanisms, and clinical applications, Foods 8 (3) (2019).
[13] G. Guyatt, A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, S. Norris, Y. Falck-Ytter, P. Glasziou, H. DeBeer, R. Jaeschke, D. Rind, J. Meerpohl, P. Dahm, H. J. Schünemann, GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables, J. Clin. Epidemiol. 64 (4) (2011) 383–394.
[14] N.E. Boutagy, A.P. Neilson, K.L. Osterberg, A.T. Smithson, T.R. Englund, B. M. Davy, M.W. Hulver, K.P. Davy, Probiotic supplementation and trimethylamine-N-oxide production following a high-fat diet, Obes. (Silver Spring) 23 (12) (2015) 2357–2363.
[15] M. Matsumoto, Y. Kitada, Y. Shimomura, Y. Naito, Bifidobacterium animalis subsp. lactis LKM512 reduces levels of intestinal trimethylamine produced by intestinal microbiota in healthy volunteers: a double-blind, placebo-controlled study, J. Funct. Foods 36 (2017) 94–101.
[16] S. Chen, P.P. Jiang, D. Yu, G.C. Liao, S.L. Wu, A.P. Fang, P.Y. Chen, X.Y. Wang, Y. Luo, J.A. Long, R.H. Zhong, Z.Y. Liu, C.L. Li, D.M. Zhang, H.L. Zhu, Effects of probiotic supplementation on serum trimethylamine-N-oxide level and gut microbiota composition in young males: a double-blinded randomized controlled trial, Eur. J. Nutr. 60 (2) (2021) 747–758.
[17] I. Bjarnason, G. Sission, B. Hayee, A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease, Inflammopharmacology 27 (3) (2019) 465–473.
[18] C. Gutiérrez-Repiso, C. Hernández-García, J.M. García-Almeida, D. Bellido, G. M. Martín-Núñez, L. Sánchez-Alcoholado, J. Alcaide-Torres, I. Sajoux, F. J. Tinahones, I. Moreno-Indias, Effect of Synbiotic supplementation in a very-low-calorie ketogenic diet on weight loss achievement and gut microbiota: a randomized controlled pilot study, Mol. Nutr. Food Res 63 (19) (2019) e1900167.
[19] X. Li, Y. Liu, X. Guo, Y. Ma, H. Zhang, H. Liang, Effect of Lactobacillus casei on lipid metabolism and intestinal microflora in patients with alcoholic liver injury, Eur. J. Clin. Nutr. 75 (8) (2021) 1227–1236.
[20] J. Moludi, H. Khedmatgozar, S.M. Nachvak, H. Abdollahzad, M. Moradinazar, A. Sadeghpour Tabaei, The effects of co-administration of probiotics and prebiotics on chronic inflammation, and depression symptoms in patients with coronary artery diseases: a randomized clinical trial, Nutr. Neurosci. 25 (8) (2022) 1659–1668.
[21] L.K. Stenman, M.J. Lehtinen, N. Meland, J.E. Christensen, N. Yeung, M. T. Saarinen, M. Courtney, R. Burcelin, M.L. Lahdeaho, J. Linros, D. Apter, M. Scheinin, H. Kloster Smerud, A. Rissanen, S. Lahtinen, Probiotic with or without fiber controls body fat mass, associated with serum zonulin, in overweight and obese adults-randomized controlled trial, EBioMedicine 13 (2016) 190–200.
[22] M. Szulińska, I. Łoniewski, S. van Hemert, M. Sobieska, P. Bogdański, Dose-dependent effects of multispecies probiotic supplementation on the lipopolysaccharide (LPS) Level and cardiometabolic profile in obese postmenopausal women: a 12-week randomized clinical trial, Nutrients 10 (6) (2018).
[23] E.P. Nyangale, S. Farmer, H.A. Cash, D. Keller, D. Chernoff, G.R. Gibson, Bacillus coagulans GBI-30, 6086 modulates faecalibacterium prausnitzii in older men and women, J. Nutr. 145 (7) (2015) 1446–1452.
[24] C. Tenorio-Jiménez, M.J. Martínez-Ramírez, I. Del Castillo-Codes, C. Arraiza-Irigoyen, M. Tercero-Lozano, J. Camacho, N. Chueca, F. García, J. Olza, J. Plaza-Díaz, L. Fontana, M. Olivares, Á. Gil, C. Gómez-Llorente, Lactobacillus reuteri V3401 reduces inflammatory biomarkers and modifies the gastrointestinal microbiome in adults with metabolic syndrome: the PROSIR study, Nutrients 11 (8) (2019).
