fermentation

MDPI

Systematic Review

Probiotic SYNBIO® Blend's Impact on Constipation in Healthy Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Maria Magdalena Coman [1,*], Nadaniela Egidi [2], Stefania Silvi [3], Renato De Leone [2] and Maria Cristina Verdenelli [1]

[1] Synbiotec S.r.l., Spin-Off of UNICAM, 62032 Camerino, Italy
[2] School of Science and Technology, University of Camerino, 62032 Camerino, Italy
[3] School of Biosciences and Veterinary Medicine, University of Camerino, 62032 Camerino, Italy
* Correspondence: magda.coman@unicam.it; Tel.: +39-0737402478

Abstract: Aims: Research on probiotics for constipation management is still growing, and plays a crucial role in the definition of a management strategy for bowel wellbeing, constipation, and related outcomes. The present systematic review and meta-analysis of the beneficial effects of the SYNBIO® blend, to consolidate the data from various clinical trials, was conducted. Methods: A literature search using PubMed, Web of Science, and Google Scholar databases was conducted. The search was limited to clinical trials that used the SYNBIO® blend, either as dietary supplements or probiotic-enriched foods. Independently, two reviewers evaluated the trial's quality and extracted all data. A 95% confidence interval (CI) of a weighted mean difference (MD) was used to pool continuous data. For the analysis, Review Manager version 5.4 was used. Results: Seven clinical trials involving a total of 1095 subjects were included in the analysis. Overall, the SYNBIO® blend significantly improved constipation relief by 0.75 (95% CI: 0.31 to 1.19; $p = 0.0008$) in 52% of the subjects, and significantly increased intestinal regularity by 1.90 compared to the placebo (95% CI: 1.02 to 2.78; $p < 0.0001$) in more than 60% of individuals. No adverse events were reported. Conclusions: The SYNBIO® blend was found to significantly improve overall constipation, intestinal regularity, abdominal pain, and intestinal cramping. This suggests that people with these specific symptoms could benefit from this probiotic combination.

Keywords: probiotics; SYNBIO® blend; constipation; intestinal regularity; gut microbiota; wellbeing

Citation: Coman, M.M.; Egidi, N.; Silvi, S.; De Leone, R.; Verdenelli, M.C. Probiotic SYNBIO® Blend's Impact on Constipation in Healthy Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Fermentation* **2024**, *10*, 518. https://doi.org/10.3390/fermentation10100518

Academic Editor: Roberta Prete

Received: 6 September 2024
Revised: 6 October 2024
Accepted: 9 October 2024
Published: 12 October 2024

1. Introduction

Constipation or chronic constipation, including primary chronic constipation, functional constipation, and constipation-predominant irritable bowel syndrome, are the most common functional gastrointestinal disorders, other than diarrhoea, which can be attributed to gut microbiota dysbiosis. Several factors, including nutrition, intestinal motility and absorption, anorectal sensorimotor function, lifestyle, and psychological factors, are involved in the complex pathophysiology of chronic constipation. This gastrointestinal disorder is mainly characterized by infrequent bowel movements, difficult or painful passage of stools, and the feeling of incomplete evacuation, alongside other symptoms [1].

This condition impacts approximately 20% of the global population and is the fourth most frequently diagnosed gastrointestinal problem among medical professionals' outpatient visits in the United States and Asia [2,3]. Current guidelines for the treatment of chronic constipation recommend, as the initial approach, dietary interventions based on increased dietary fibre intake followed by the use of laxatives. Despite an increasing number of evidence-based studies demonstrating the effectiveness of various therapies, nearly half of individuals with chronic constipation still have unmet expectations regarding the relief

of their symptoms. Other concerns of these therapies include safety, side effects, inconvenience, and the taste of these medicines [4]. As a result of this, over the last few decades there has been a noticeable increase in research on probiotic efficacy in the treatment of constipation. The administration of probiotics has the potential to improve constipation through several potential mechanisms: modulating the gut microbiota composition, stimulating the production of metabolites derived from the intestinal microbiota, improving the intestinal epithelial defence responses and intestinal secretion functions, and regulating the nervous and endocrine systems that influence gut secretion and motility [1,5].

A dynamic community of 40 trillion microbes, known as the gut microbiome, resides in the gastrointestinal (GI) tract and due to its mutualistic relationship with the host, microbes and host have co-evolved. The host's metabolism, endocrine, neurological, and immune systems are impacted and influenced by the gut microbiota [5–7].

The pathophysiology of constipation has been linked to disruptions in the intestinal microbiota composition. After probiotic supplementation, the relative abundance of beneficial bacteria, such as lactobacilli and bifidobacteria, can increase, while populations of potentially harmful bacteria decrease. The amelioration of symptoms related to constipation have been linked to increases in the Firmicutes/Bacteroidetes ratio [2,5,8]. Probiotic supplementation can also alter the metabolic profile of the gut microbiota contributing to gut motility and secretion, for example by increasing the short chain fatty acid (SCFA) content [5]. On the other hand, probiotics influence intestinal epithelial defence responses by strengthening the intestinal barrier, directly increasing the expression of tight junction proteins and stimulating mucin secretion, therefore reducing an intestinal pathogen's ability to adhere to mucosal epithelial cells [9]. Recent evidence suggests that probiotic supplementation alleviates constipation symptoms by stimulating the enteric and central nervous systems, acting through the gut–brain axis.

The current evidence on the efficacy of probiotics in treating chronic constipation in adults is still inconclusive. It remains unclear which specific species or strains, dosage, and supplementation duration of probiotics are most effective, which poses challenges when making recommendations for clinical practice. Several studies have highlighted the need for an updated comprehensive examination and statistical analysis to address this matter. Therefore, the objective of the present review is to investigate the impact of the SYNBIO® blend, a 1:1 mixture of two probiotic strains *Lacticaseibacillus rhamnosus* IMC 501® (DSM 16104), and *Lacticaseibacillus paracasei* IMC 502® (DSM 16105), on the intestinal and general wellbeing of healthy individuals. Several studies were selected and analysed to assess the host response to SYNBIO® blend supplementation in terms of constipation conditions and symptoms, stool output, other clinical outcomes directly connected to constipation, quality of life, and adverse effects.

2. Materials and Methods

2.1. Eligibility Criteria

The eligibility criteria, listed in Table 1, were defined using the PICOS (patient, intervention, comparators, outcome, study design) approach.

Table 1. Inclusion and exclusion criteria and data extracted following the PICOS approach.

PICOS	Inclusion and Exclusion Criteria	Data Extraction
Patients	Adult populations aged ≥18 years, otherwise healthy. No restrictions for age, gender, or ethnicity.	Age, gender, location, inclusion and exclusion criteria, and number of subjects in the intervention and comparator group.
Interventions	SYNBIO® blend of two live probiotic strains. Probiotics may be administered as capsule or as enriched food products (as long as the control group is such that the effect of the probiotic alone can be isolated).	Combination of two probiotic strains. The dose and schedule of probiotic and duration of intervention period were also recorded.

Table 1. *Cont.*

PICOS	Inclusion and Exclusion Criteria	Data Extraction
Comparators	Trials were included if they used a placebo as a control. For trials in which the probiotic intervention was an enriched food product, an acceptable comparator was taken to be the food product without the probiotics.	Type and dose of comparator.
Outcomes	Reports of the clinical outcomes of constipation, stool frequency, stool consistency, other gastrointestinal symptoms (bloating, abdominal pain), or adverse effects/compliance.	Outcomes measured, their method of assessment, and endpoint values for the effect of the intervention on outcomes compared with the control group.
Study design	Randomized controlled trials only with ≥2 study groups, as long as it was possible to extract data only on probiotic and placebo groups. Both parallel and crossover studies were eligible.	Type of study design, fulfilment of intention-to-treat analysis, adequacy of randomization, and allocation concealment and blinding.

PICOS—Patient, Intervention, Comparators, Outcome, Study design.

The relevant criteria of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [10] and the guidelines of assessing the methodological quality of systematic reviews (AMSTAR) [11] were followed in this systematic review.