[25] J.M. Lecerf, F. Dépeint, E. Clerc, Y. Dugenet, C.N. Niamba, L. Rhazi, A. Cayzeele, G. Abdelnour, A. Jaruga, H. Younes, H. Jacobs, G. Lambrey, A.M. Abdelnour, P. R. Pouillart, Xylo-oligosaccharide (XOS) in combination with inulin modulates both the intestinal environment and immune status in healthy subjects, while XOS alone only shows prebiotic properties, Br. J. Nutr. 108 (10) (2012) 1847–1858.
[26] E.E. Canfora, C.M. van der Beek, G.D.A. Hermes, G.H. Goossens, J.W.E. Jocken, J. J. Holst, H.M. van Eijk, K. Venema, H. Smidt, E.G. Zoetendal, C.H.C. Dejong, K. Lenaerts, E.E. Blaak, Supplementation of diet with galacto-oligosaccharides increases bifidobacteria, but not insulin sensitivity, in obese prediabetic individuals, Gastroenterology 153 (1) (2017) 87–97, e83.
[27] E.M. Dewulf, P.D. Cani, S.P. Claus, S. Fuentes, P.G. Puylaert, A.M. Neyrinck, L. B. Bindels, W.M. de Vos, G.R. Gibson, J.P. Thissen, N.M. Delzenne, Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women, Gut 62 (8) (2013) 1112–1121.
[28] A. Karim, T. Muhammad, M. Shahid Iqbal, R. Qaisar, A multistrain probiotic improves handgrip strength and functional capacity in patients with COPD: a randomized controlled trial, Arch. Gerontol. Geriatr. 102 (2022) 104721.
[29] S. Jung, K.M. Kim, S.M. Youn, K.N. Kim, A randomized, double-blind, placebo-controlled trial to evaluate the effects of multi-strain synbiotic in patients with functional diarrhea and high fecal calprotectin levels: a pilot study, Nutrients 14 (23) (2022).
[30] I. Kaur, V. Suri, N. Sachdeva, S.V. Rana, B. Medhi, N. Sahni, J. Ahire, A. Singh, Efficacy of multi-strain probiotic along with dietary and lifestyle modifications on polycystic ovary syndrome: a randomised, double-blind placebo-controlled study, Eur. J. Nutr. 61 (8) (2022) 4145–4154.
[31] M. Jung, S. Jung, N. Kim, H. Ahn, H. Yun, K.N. Kim, A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of lactiplantibacillus plantarum CJLP243 in patients with functional diarrhea and high fecal calprotectin levels, Nutrients 14 (2) (2022).
[32] L. Liu, X. Chen, L. Liu, H. Qin, Clostridium butyricum potentially improves immunity and nutrition through alteration of the microbiota and metabolism of elderly people with malnutrition in long-term care, Nutrients 14 (17) (2022).
[33] S.M. Garvey, E. Mah, T.M. Blonquist, V.N. Kaden, J.L. Spears, The probiotic Bacillus subtilis BS50 decreases gastrointestinal symptoms in healthy adults: a randomized, double-blind, placebo-controlled trial, Gut Microbes 14 (1) (2022) 2122668.
[34] K.E. Freedman, J.L. Hill, Y. Wei, A.R. Vazquez, D.S. Grubb, R.E. Trotter, S. D. Wrigley, S.A. Johnson, M.T. Foster, T.L. Weir, Examining the gastrointestinal and immunomodulatory effects of the novel probiotic bacillus subtilis DE111, Int J. Mol. Sci. 22 (5) (2021).
[35] A. Ghavami, F. Khorvash, Z. Heidari, S. Khalesi, G. Askari, Effect of synbiotic supplementation on migraine characteristics and inflammatory biomarkers in women with migraine: results of a randomized controlled trial, Pharm. Res. 169 (2021) 105668.
[36] C. Chaiyasut, B.S. Sivamaruthi, P. Kesika, S. Khongtan, N. Khampithum, S. Thangaleela, S. Peerajan, A. Bumrungpert, K. Chaiyasut, S. Sirilun, P. Sittiprapaporn, Synbiotic supplementation improves obesity index and metabolic biomarkers in thai obese adults: a randomized clinical trial, Foods 10 (7) (2021).