2.2. Strategy and Data Extraction

The authors strategy was to select clinical trials that used the SYNBIO® blend as a probiotic supplement, based on combinations of the keywords: "probiotic", "SYNBIO®", "intestinal/bowel wellbeing", and "constipation". Two assessors independently screened the titles and abstracts of each study, while the full texts were considered for further evaluation.

Two reviewers (MMC and DE) extracted the data for the probiotic versus placebo groups for a separate comparison, collecting data also as binary outcomes (responding to supplementation, any changes, and worsening response).

A mean difference (MD) was computed for each outcome (constipation, intestinal regularity, stool frequency, stool volume, stool consistency, ease of defecation, bloating, abdominal pain, and intestinal cramping) using the same method and reported with the same units (Table 2). Where necessary, standard deviations (SDs) were calculated from standard errors (SEs) or 95% confident limits (CIs). In addition, data were stratified according to different characteristics, such as proportion of females/males, age, duration of the supplementation period, type of product, and dosage of the probiotic supplementation, and further analysed.

Table 2. Outcomes and evaluation score of the questionnaires used in RCTs.

Questionnaires	Outcomes	Score Scale	References
Intestinal wellbeing	Constipation, intestinal regularity, stool frequency, stool volume, ease of defecation, bloating, abdominal pain, intestinal cramping	10-point Likert scale: −5, 0, +5 (−5 means strong worsening, 0 means no changes, +5 means strong improvement)	[12,13]
Psychological General Wellbeing Index	22 items for 6 dimensions: anxiety, depression, self-control, positive wellbeing, general wellbeing, and vitality	From 0 (worst) to 100 (best)	[14]
Bristol Stool Form Scale	Stool consistency	From type 1 to type 7 (type 1–2 indicates constipation, type 3–4 indicates ideal stools, type 5–7 indicates diarrhoea or severe diarrhoea)	[15]

2.3. Quality Assessment and Assessment of Risk of Bias

Two reviewers (MMC and MCV) assessed the quality of each randomized controlled trial (RCT) using the previously validated 5-point Jadad scale [16]. Studies with scores of 3 or more were considered of high quality. In addition, the risk of bias in each study and the risk of bias across all studies were evaluated and shown with figures generated by RevMan 5.4.1 software [17]. Judgements were classified as "low risk of bias", "unclear risk of bias", or "high risk of bias". In addition, the work has been reported in line with PRISMA and AMSTAR guidelines.

2.4. Data Synthesis and Statistical Analysis

Continuous variable data were measured with MD or standardized mean difference (SMD). Using the *Ph* (*p* value for heterogeneity) value and I^2 statistic, which range from 0% to 100%, to quantify the influence of heterogeneity across studies, the chi-square-based Q statistical test [18] was used. A 50% (Ph) and 75% (I^2) threshold were used for significant and noteworthy heterogeneity. A random-effects model was used to estimate pooled data [19], while $Ph < 0.10$ was considered to denote significant heterogeneity [20]. If pooled results with 95% CI did not overlap with 1 or pooled MDs with 95% CI did not overlap with 0, the effects of the outcome measures were considered statistically significant.

Subgroup analyses were also performed to investigate heterogeneity and to explore the effects of probiotic dose, supplementation format, and duration. For subgroup analyses, a *p*-value of <0.1 was considered statistically significant.

In the meta-analyses, the data show the differences between the score after the supplementation and before it started. Hence, data are discrete and vary from a minimum of -5 to a maximum of 5. A positive value x, between 1 and 5, means that the subject undergoing probiotic integration observed an improvement (Imp.) in their condition of x classes. Analogously, a value x between -5 and -1, means the subject has worsened by $|x|$ classes (Wor.). Finally, a null value means an unchanged condition (Unc.). To evaluate these data, the authors consider: the mean obtained with probiotics μ^{PB}; the mean obtained with placebo μ^{PL}; the probability of observing an improvement with probiotics or placebo ϕ^{PB+}, ϕ^{PL+}; the probability of observing a worsening with probiotics or placebo ϕ^{PB-}, ϕ^{PL-}; and the probability of seeing no changes with probiotics or placebo $\phi^{PB=}$, $\phi^{PL=}$. The 95% CI, the mean, the sampled SD, the difference of means, and the difference of proportions (Diff.), were evaluated between probiotic and placebo groups. The probability that the mean is greater than 1 (PM > 1) as an indicator of the percentage of individuals having an improvement of at least one class was calculated.

3. Results

3.1. Characteristics, and Quality Assessment of Included Studies

The research method produced 105 citations, but only 28 published scientific papers were found to be relevant and were further evaluated. Out of these 28, 6 publications with 1125 participants were defined eligible and were included in the meta-analyses (Figure 1). The clinical trials (Cecchini et al., 2016; Coman et al., 2017, Coman et al., 2023; Silvi et al., 2014; Verdenelli et al., 2011a; Verdenelli et al., 2011b) [12,13,21–24] which assessed the SYNBIO® blend were found. Figure 1 provides a summary and the procedure of the research, while Table 3 contains the list of the studies' additional features.

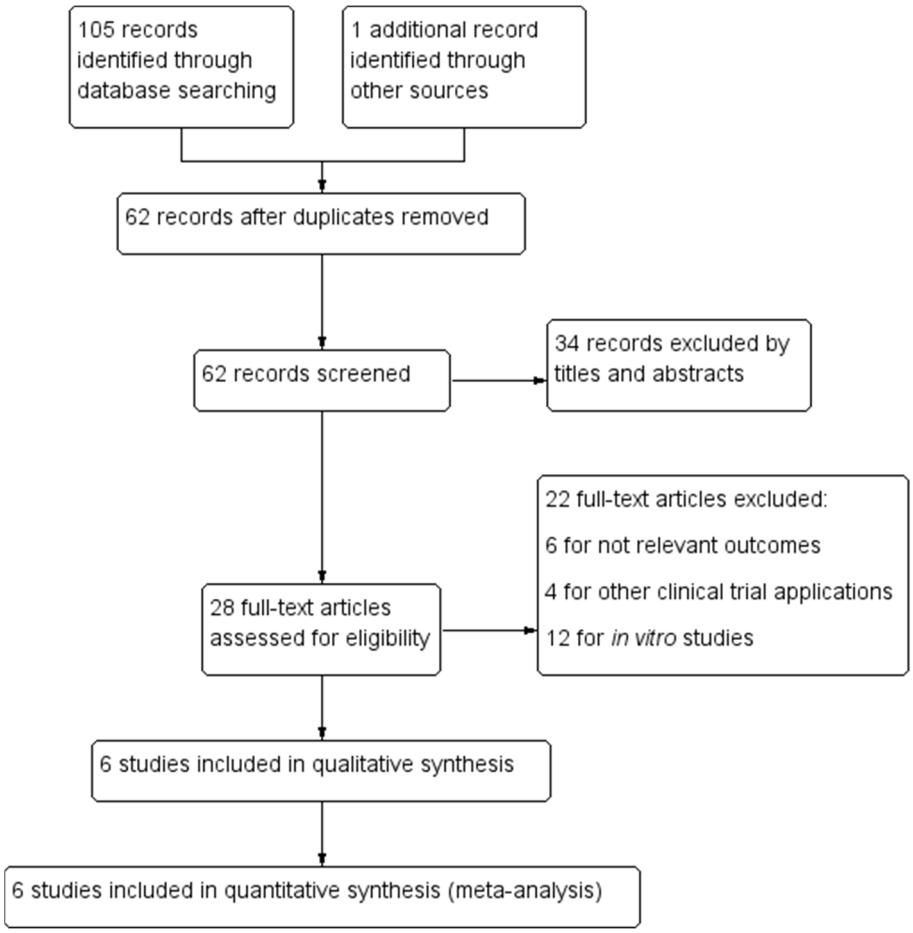


Figure 1. PRISMA flow diagram of literature search and selection of included studies in the systematic review (for the meta-analysis).