[37] C. Chaiyasut, Y. Tirawat, B.S. Sivamaruthi, P. Kesika, S. Thangaleela, S. Khongtan, N. Khampithum, S. Peerajan, K. Chaiyasut, S. Sirilun, P. Sittiprapaporn, Effect of lactobacillus paracasei HII01 supplementation on total cholesterol, and on the parameters of lipid and carbohydrate metabolism, oxidative stress, inflammation and digestion in thai hypercholesterolemic subjects, Appl. Sci. 11 (10) (2021) 4333.
[38] E. Guillemard, M. Poirel, F. Schäfer, L. Quinquis, C. Rossoni, C. Keicher, F. Wagner, H. Szajewska, F. Barbut, M. Derrien, P. Malfertheiner, A randomised, controlled trial: effect of a multi-strain fermented milk on the gut microbiota recovery after helicobacter pylori therapy, Nutrients 13 (9) (2021).
[39] S. Li, Y. Yin, D. Xiao, Y. Zou, Supplemental bifid triple viable capsule treatment improves inflammatory response and T cell frequency in ulcerative colitis patients, BMC Gastroenterol. 21 (1) (2021) 314.
[40] J. Moludi, H.S. Kafil, S.A. Qaisar, P. Gholizadeh, M. Alizadeh, H.J. Vayghyan, Effect of probiotic supplementation along with calorie restriction on metabolic endotoxemia, and inflammation markers in coronary artery disease patients: a double blind placebo controlled randomized clinical trial, Nutr. J. 20 (1) (2021) 47.
[41] M. Sohn, G.Y. Na, J. Chu, H. Joung, B.K. Kim, S. Lim, Efficacy and safety of lactobacillus plantarum k50 on lipids in koreans with obesity: a randomized, double-blind controlled clinical trial, Front Endocrinol. 12 (2021) 790046.
[42] A.H. Tan, S.Y. Lim, K.K. Chong, A.M. MAA, J.W. Hor, J.L. Lim, S.C. Low, C. W. Chong, S. Mahadeva, A.E. Lang, Probiotics for constipation in parkinson disease: a randomized placebo-controlled study, Neurology 96 (5) (2021) e772–e782.
[43] E.R. Louzada, S.M.L. Ribeiro, Synbiotic supplementation, systemic inflammation, and symptoms of brain disorders in elders: a secondary study from a randomized clinical trial, Nutr. Neurosci. 23 (2) (2020) 93–100.
[44] T. Palacios, L. Vitetta, S. Coulson, C.D. Madigan, Y.Y. Lam, R. Manuel, D. Briskey, C. Hendy, J.N. Kim, T. Ishoey, M.J. Soto-Giron, E.M. Schott, G. Toledo, I.

D. Caterson, Targeting the intestinal microbiota to prevent type 2 diabetes and enhance the effect of metformin on glycaemia: a randomised controlled pilot study, Nutrients 12 (7) (2020).
[45] A. Horvath, B. Leber, N. Feldbacher, N. Tripolt, F. Rainer, A. Blesl, M. Trieb, G. Marsche, H. Sourij, V. Stadlbauer, Effects of a multispecies synbiotic on glucose metabolism, lipid marker, gut microbiome composition, gut permeability, and quality of life in diabesity: a randomized, double-blind, placebo-controlled pilot study, Eur. J. Nutr. 59 (7) (2020) 2969–2983.
[46] A. Janczy, E. Aleksandrowicz-Wrona, Z. Kochan, S. Małgorzewicz, Impact of diet and synbiotics on selected gut bacteria and intestinal permeability in individuals with excess body weight - A Prospective, Randomized Study, Acta Biochim Pol. 67 (4) (2020) 571–578.
[47] C.M.R.G. de Carvalho, L.A. Luzia, P.H. Rondó, S.M.L. Ribeiro, Associations between vitamin D, systemic inflammation and synbiotic supplementation: secondary study from a randomized clinical trial, Nutrire 45 (1) (2019).
[48] A. Duseja, S.K. Acharya, M. Mehta, S. Chhabra, Shalimar, S. Rana, A. Das, S. Dattagupta, R.K. Dhiman, Y.K. Chawla, High potency multistrain probiotic improves liver histology in non-alcoholic fatty liver disease (NAFLD): a randomised, double-blind, proof of concept study, BMJ Open Gastroenterol. 6 (1) (2019).