Based on the established standards, every RCT was of high quality and had a Jaded score ≥ 3. Furthermore, the RCT's risk of bias was assessed separately for each trial (Figures 2 and 3). Overall, good methodological quality was shown by the risk of bias analysis. Regarding random sequence generation (selection bias) and performance bias, all RCTs demonstrated a low risk of bias. The main areas where unclear bias risk was noted were in attrition, detection, and other biases. None of the studies had any category ranked as high risk of bias.

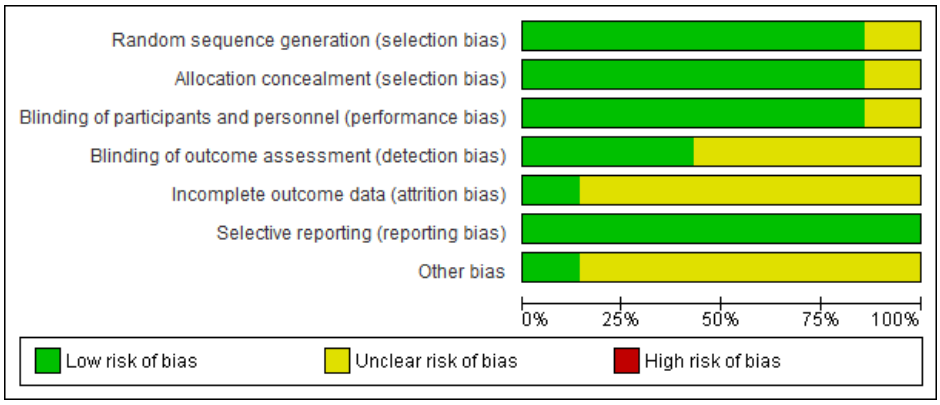


Figure 2. Risk of bias: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 3. Characteristics of clinical trials of SYNBIO® blend vs. placebo on bowel habits and PGWBI.

Study, Year (Ref)	Study Design	Sample Size (% Female)			Age (Years) Mean ± SD		Intervention				Comparator (Dose)	Outcomes Included in Meta-Analysis
		Total	Probiotic Group	Placebo Group	Probiotic Group	Placebo Group	Type	Dose (CFU/Daily)	Form	Duration (Weeks)		
Verdenelli et al., 2011a [12]	Double blind, randomized, parallel, placebo-controlled	47	24 (60)	23 (48)	29.9 ± 7.8	30.2 ± 7.4	SYNBIO® Blend	1.0×10^9	Probiotic food	12	Food without probiotics	Intestinal wellbeing and PGWBI
Verdenelli et al., 2011b [13]	Double blind, randomized, parallel, placebo-controlled	153	77 (57)	76 (55)	35.4 ± 4.9	34.7 ± 8.3	SYNBIO® Blend	1.0×10^9	Dietary supplement	12	Placebo capsules of maltodextrin	Intestinal wellbeing and PGWBI
Silvi et al., 2014a [21]	Double blind, randomized, parallel, placebo-controlled	421	208 (56)	213 (55)	44.1 ± 1.4	44.0 ± 1.2	SYNBIO® Blend	1.0×10^9	Dietary supplement	12	Placebo capsules of maltodextrin	Intestinal wellbeing and PGWBI
Silvi et al., 2014b [21]	Double blind, randomized, parallel, placebo-controlled	427	217 (54)	210 (57)	45.0 ± 0.9	44.0 ± 0.9	SYNBIO® Blend	1.0×10^9	Probiotic food	12	Food without probiotics	Intestinal wellbeing and PGWBI
Cecchini et al., 2016 [22]	Single arm, open label controlled towards the baseline	30	30 (40)	0	23.5 ± 8.7	-	SYNBIO® Blend	1.5×10^{10}	Dietary supplement	24	-	Intestinal wellbeing and PGWBI
Coman et al., 2017 [23]	Double blind, randomized, parallel, placebo-controlled	10	5 (60)	5 (80)	30.0 ± 12.9	26.6 ± 4.2	SYNBIO® Blend	1.0×10^9	Probiotic food	4	Food without probiotics	Intestinal wellbeing and PGWBI
Coman et al., 2023 [24]	Double blind, randomized, parallel, placebo-controlled	37	19 (32)	18 (39)	46.6 ± 3.0	44.3 ± 1.8	SYNBIO® Blend	1.5×10^{10}	Dietary supplement	4	Placebo capsules of maltodextrin	Intestinal wellbeing and PGWBI

CFU: Colony Forming Units; Intestinal wellbeing: constipation, intestinal regularity, stool volume and consistency, ease of defecation, bloating, flatulence, feeling of incomplete defecation, abdominal pains, intestinal cramps; PGWBI: Psychological General Well-Being Index.

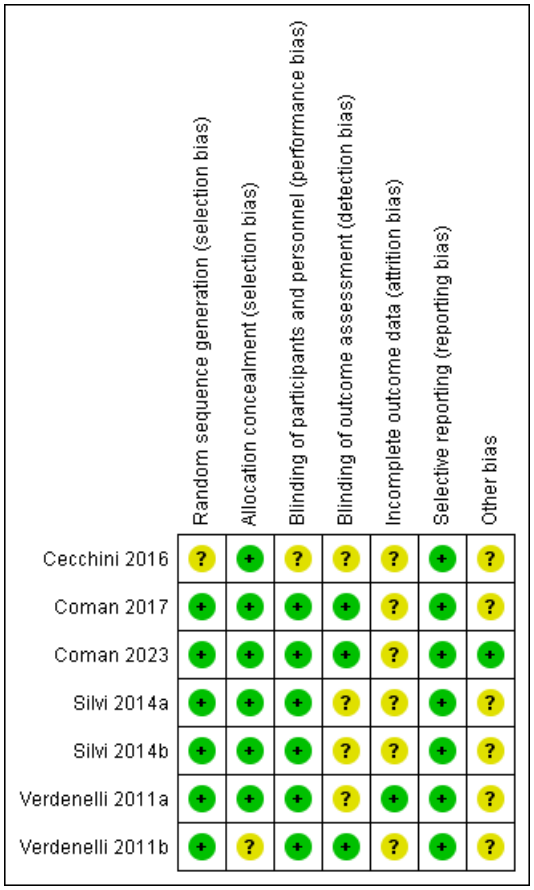


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (green with plus mark—low risk of bias, yellow with question mark—unclear risk of bias, red with an x—high risk of bias) [12,13,21–24].

3.2. Studies Using SYNBIO® Blend Pertinent to the Meta-Analyses

The probiotic blend was used in 6 clinical trials (Cecchini et al., 2016; Coman et al., 2017, Coman et al., 2023; Silvi et al., 2014; Verdenelli et al., 2011a; Verdenelli et al., 2011b) [12,13,21–24]. In one of them (Cecchini et al., 2016) [22] only the results from the probiotic group were included in the meta-analyses, since there was no placebo group in this trial. On the other hand, one published paper (Silvi et al., 2014) [21] was analysed as two separate studies since the publication included two independent and identically designed clinical studies, one with the SYNBIO® blend delivered as a dietary supplement in capsules, (referenced as Silvi et al., 2014a [21]) and the other with the SYNBIO® blend delivered as probiotic-enriched foods (referenced as Silvi et al., 2014b [21]), while each study had its own independent placebo group.

3.3. Effect of SYNBIO® Blend on Overall Constipation

Six clinical trials were selected for overall constipation data analysis, with a total of 550 subjects assigned to probiotic groups, and 545 subjects to the placebo groups.

The pooled data analysis indicated that probiotics significantly improved constipation score by 0.75 (95% CI: 0.31 to 1.19; $p = 0.0008$) (Figure 4). The random-effects analysis identified significant heterogeneity across studies for this parameter ($Ph < 0.00001$ and $I^2 = 91\%$).

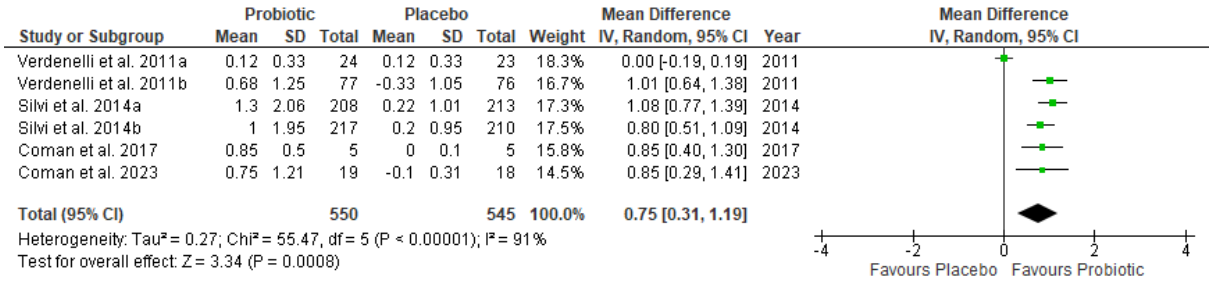


Figure 4. Forest plot comparing probiotic and placebo groups in term of overall constipation (n = 1095), considering a 10-point combined Likert scale (−5, 0, +5). Values calculated as mean differences (95% CIs) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [12,13,21,23,24].

Table 4 makes it evident that SYNBIO® blend consumption improved overall constipation in all studies, and in particular in Silvi et al. (20014a) [21], Silvi et al. (2014b) [21], and Coman et al. (2023) [24], with an average recorded improvement of 1.30, 1.00, and 1.21, respectively. These changes correspond to an improvement in constipation symptoms of at least one class in 95% of individuals consuming the SYNBIO® blend. In fact, at the 95% confidence interval, in Silvi et al., 2014a [21] for example, the probability of having a mean improvement of at least one class (PM > 1) is 0.98. Moreover, 52% of the sampled individuals improved their health status in terms of constipation (Imp.), 33% of the sampled individuals remained unchanged (Unc.), and 15% had symptoms which worsened (Wor.).

Table 4. Effects of SYNBIO® blend on overall constipation.

Studies Probiotic Groups	Overall Constipation							
	μ^{PB}				ϕ^{PB+}	$\phi^{PB=}$	ϕ^{PB-}	PM > 1
	Mean	SD	N. of Subjects	CI	% Imp.	% Unc.	% Wor.	
Verdenelli et al., 2011a [12]	0.12	0.33	24	[−0.02; 0.26]	12	88	0	0.00
Verdenelli et al., 2011b [13]	0.68	1.25	77	[0.39; 0.96]	31	68	1	0.01
Silvi et al., 2014a [21]	1.30	2.06	208	[1.02; 1.58]	52	33	15	0.98
Silvi et al., 2014b [21]	1.00	1.95	217	[0.74; 1.25]	46	37	17	1.00
Cecchini et al., 2016 [22]	0.40	0.40	30	[0.25; 0.54]	20	80	0	0.00
Coman et al., 2017 [23]	0.85	0.50	5	[0.41; 1.29]	20	80	0	0.00
Coman et al., 2023 [24]	1.21	0.57	19	[0.18; 1.31]	35	65	0	0.18

μ^{PB}—mean of score changing obtained with probiotics; ϕ^{PB+}—probability of having an improvement (Imp.) with probiotics; ϕ^{PB-}—probability of having a worsening (Wor.) with probiotics; $\phi^{PB=}$—probability of having no changes with probiotics (Unc.—unchanged), expressed as percentages; PM > 1—probability of having a mean improvement of at least one class.

Table 5 shows the effects of probiotic and placebo supplementation on constipation. In all the studies, the probability that the probiotic (ϕ^{PB+}) improves constipation is higher or equal to that of the placebo (ϕ^{PL+}). In addition, individuals taking the SYNBIO® blend had a lower probability of worsening or unchanged constipation symptoms ($\phi^{PB-} \leq \phi^{PL-}$ and $\phi^{PB=} \leq \phi^{PL=}$, respectively). The computed 95% CIs show a clear positive effect in favour of SYNBIO® blend supplementation, except a few cases with similar effects (Verdenelli et al., 2011a [12]; Coman et al., 2017 [23]).

Table 5. Comparison between SYNBIO® blend and placebo effects on constipation.

Constipation	Probiotic				Placebo				Differences of Proportions					
	Number of Subjects	ϕ^{PB+}	$\phi^{PB=}$	ϕ^{PB-}	Number of Subjects	ϕ^{PL+}	$\phi^{Pl=}$	ϕ^{PL-}	ϕ^{PB+}-ϕ^{PL+}		$\phi^{PB=}$-$\phi^{PL=}$		ϕ^{PB-}-ϕ^{PL-}	
		Imp.	Unc.	Wor.		Imp.	Unc.	Wor.	Imp.	CI	Unc.	CI	Wor.	CI
Verdenelli et al., 2011a [12]	24	0.12	0.88	0.00	23	0.12	0.88	0.00	0.00	[−0.18; 0.18]	0.00	[−0.18; 0.18]	0.00	[0.00; 0.00]
Verdenelli et al., 2011b [13]	77	0.31	0.68	0.01	76	0.05	0.75	0.20	0.26	[0.14; 0.37]	−0.07	[−0.21; 0.07]	−0.19	[−0.27; −0.09]
Silvi et al., 2014a [21]	208	0.52	0.33	0.15	213	0.26	0.58	0.16	0.26	[0.17; 0.35]	−0.25	[−0.34; −0.15]	−0.01	[−0.08; −0.06]
Silvi et al., 2014b [21]	217	0.46	0.37	0.16	210	0.31	0.45	0.23	0.15	[0.05; 0.23]	−0.08	[−0.16; −0.02]	−0.07	[−0.14; 0.01]
Cecchini et al., 2016 [22]	30	0.20	0.80	0.00										
Coman et al., 2017 [23]	5	0.20	0.80	0.00	5	0.20	0.80	0.00	0.00	[−0.50; 0.50]	0.00	[−0.50; 0.50]	0.00	[0.00; 0.00]
Coman et al., 2023 [24]	19	0.35	0.65	0.00	18	0.00	0.90	0.10	0.35	[0.14; 0.56]	−0.25	[−0.50; 0.00]	−0.10	[−0.23; 0.03]

ϕ^{PB+}. ϕ^{PL+}—probability of having an improvement (Imp.) with probiotics or placebo; ϕ^{PB-}. ϕ^{PL-}—probability of having a worsening (Wor.) with probiotics or placebo; $\phi^{PB=}$. $\phi^{PL=}$—probability of having no changes with probiotics or placebo (Unc.—unchanged).

3.4. Effect of SYNBIO® Blend on Intestinal Regularity

The pooled analysis indicates that probiotics significantly improved the intestinal regularity score by 1.90 compared to the placebo (95% CI: 1.02 to 2.78; $p < 0.0001$) (Figure 5). The random-effects analysis identified significant heterogeneity in this parameter across studies ($Ph < 0.00001$ and $I^2 = 97\%$).

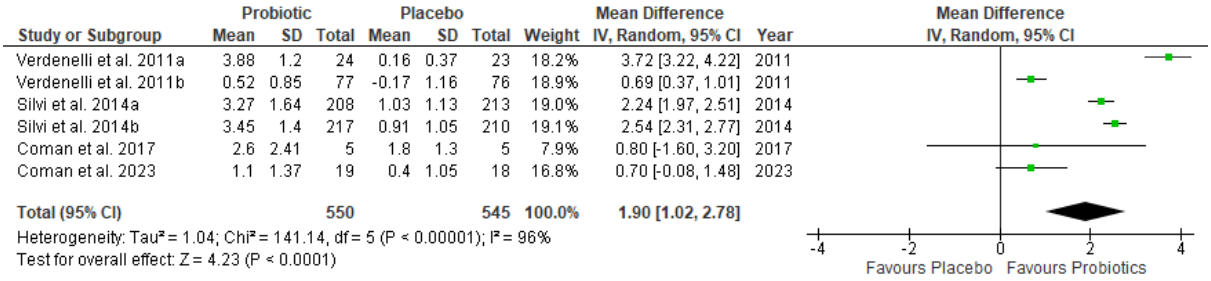


Figure 5. Forest plot comparing probiotic and placebo groups for intestinal regularity (n = 1095), considering a 10-point combined Likert scale (−5, 0, +5). Values calculated as mean differences (95% CIs) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [12,13,21,23,24].