[49] S. Sabico, A. Al-Mashharawi, N.M. Al-Daghri, K. Wani, O.E. Amer, D.S. Hussain, M.G. Ahmed Ansari, M.S. Masoud, M.S. Alokail, P.G. McTernan, Effects of a 6-month multi-strain probiotics supplementation in endotoxemic, inflammatory and cardiometabolic status of T2DM patients: a randomized, double-blind, placebo-controlled trial, Clin. Nutr. 38 (4) (2019) 1561–1569.
[50] J.R. Townsend, D. Bender, W.C. Vantrease, P.A. Sapp, A.M. Toy, C.A. Woods, K. D. Johnson, Effects of probiotic (Bacillus subtilis de111) supplementation on immune function, hormonal status, and physical performance in division i baseball players, Sports 6 (3) (2018).
[51] N.M. de Roos, S. van Hemert, J.M.P. Rovers, M.G. Smits, B.J.M. Witteman, The effects of a multispecies probiotic on migraine and markers of intestinal permeability-results of a randomized placebo-controlled study, Eur. J. Clin. Nutr. 71 (12) (2017) 1455–1462.
[52] A.C. Gomes, R.G. de Sousa, P.B. Botelho, T.L. Gomes, P.O. Prada, J.F. Mota, The additional effects of a probiotic mix on abdominal adiposity and antioxidant Status: a double-blind, randomized trial, Obes. (Silver Spring) 25 (1) (2017) 30–38.
[53] S. Sabico, A. Al-Mashharawi, N.M. Al-Daghri, S. Yakout, A.M. Alnaami, M. S. Alokail, P.G. McTernan, Effects of a multi-strain probiotic supplement for 12 weeks in circulating endotoxin levels and cardiometabolic profiles of medication naïve T2DM patients: a randomized clinical trial, J. Transl. Med 15 (1) (2017) 249.
[54] C.L. Kvasnovsky, I. Bjarnason, A.N. Donaldson, R.A. Sherwood, S. Papagrigoriadis, A randomized double-blind placebo-controlled trial of a multi-strain probiotic in treatment of symptomatic uncomplicated diverticular disease, Inflammopharmacology (2017).
[55] S.M. Ferolla, C.A. Couto, L. Costa-Silva, G.N. Armiliato, C.A. Pereira, F.S. Martins, Mde L. Ferrari, E.G. Vilela, H.O. Torres, A.S. Cunha, T.C. Ferrari, Beneficial effect of synbiotic supplementation on hepatic steatosis and anthropometric parameters, but not on gut permeability in a population with nonalcoholic steatohepatitis, Nutrients 8 (7) (2016).
[56] W. Zhou, Saccharomyces boulardii powder combined with mesalazine for treatment of active ulcerative colitis: curative effect and impact on fecal calprotectin and serum inflammatory factors, World Chin. J. Dig. 25 (22) (2017) 2065–2070.
[57] J.D. Roberts, C.A. Suckling, G.Y. Peedle, J.A. Murphy, T.G. Dawkins, M. G. Roberts, An exploratory investigation of endotoxin levels in novice long distance triathletes, and the effects of a multi-strain probiotic/prebiotic, antioxidant intervention, Nutrients 8 (11) (2016).
[58] S.J. Lee, S. Bose, J.G. Seo, W.S. Chung, C.Y. Lim, H. Kim, The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: a randomized double-blind controlled clinical trial, Clin. Nutr. 33 (6) (2014) 973–981.
[59] E. Iemoli, D. Trabattoni, S. Parisotto, L. Borgonovo, M. Toscano, G. Rizzardini, M. Clerici, E. Ricci, A. Fusi, E. De Vecchi, S. Piconi, L. Drago, Probiotics reduce gut microbial translocation and improve adult atopic dermatitis, J. Clin. Gastroenterol. 46 (2012) S33–40 (Suppl).
[60] M. Lamprecht, S. Bogner, G. Schippinger, K. Steinbauer, F. Fankhauser, S. Hallstroem, B. Schuetz, J.F. Greilberger, Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial, J. Int. Soc. Sports Nutr. 9 (1) (2012) 45.
[61] M. Malaguarnera, M. Vacante, T. Antic, M. Giordano, G. Chisari, R. Acquaviva, S. Mastrojeni, G. Malaguarnera, A. Mistretta, G. Li Volti, F. Galvano, Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis, Dig. Dis. Sci. 57 (2) (2012) 545–553.