Table 6 highlights that SYNBIO® blend supplementation significantly improves intestinal regularity with mean differences ranging between 1.10 and 3.88, which corresponds to a mean improvement of the intestinal regularity from 1 to almost 4 classes from the total 5. Except for Coman et al., 2017 [23], the percentage of individuals with significantly improved intestinal regularity varies from 45% to 100%, whereas the percentage of sampled individuals with unchanged intestinal regularity was 0% to 55%.

Table 6. Effects of the SYNBIO® blend on intestinal regularity.

Studies Probiotic Groups	Intestinal Regularity							
	μ^{PB}				ϕ^{PB+}	$\phi^{PB=}$	ϕ^{PB-}	PM > 1
	Mean	SD	Number of Subjects	CI	% Imp.	% Unc.	% Wor.	
Verdenelli et al., 2011a [12]	3.88	1.20	24	[3.39; 4.37]	100	0	0	1.00
Verdenelli et al., 2011b [13]	0.52	0.85	77	[0.33; 0.71]	32	68	0	0.00
Silvi et al., 2014a [21]	3.27	1.64	208	[3.05; 3.50]	91	8	1	1.00
Silvi et al., 2014b [21]	3.45	1.40	217	[3.27; 3.64]	94	6	0	1.00
Cecchini et al., 2016 [22]	1.90	0.50	30	[1.72; 2.08]	60	37	3	1.00
Coman et al., 2017 [23]	2.60	2.41	5	[−12.3; 17.5]	60	40	0	0.89
Coman et al., 2023 [24]	1.10	1.37	19	[0.46; 1.74]	45	55	0	0.63

μ^{PB}—mean of score changing obtained with probiotics; ϕ^{PB+}—probability of having an improvement (Imp.) with probiotics; ϕ^{PB-}—probability of having a worsening (Wor.) with probiotics; $\phi^{PB=}$—probability of having no change with probiotics (Unc.—unchanged); expressed as percentages; PM > 1—probability of having a mean improvement of at least one class.

Table 7 shows the comparison of probiotic and placebo supplementation on intestinal regularity. In all the studies, except Coman et al., 2017 [23], the probability of having an improvement with the SYNBIO® blend ϕ^{PB+} is higher than with placebo ϕ^{PL+}, while worsening of symptoms was negligible for the probiotic group ϕ^{PB-}, and no differences were found between the probiotic and the placebo groups in the number of individuals that had their scores for intestinal regularity unchanged ($\phi^{PB=} \leq \phi^{PL=}$). The computed 95% CIs show a positive effect in favour of the SYNBIO® blend except in Coman et al., 2017 [23].

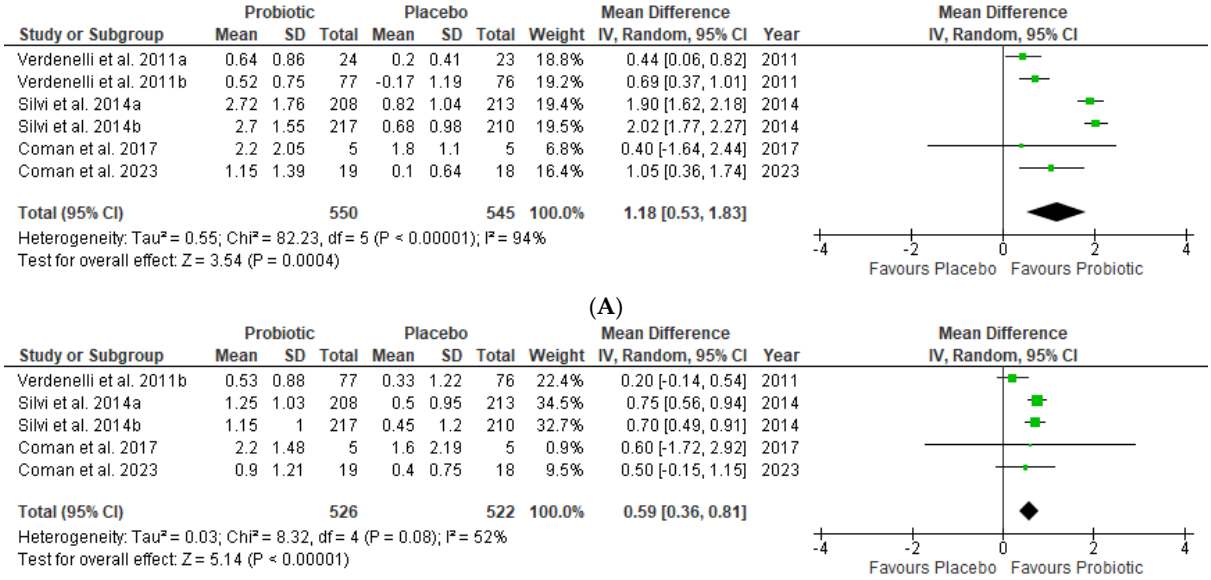
Table 7. Comparison between the SYNBIO® blend and placebo supplementation effect on intestinal regularity.

Intestinal Regularity	Probiotic				Placebo				Differences of Proportions					
	Number of Subjects	ϕ^{PB+}	$\phi^{PB=}$	ϕ^{PB-}	Number of Subjects	ϕ^{PL+}	$\phi^{Pl=}$	ϕ^{PL-}	ϕ^{PB+}-ϕ^{PL+}		$\phi^{PB=}$-$\phi^{PL=}$		ϕ^{PB-}-ϕ^{PL-}	
		Imp.	Unc.	Wor.		Imp.	Unc.	Wor.	Imp.	CI	Unc.	CI	Wor.	CI
Verdenelli et al., 2011a [12]	24	1.00	0.00	0.00	23	0.16	0.84	0.00	0.84	[0.70; 0.98]	−0.84	[−0.98; 0.70]	0.00	[0.00; 0.00]
Verdenelli et al., 2011b [13]	77	0.32	0.68	0.00	76	0.14	0.64	0.22	0.18	[0.05; 0.31]	0.04	[−0.12; 0.18]	−0.22	[−0.30; −0.12]
Silvi et al., 2014a [21]	208	0.91	0.08	0.01	213	0.68	0.23	0.09	0.23	[0.16; 0.31]	−0.15	[−0.22; 0.09]	−0.08	[−0.12; −0.04]
Silvi et al., 2014b [21]	217	0.94	0.06	0.00	210	0.61	0.35	0.04	0.33	[0.26; 0.41]	−0.29	[−0.37; −0.23]	−0.04	[−0.06; −0.01]
Cecchini et al., 2016 [22]	30	0.60	0.37	0.03										
Coman et al., 2017 [23]	5	0.60	0.40	0.00	5	0.80	0.20	0.00	−0.20	[−0.75; 0.35]	0.20	[−0.35; 0.75]	0.00	[0.00; 0.00]
Coman et al., 2023 [24]	19	0.45	0.55	0.00	18	0.25	0.70	0.05	0.20	[0.20; 0.49]	−0.15	[−0.45; 0.14]	−0.05	[−0.15; 0.05]

ϕ^{PB+}. ϕ^{PL+}—probability of having an improvement (Imp.) with probiotics or placebo; ϕ^{PB-}. ϕ^{PL-}—probability of having a worsening (Wor.) with probiotics or placebo; $\phi^{PB=}$. $\phi^{PL=}$—probability of having no changes with probiotics or placebo (Unc.—unchanged).

3.5. Effect of SYNBIO® Blend on Stool Volume and Consistency

The random-effects analysis also highlighted that probiotic consumption, either as dietary supplementation or probiotic-enriched foods, significantly increased the mean score of stool volume and consistency by 1.18 and 0.59, respectively, compared to the placebo (95% CI: 0.53–1.83; $p = 0.0004$ for stool volume, and 0.36–0.81; $p < 0.00001$ for stool consistency), meaning that stools were softer with SYNBIO® blend supplementation (Figure 6). Significant heterogeneity of both parameters was observed ($Ph < 0.00001$ and $I^2 = 94\%$ for stool volume and $Ph = 0.08$ and $I^2 = 52\%$ for stool consistency). The Bristol stool scale was the method used in all the studies for stool consistency monitoring.