[62] N. Mangalat, Y. Liu, N.Y. Fatheree, M.J. Ferris, M.R. Van Arsdall, Z. Chen, M. H. Rahbar, W.A. Gleason, J. Norori, D.Q. Tran, J.M. Rhoads, Safety and tolerability of Lactobacillus reuteri DSM 17938 and effects on biomarkers in healthy adults: results from a randomized masked trial, PLoS One 7 (9) (2012) e43910.
[63] L.H. Yang, H. Guo, J. Cai, X.W. Cai, G.L. Liu, D.F. Chen, Intervention effect of microbiological capsules containing Bacillus subtilis and Enterococcus on intestinal flora in patients with NASH, World Chin. J. Dig. 20 (20) (2012) 1873–1878.
[64] B. Leber, N.J. Tripolt, D. Blattl, M. Eder, T.C. Wascher, T.R. Pieber, R. Stauber, H. Sourij, K. Oettl, V. Stadlbauer, The influence of probiotic supplementation on gut permeability in patients with metabolic syndrome: an open label, randomized pilot study, Eur. J. Clin. Nutr. 66 (10) (2012) 1110–1115.
[65] E.C. Deehan, Z. Zhang, A. Riva, A.M. Armet, M.E. Perez-Muñoz, N.K. Nguyen, J. A. Krysa, B. Seethaler, Y.Y. Zhao, J. Cole, F. Li, B. Hausmann, A. Spittler, J. A. Nazare, N.M. Delzenne, J.M. Curtis, W.V. Wismer, S.D. Proctor, J.A. Bakal, S. C. Bischoff, D. Knights, C.J. Field, D. Berry, C.M. Prado, J. Walter, Elucidating the role of the gut microbiota in the physiological effects of dietary fiber, Microbiome 10 (1) (2022).
[66] A. Becker, G.P. Schmartz, L. Gröger, N. Grammes, V. Galata, H. Philippeit, J. Weiland, N. Ludwig, E. Meese, S. Tierling, J. Walter, A. Schwiertz, J. Spiegel, G. Wagenpfeil, K. Faßbender, A. Keller, M.M. Unger, Effects of resistant starch on symptoms, fecal markers, and gut microbiota in Parkinson's disease - the RESISTA-PD trial, Genom. Proteom. Bioinforma. 20 (2) (2022) 274–287.
[67] M.A. Farhangi, P. Dehghan, V. Musazadeh, M. Kavyani, P. Maleki, Effectiveness of omega-3 and prebiotics on adiponectin, leptin, liver enzymes lipid profile and anthropometric indices in patients with non-alcoholic fatty liver disease: a randomized controlled trial, J. Funct. Foods 92 (2022) 105074.
[68] E. Vaghef-Mehrabani, R. Harouni, M. Behrooz, F. Ranjbar, M. Asghari-Jafarabadi, M. Ebrahimi-Mameghani, Effects of inulin supplementation on inflammatory biomarkers and clinical symptoms of women with obesity and depression on a calorie-restricted diet: a randomized controlled clinical trial, Br. J. Nutr. (2022) 1–28.
[69] S. Saleh-Ghadimi, P. Dehghan, B. Sarmadi, P. Maleki, Improvement of sleep by resistant dextrin prebiotic in type 2 diabetic women coincides with attenuation of metabolic endotoxemia: involvement of gut–brain axis, J. Sci. Food Agric. 102 (12) (2022) 5229–5237.
[70] A.M. Neyrinck, J. Rodriguez, Z. Zhang, B. Seethaler, C.R. Sánchez, M. Roumain, S. Hiel, L.B. Bindels, P.D. Cani, N. Paquot, M. Cnop, J.A. Nazare, M. Laville, G. G. Muccioli, S.C. Bischoff, J. Walter, J.P. Thissen, N.M. Delzenne, Prebiotic dietary fibre intervention improves fecal markers related to inflammation in obese patients: results from the Food4Gut randomized placebo-controlled trial, Eur. J. Nutr. 60 (6) (2021) 3159–3170.
[71] M. Kavyani, S. Saleh-Ghadimi, P. Dehghan, M. Abbasalizad Farhangi, M. Khoshbaten, Co-supplementation of camelina oil and a prebiotic is more effective for in improving cardiometabolic risk factors and mental health in patients with NAFLD: a randomized clinical trial, Food Funct. 12 (18) (2021) 8594–8604.