(**A**)

(**B**)

Figure 6. Forest plot comparing probiotic and placebo groups for stool volume (**A**) and stool consistency (**B**), considering a 10-point combined Likert scale (−5, 0, +5). Values calculated as mean differences (95% CIs) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [12,13,21,23,24].

3.6. Effect of SYNBIO® Blend on Other Outcomes Related to Constipation

Table 8 shows the overall effect of SYNBIO® blend supplementation compared to placebo on other outcomes related to constipation, such as ease of defecation, bloating, abdominal pain, and intestinal cramping. The largest improvements were registered for ease of defecation and bloating, with significantly higher values of 1.2 (95% CI: 0.64 to 1.77; $p < 0.0001$) and 0.69 (95% CI: 0.19 to 1.18; $p = 0.006$), respectively.

Table 8. Pooled analysis of the efficacy of the SYNBIO® blend for constipation in term of other outcomes (ease of defecation, bloating, abdominal pain, and intestinal cramping).

Outcomes	Number of Studies	Number of Subjects	Pooled Results			
			MD	95% CI	*p* Value	AEM
Ease of defecation	6	1095	1.20	0.64, 1.77	<0.0001	REM
Bloating	5	1048	0.69	0.19, 1.18	0.006	REM
Abdominal pain	5	1048	0.35	−0.02, 0.71	0.07	REM
Intestinal cramping	5	1048	0.13	−0.03, 0.30	0.11	REM

MD: mean difference; CI: confidence interval; AEM: analytical effect model; REM: random-effects model.

In addition, the meta-analyses show that the SYNBIO® blend improved the overall severity of incomplete evacuation, and flatulence severity was close to statistical significance ($p > 0.05$).

3.7. Effect of SYNBIO® Blend on Psychological General Well-Being Index (PGWBI)

Five clinical studies, including 1,048 subjects, reported PGWBI scores in both the probiotic and placebo groups. Overall, SYNBIO® blend supplementation improved the psychological general wellbeing of subjects when compared to the placebo group, with an improved score effect of 8.46 (95% CI: 8.15 to 8.78; $p < 0.00001$), which translates to an improved quality of life (Figure 7).

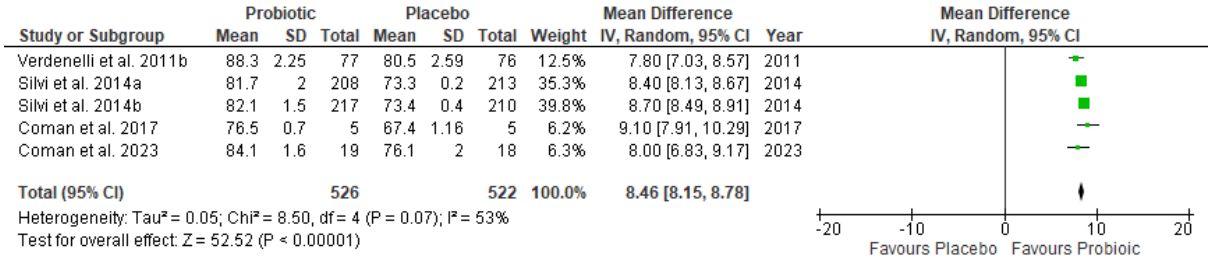


Figure 7. Forest plot comparing probiotic and placebo groups for PGWBI (n = 1048), considering the global score ranged from 0 to 100 (best). Values calculated as mean differences (95% CIs) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [13,21,23,24].

3.8. Response to SYNBIO® Blend Supplementation—The Effect of Dose, Form, and Duration

The data analysis indicates a slightly but not significantly higher benefit of SYNBIO® blend supplementation on overall constipation when consumed in a dose of 1.5×10^{10} CFU or 1.0×10^{9} CFU (0.75, 95% CI: 0.31–1.19; $p = 0.77$) (Figure 8).

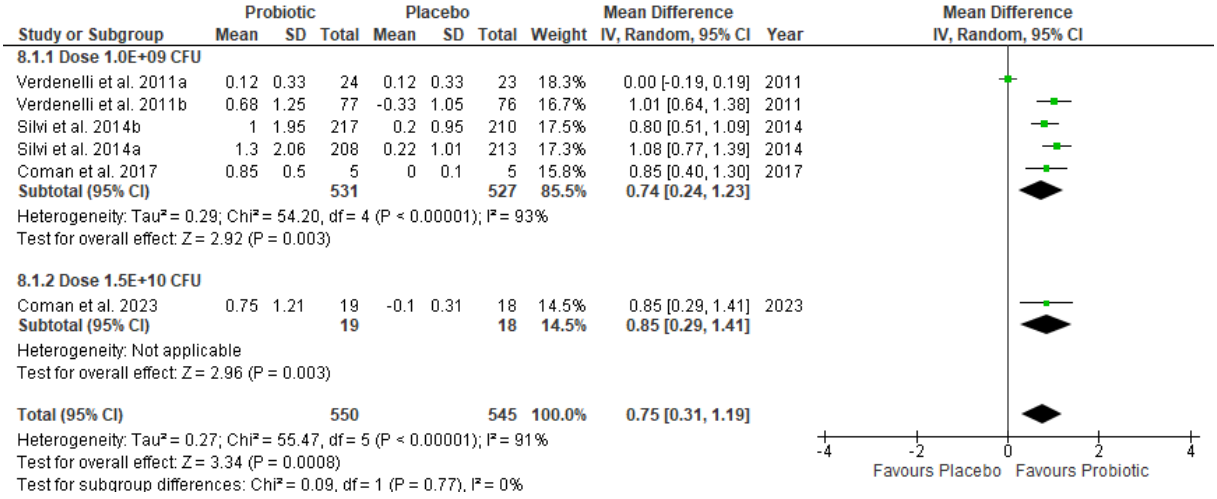


Figure 8. Forest plot comparing probiotic and placebo groups on constipation (1.0×10^{9} and 1.5×10^{10} CFU/daily dose, n = 1095), considering a 10-point combined Likert scale (−5, 0, +5). Values calculated as mean differences (95% CIs) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [12,13,21,23,24].

Moreover, the benefit of SYNBIO® blend supplementation on overall constipation compared to placebo was not significantly different when consumed as a dietary supple-

ment or as probiotic-enriched foods ($p = 0.15$), although the dietary supplements resulted in a higher MD (1.02; 95% CI: 0.80 to 1.24; $p < 0.00001$) than probiotic-enriched foods (0.53; 95% CI: −0.09 to 1.15; $p = 0.09$) (Figure 9).

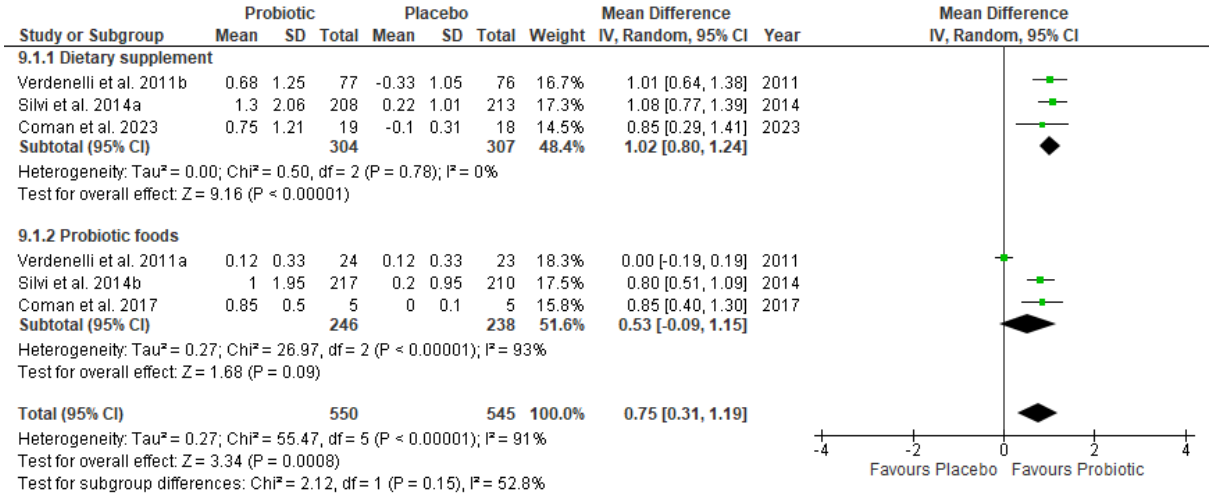


Figure 9. Forest plot comparing probiotic and placebo groups on overall constipation delivered as dietary supplements or probiotic-enriched foods, n = 1095), considering a 10-point combined Likert scale (−5, 0, +5). Values calculated as mean differences (95% CIs) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [12,13,21,23,24].