[72] M. Müller, G.D.A. Hermes, E.C. Emanuel, J.J. Holst, E.G. Zoetendal, H. Smidt, F. Troost, F.G. Schaap, S.O. Damink, J.W.E. Jocken, K. Lenaerts, A.A.M. Masclee, E.E. Blaak, Effect of wheat bran derived prebiotic supplementation on gastrointestinal transit, gut microbiota, and metabolic health: a randomized controlled trial in healthy adults with a slow gut transit, Gut Microbes 12 (1) (2020).
[73] M.A. Farhangi, P. Dehghan, N. Namazi, Prebiotic supplementation modulates advanced glycation end-products (AGEs), soluble receptor for AGEs (sRAGE), and cardiometabolic risk factors through improving metabolic endotoxemia: a randomized-controlled clinical trial, Eur. J. Nutr. 59 (7) (2020) 3009–3021.
[74] M.A. Farhangi, A.Z. Javid, B. Sarmadi, P. Karimi, P. Dehghan, A randomized controlled trial on the efficacy of resistant dextrin, as functional food, in women with type 2 diabetes: targeting the hypothalamic-pituitary-adrenal axis and immune system, Clin. Nutr. 37 (4) (2018) 1216–1223.
[75] E.E. Canfora, C.M. van der Beek, G.D.A. Hermes, G.H. Goossens, J.W.E. Jocken, J. J. Holst, H.M. van Eijk, K. Venema, H. Smidt, E.G. Zoetendal, C.H.C. Dejong, K. Lenaerts, E.E. Blaak, Supplementation of diet with galacto-oligosaccharides increases bifidobacteria, but not insulin sensitivity, in obese prediabetic individuals, Gastroenterology 153 (1) (2017) 87–97, e83.
[76] M. Gonai, A. Shigehisa, I. Kigawa, K. Kurasaki, O. Chonan, T. Matsuki, Y. Yoshida, M. Aida, K. Hamano, Y. Terauchi, Galacto-oligosaccharides ameliorate dysbiotic Bifidobacteriaceae decline in Japanese patients with type 2 diabetes, Benef. Microbes 8 (5) (2017) 705–716.
[77] J.A. Parnell, T. Klancic, R.A. Reimer, Oligofructose decreases serum lipopolysaccharide and plasminogen activator inhibitor-1 in adults with overweight/obesity, Obes. (Silver Spring) 25 (3) (2017) 510–513.
[78] P. Karimi, M.A. Farhangi, B. Sarmadi, B.P. Gargari, A. Zare Javid, M. Pouraghaei, P. Dehghan, The therapeutic potential of resistant starch in modulation of insulin resistance, endotoxemia, oxidative stress and antioxidant biomarkers in women with type 2 diabetes: a randomized controlled clinical trial, Ann. Nutr. Metab. 68 (2) (2016) 85–93.
[79] S.T. Clarke, J.M. Green-Johnson, S.P. Brooks, D.D. Ramdath, P. Bercik, C. Avila, G.D. Inglis, J. Green, L.J. Yanke, L.B. Selinger, M. Kalmokoff, beta2-1 Fructan supplementation alters host immune responses in a manner consistent with increased exposure to microbial components: results from a double-blinded, randomised, cross-over study in healthy adults, Br. J. Nutr. 115 (10) (2016) 1748–1759.
[80] A. Aliasgharzadeh, P. Dehghan, B.P. Gargari, M. Asghari-Jafarabadi, Resistant dextrin, as a prebiotic, improves insulin resistance and inflammation in women with type 2 diabetes: a randomised controlled clinical trial, Br. J. Nutr. 113 (2) (2015) 321–330.
[81] P. Dehghan, B.P. Gargari, M.A. Jafar-Abadi, A. Aliasgharzadeh, Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial, Int. J. Food Sci. Nutr. 65 (1) (2014) 117–123.
[82] J. Vulevic, A. Juric, G. Tzortzis, G.R. Gibson, A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates

the fecal microbiota and immune function of overweight adults1-3, J. Nutr. 143 (3) (2013) 324–331.
[83] S. Mishra, S. Jain, B. Agadzi, H. Yadav, A cascade of microbiota-leaky gut-inflammation- is it a key player in metabolic disorders? Curr. Obes. Rep. 14 (1) (2025) 32.
[84] Z. DiMattia, J.J. Damani, E. Van Syoc, C.J. Rogers, Effect of probiotic supplementation on intestinal permeability in overweight and obesity: a systematic review of randomized controlled trials and animal studies, Adv. Nutr. 15 (1) (2024) 100162.