Regarding the supplementation duration, no significant differences were found between 4 weeks and 12 weeks ($p = 0.69$) (Figure 10).

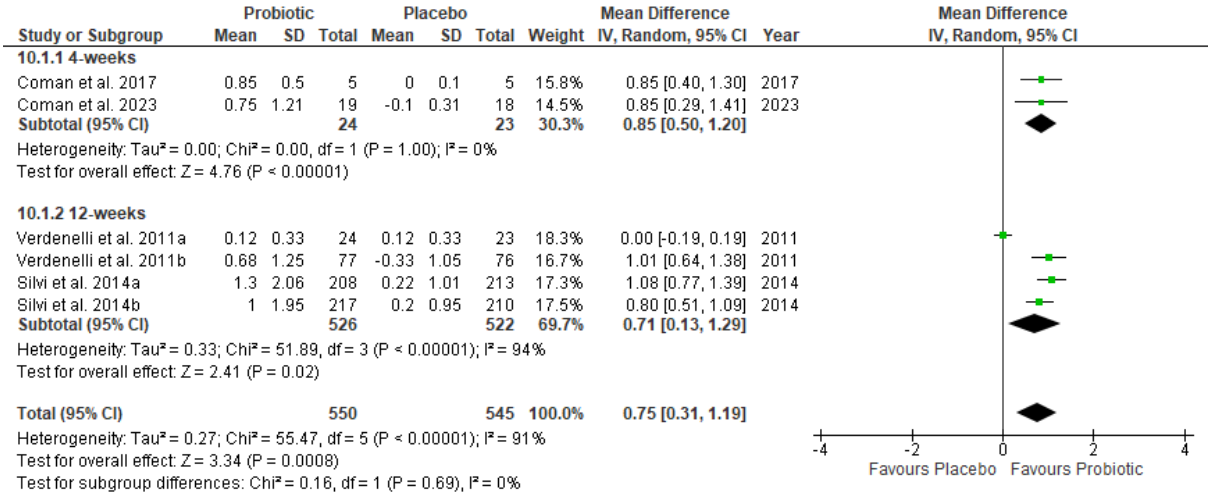


Figure 10. Forest plot comparing probiotic and placebo groups on overall constipation depending on treatment duration (4 weeks and 12 weeks) (n = 1095), considering a 10-point combined Likert scale (−5, 0, +5). Values calculated as mean differences (95% Cis) using a random-effects model. CI: confidential interval; IV: inverse variance; SD: standard deviation (green square indicates the effect and the weight assigned to the study; horizontal line depicts the confidence interval; black rhombus shows the overall result) [12,13,21,23,24].

3.9. Adverse Events with Probiotics

No adverse events were reported in any of the studies analysed in the present review, neither in the probiotic nor the placebo groups.

In the studies where SYNBIO® probiotic-enriched foods were used [13,21,23], the study products were rated as "good" or "very good" by subjects.

4. Discussion

The present systematic review and meta-analysis shows that the SYNBIO® blend is significantly effective in improving constipation, in terms of statistically significant improvement in intestinal regularity, stool frequency, stool volume and consistency, ease of defecation, bloating, abdominal pain, and intestinal cramping scores. It is evident that the SYNBIO® blend ameliorates constipation in otherwise healthy people, through several mechanisms which significantly shorten gastrointestinal transit, and increase stool frequency, thus improving also stool consistency and the other factors related to constipation.

One of the main strengths of this systematic review and meta-analysis is the use of a rigorous and appropriate methodology, which is in line with the standards set by other recent reviews and meta-analyses [1,25–27] using comparable methodological techniques. The strict standards for research selection, data extraction, and analysis process followed in this review guarantee the reliability and reproducibility of its findings, providing robust conclusions. This methodological rigor increases the analysis's overall quality and reduces biases, making the results more credible and comparable to other high-quality research in the field. The eligibility assessment and data extraction were carried out independently and in duplicate. To reduce the probability that the probiotic supplementation effect would be overstated, the data were pooled using a random-effects model. Additionally, the probiotic supplementation effects based on dosage, type, and duration, were evaluated. The primary goal of the present meta-analysis and all of these methodological elements make this review unique and original.

The present findings are in line with current evidence, meta-analyses and systematic reviews highlighting that in general, probiotics have significant, however limited, effects on gastrointestinal symptoms of which constipation is included [1,4,27]. However, future research should indeed focus on examining several variables to broaden the relevance and applicability of findings across diverse groups, including subjects suffering from acute (short-term) or chronic (long-lasting) constipation and stratified by age (age-related changes in gut microbiota), gender (hormonal differences), and race (genetic diversity across racial groups), considering also lifestyle factors (diet, physical activity) and medical history. The present systematic review and meta-analysis has some limitations which arise from the type of the studies involved in the synthesis. Limitations consist also in not including objective data on fibre intake in the studies, recognizing that fibre is a well-established contributor to gut health. However, highlighting other key dietary components (such as fatty acids, phytochemicals, and vitamins) can provide a more comprehensive understanding of factors influencing gut health. By including all these components, future studies could offer a more comprehensive view of how diet influences gut microbiota and metabolism, potentially leading to more effective dietary interventions for gut health.

Furthermore, the current statistical results also imply that the SYNBIO® blend may be beneficial, even if not substantially, for those people experiencing symptoms such as incomplete evacuation and flatulence, which impact more than 50% of individuals with constipation [28].

On the other hand, no discernible variations regarding the supplementation type and duration were found, in line with evidence reported in another similar meta-analysis [29]. Regarding the SYNBIO® blend dosage, some parameters analysed were more prominent at 1.5×10^{10} CFU/day compared with 1.0×10^{9} CFU/day, although not significant.

Current research demonstrates that the gut microbiota composition plays a crucial role in both the aetiology and management of functional constipation. When compared to healthy subjects, constipated individuals had lower abundance of Bifidobacteria and Lactobacilli and higher numbers of Bacteroidetes [4,30–32]. The studies considered in the present meta-analyses demonstrated that the SYNBIO® blend modulates the gut microbiota composition, significantly increasing the abundance of beneficial bacteria groups (Lacto-

bacilli and Bifidobacteria) and decreasing bacteria generally associated with dysbiosis and diseases (Bacteroidetes, Clostridium, and Enterobacteriaceae) [12,13,21–24]. Also, Ding and co-workers [26] reported that a probiotic supplementation represented a proactive effort towards helping people with constipation restore their gut structural imbalance. Some microorganisms, such as Lactobacilli and Bifidobacteria, essential for a healthy gut function, break down indigestible foods and produce metabolites like serotonin and short-chain fatty acids that stimulate the motility of the stomach. It is speculated that increased SCFA content can restore normal gut motility, which is considered one of the main mechanisms of action of probiotics for constipation improvement [29,32–35]. In this regard, several studies confirmed the capacity of the SYNBIO® blend to increase acetic, propionic, and butyric acids in the gastrointestinal environment, which are directly related to beneficial effects on the intestinal wellbeing of the host [36–38]. However, several studies that show improvements in constipation-related outcomes do not report changes in SCFAs [31,33,39], suggesting that this is not the only mechanism behind constipation alleviation by probiotics.