[85] Y. Zheng, Z. Zhang, P. Tang, Y. Wu, A. Zhang, D. Li, C.Z. Wang, J.Y. Wan, H. Yao, C.S. Yuan, Probiotics fortify intestinal barrier function: a systematic review and meta-analysis of randomized trials, Front Immunol. 14 (2023) 1143548.
[86] R.A. Amirhossein, S. Mehdi, A. Meysam, A.T. Samira, R. Sepideh, A. Amir, The effects of probiotic/synbiotic on serum level of zonulin as a biomarker of intestinal permeability: a systematic review and meta-analysis, Iran. J. Public Health 49 (7) (2020).
[87] A. Wierzbicka, D. Mankowska-Wierzbicka, M. Mardas, M. Stelmach-Mardas, Role of probiotics in modulating human gut microbiota populations and activities in patients with colorectal cancer-a systematic review of clinical trials, Nutrients 13 (4) (2021).
[88] T. Liu, C. Wang, Y.Y. Wang, L.L. Wang, O. Ojo, Q.Q. Feng, X.S. Jiang, X.H. Wang, Effect of dietary fiber on gut barrier function, gut microbiota, short-chain fatty acids, inflammation, and clinical outcomes in critically ill patients: a systematic review and meta-analysis, JPEN J. Parenter. Enter. Nutr. 46 (5) (2022) 997–1010.
[89] J. Moludi, V. Maleki, H. Jafari-Vayghyan, E. Vaghef-Mehrabany, M. Alizadeh, Metabolic endotoxemia and cardiovascular disease: a systematic review about potential roles of prebiotics and probiotics, Clin. Exp. Pharmacol. Physiol. 47 (6) (2020) 927–939.
[90] Stankiewicz M., Kaska Ł., Małgorzewicz S. Nutrients.
[91] Q. Guo, Y. Li, X. Dai, B. Wang, J. Zhang, H. Cao, Polysaccharides: the potential prebiotics for metabolic associated fatty liver disease (MAFLD) 15 (17) (2023).
[92] V. Navalón-Monllor, L. Soriano-Romaní, M. Silva, M.-C.L. de las Hazas, N. Hernando-Quintana, T. Suárez Diéguez, P.M. Esteve, J.A. Nieto, Microbiota dysbiosis caused by dietetic patterns as a promoter of Alzheimer's disease through metabolic syndrome mechanisms, Food Funct. 14 (16) (2023) 7317–7334.
[93] M. Mahdavi-Roshan, A. Salari, J. Kheirkhah, Z. Ghorbani, The effects of probiotics on inflammation, endothelial dysfunction, and atherosclerosis progression: a mechanistic overview, Heart Lung Circ. 31 (5) (2022) e45–e71.
[94] K. Lau, V. Srivatsav, A. Rizwan, A. Nashed, R. Liu, R. Shen, M. Akhtar, Bridging the gap between gut microbial dysbiosis and cardiovascular diseases, Nutrients 9 (8) (2017) 859.
[95] A. Lässiger-Herfurth, G. Pontarollo, A. Grill, C. Reinhardt, The gut microbiota in cardiovascular disease and arterial thrombosis, Microorganisms 7 (12) (2019) 691.
[96] T.T.B. Nguyen, Y.Y. Jin, H.-J. Chung, S.-T. Hong, Pharmabiotics as an emerging medication for metabolic syndrome and its related diseases, Molecules 22 (10) (2017) 1795.
[97] B.A. Kappel, M. Federici, Gut microbiome and cardiometabolic risk, Rev. Endocr. Metab. Disord. (2019).
[98] J. Moludi, V. Maleki, H. Jafari-Vayghyan, E. Vaghef-Mehrabany, M. Alizadeh, Metabolic endotoxemia and cardiovascular disease: a systematic review about potential roles of prebiotics and probiotics, Clin. Exp. Pharm. Physiol. 47 (6) (2020) 927–939.
[99] C.F. Semenkovich, Insulin resistance and atherosclerosis, J. Clin. Invest 116 (7) (2006) 1813–1822.
[100] R.W. Alexander, Hypertension and the pathogenesis of atherosclerosis, Hypertension 25 (2) (1995) 155–161.
[101] K.R. Ekawidyani, M. Abdullah, Diet, nutrition and intestinal permeability: a mini review, Asia Pac. J. Clin. Nutr. 32 (1) (2023) 8–12.
[102] B. Ohlsson, M. Orho-Melander, P.M. Nilsson, Higher levels of serum zonulin may rather be associated with increased risk of obesity and hyperlipidemia, than with gastrointestinal symptoms or disease manifestations, Int. J. Mol. Sci. 18 (3) (2017) 582.
[103] J. Sato, A. Kanazawa, K. Azuma, F. Ikeda, H. Goto, K. Komiya, R. Kanno, Y. Tamura, T. Asahara, T. Takahashi, K. Nomoto, Y. Yamashiro, H. Watada, Probiotic reduces bacterial translocation in type 2 diabetes mellitus: a randomised controlled study, Sci. Rep. 7 (1) (2017) 12115.
[104] P. Toejing, N. Khampithum, S. Sirilun, C. Chaiyasut, N. Lailerd, Influence oF Lactobacillus paracasei HII01 supplementation on glycemia and inflammatory biomarkers in Type 2 diabetes: a randomized clinical trial, Foods 10 (7) (2021).
[105] Robles-Vera I., Toral M., de la Visitación N., Sánchez M., Gómez-Guzmán M., Romero M., Yang T., Izquierdo-Garcia J.L., Jiménez R., Ruiz-Cabello J., Guerra-Hernández E., Raizada M.K., Pérez-Vizcaíno F., Duarte J. Probiotics Prevent Dysbiosis and the Raise in Blood Pressure in Genetic Hypertension: Role of Short-chain Fatty Acids. Molecular Nutrition & Food Research;n/a(n/a):1900616.
[106] P. Markowiak-Kopeć, K. Śliżewska, The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome, Nutrients 12 (4) (2020) 1107.
[107] A. Kazemi, S. Soltani, S. Ghorabi, A. Keshtkar, E. Daneshzad, F. Nasri, S. M. Mazloomi, 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. (2019).
[108] Z. Ghorbani, A. Kazemi, T. U.P. Bartolomaeus, F. Martami, M. Noormohammadi, A. Salari, U. Löber, H.A. Balou, S. K. Forslund, M. Mahdavi-Roshan, The effect of probiotic and synbiotic supplementation on lipid parameters among patients with cardiometabolic risk factors: a systematic review and meta-analysis of clinical trials, Cardiovasc. Res. 119 (4) (2022) 933–956.
[109] P.D. Cani, S. Possemiers, T. Van de Wiele, Y. Guiot, A. Everard, O. Rottier, L. Geurts, D. Naslain, A. Neyrinck, D.M. Lambert, G.G. Muccioli, N.M. Delzenne, Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability, Gut 58 (8) (2009) 1091–1103.
[110] L. Vitetta, N.N. Gorgani, G. Vitetta, J.D. Henson, Prebiotics progress shifts in the intestinal microbiome that benefits patients with type 2 diabetes mellitus, Biomolecules 13 (9) (2023).
[111] G.B. Bamigbade, A.J. Subhash, A. Kamal-Eldin, L. Nyström, M. Ayyash, An updated review on prebiotics: insights on potentials of food seeds waste as source of potential prebiotics, Molecules 27 (18) (2022).
[112] B. Pourghassem Gargari, P. Dehghan, A. Aliasgharzadeh, M. Asghari Jafar-Abadi, Effects of high performance inulin supplementation on glycemic control and antioxidant status in women with type 2 diabetes, Diabetes Metab. J. 37 (2) (2013) 140–148.
[113] B. Leech, J. Schloss, A. Steel, Association between increased intestinal permeability and disease: a systematic review, Adv. Integr. Med. 6 (1) (2019) 23–34.
[114] F. Hietbrink, M.G. Besselink, W. Renooij, M.B. de Smet, A. Draisma, H. van der Hoeven, P. Pickkers, Systemic inflammation increases intestinal permeability during experimental human endotoxemia, Shock 32 (4) (2009) 374–378.
[115] O'Morain V.L., Ramji D.P. The Potential of Probiotics in the Prevention and Treatment of Atherosclerosis. Molecular Nutrition & Food Research;n/a(n/a): 1900797.
[116] T. Liang, L. Wu, Y. Xi, Y. Li, X. Xie, C. Fan, L. Yang, S. Yang, X. Chen, J. Zhang, Q. Wu, Probiotics supplementation improves hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes mellitus: an update of meta-analysis, Crit. Rev. Food Sci. Nutr. (2020) 1–19.