The immune system is known to affect gut motility and there is growing evidence that many individuals that report constipation also have low-grade inflammation [29,31–33,35]. The SYNBIO® blend, taken either as enriched foods or dietary supplements, have shown to reduce different parameters of inflammation (e.g., sIgA, hsCRP) and counteract inflammatory processes in humans [23,24,37].

Indeed, by targeting gut motility, microbiota composition, and inflammation, probiotics have the potential to impact the pathophysiological causes of constipation through several important pathways [29,31,35]. Recent clinical research indicates that probiotics can effectively cure constipation, resulting in notable enhancements in gastrointestinal regulatory peptides, neurotransmitters, neurotrophic factors, and gut microbiota composition [32,40]. Also, according to Yan and co-workers [35], consuming probiotics increased the frequency of stools, reduced bloating and gastrointestinal discomfort, and enhanced the individuals' overall quality of life. The findings of the present review and the clinical trials analysed are in line with the evidence present in the literature [1,4,5,31,33,35]. In summary, the potential mechanisms of probiotics' action on constipation, effectively reducing its incidence, include: (I) lowering the pH in the gut, stimulating digestive enzyme production, and facilitating food breakdown and absorption; (II) promoting gut motility, facilitating food's fast passage through the gut, and minimizing the incidence of constipation; (III) modulating the gut microbiota, increasing the abundance of beneficial bacteria, and inhibiting the growth of harmful bacteria; and (IV) promoting water absorption in the gut, making faeces soft and easy to pass, and minimizing the incidence of constipation [25,29,31,32].

Probiotics are becoming more and more popular as a new alternative approach for constipation management due to their positive impact on quality of life and potential reduction of symptoms associated with constipation. However, there are still conflicting data about the efficacy of probiotics; certain strains seem to have positive effects, while others appear negligible. This emphasizes that probiotic effects may vary depending on the strain, and that in order to develop future clinical recommendations for probiotic use in constipation, each strain must be tested in high-quality research clinical trials using standardized and validated assessment protocols, as also reported in the literature [29,31,32,35,41]. This, together with the increasing use of probiotics for constipation, suggests that the general public needs to be made aware of the present status of the research findings on probiotics for constipation through clear and correct communication. Probiotics (including the SYNBIO® blend) offer a promising long-term approach without any side effects compared to laxatives, but act slowly and may not be as effective on the subjects in the same way. Combining probiotics with dietary fibre could enhance outcomes, while laxatives should be reserved for acute cases or specific medical conditions where rapid relief is required, under clinical recommendations. Healthcare professionals should be informed/educated about the importance of probiotic usage among the general public as well as the strain-specificity of its effects.

5. Conclusions

Overall, the SYNBIO® blend reduces the severity of constipation, through intestinal regularity and other integrative symptoms. The statistical evaluation of several clinical trials supports the use of the SYNBIO® blend for improvement in ease of defecation and abdominal pain, intestinal cramping, and stool frequency, significantly benefiting the general wellbeing status of individuals. The SYNBIO® blend may be a suitable natural substitute for conventional treatment methods for constipation, like dietary fibres or laxatives, which usually carry unpleasant side effects.

Author Contributions: Conceptualization, M.M.C. and M.C.V.; methodology, M.M.C. and N.E.; software, M.M.C. and N.E; validation, M.M.C., M.C.V., N.E. and R.D.L.; formal analysis, M.M.C. and N.E.; investigation, M.M.C. and M.C.V.; resources, M.M.C. and M.C.V.; data curation, M.M.C.; writing—original draft preparation, M.M.C.; writing—review and editing, M.M.C. and M.C.V.; visualization, M.M.C., M.C.V., S.S. and R.D.L.; supervision, M.C.V.; project administration, M.M.C. and M.C.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are unavailable due to privacy or ethical restrictions.

Conflicts of Interest: The authors declare no conflicts of interest. The authors Maria Magdalena Coman and Maria Cristina Verdenelli are employed by Synbiotec S.r.l., a spin-off of UNICAM, Camerino, Italy.

References

1. van der Schoot, A.; Helander, C.; Whelan, K.; Dimidi, E. Probiotics and synbiotics in chronic constipation in adults: A systematic review and meta-analysis of randomized controlled trials. *Clin. Nutr.* **2022**, *41*, 2759–2777. [CrossRef] [PubMed]
2. Lin, X.; Liu, Y.; Ma, L.; Ma, X.; Shen, L.; Ma, X.; Chen, Z.; Chen, H.; Li, D.; Su, Z.; et al. Constipation induced gut microbiota dysbiosis exacerbates experimental autoimmune encephalomyelitis in C57BL/6 mice. *J. Transl. Med.* **2021**, *19*, 317. [CrossRef] [PubMed]
3. Peery, A.F.; Crockett, S.D.; Murphy, C.C.; Jensen, E.T.; Kim, H.P.; Egberg, M.D.; Lund, J.L.; Moon, A.M.; Pate, V.; Barnes, E.L.; et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2021. *Gastroenterology* **2022**, *162*, 621–644. [CrossRef] [PubMed]
4. Šola, K.F.; Vladimir-Knežević, S.; Hrabač, P.; Mucalo, I.; Saso, L.; Verbanac, D. The effect of multistrain probiotics on functional constipation in the elderly: A randomized controlled trial. *Eur. J. Clin. Nutr.* **2022**, *76*, 1675–1681. [CrossRef] [PubMed]
5. Pan, R.; Wang, L.; Xu, X.; Chen, Y.; Wang, H.; Wang, G.; Zhao, J.; Chen, W. Crosstalk between the Gut Microbiome and Colonic Motility in Chronic Constipation: Potential Mechanisms and Microbiota Modulation. *Nutrients* **2022**, *14*, 3704. [CrossRef]
6. Reigstad, C.S.; Kashyap, P.C. Beyond phylotyping: Understanding the impact of gut microbiota on host biology. *Neurogastroenterol. Motil.* **2013**, *25*, 358–372. [CrossRef]
7. Tierney, B.T.; Yang, Z.; Luber, J.M.; Beaudin, M.; Wibowo, M.C.; Baek, C.; Mehlenbacher, E.; Patel, C.J.; Kostic, A.D. The Landscape of Genetic Content in the Gut and Oral Human Microbiome. *Cell Host Microbe* **2019**, *26*, 283–295.e8. [CrossRef]
8. Major, G.; Spiller, R. Irritable bowel syndrome, inflammatory bowel disease and the microbiome. *Curr. Opin. Endocrinol. Diabetes Obes.* **2014**, *21*, 15–21. [CrossRef]
9. Bhat, M.I.; Sowmya, K.; Kapila, S.; Kapila, R. Potential Probiotic Lactobacillus rhamnosus (MTCC-5897) Inhibits Escherichia coli Impaired Intestinal Barrier Function by Modulating the Host Tight Junction Gene Response. *Probiotics Antimicrob. Proteins* **2020**, *12*, 1149–1160. [CrossRef]
10. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* **2009**, *339*, b2535. [CrossRef]
11. Shea, B.J.; Reeves, B.C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; Kristjansson, E.; et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **2017**, *358*, j4008. [CrossRef] [PubMed]
12. Verdenelli, M.C.; Silvi, S.; Cecchini, C.; Orpianesi, C.; Cresci, A. Influence of a combination of two potential probiotic strains, Lactobacillus rhamnosus IMC 501® and Lactobacillus paracasei IMC 502® on bowel habits of healthy adults: Effect of probiotics on healthy humans. *Lett. Appl. Microbiol.* **2011**, *52*, 596–602. [CrossRef] [PubMed]
13. Verdenelli, M.C.; Silvi, S.; Cecchini, C.; Orpianesi, C.; Cresci, A. Effect of probiotic combination Synbio on respiratory and gastrointestinal symptoms in athletes. *Prebiotics Probiotics* **2011**, 13–16.

14. Dupuy, H. The Psychological General Well-Being (PGWB) index. In *Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies*; Le Jacq Publishing: New York, NY, USA, 1984; pp. 170–183.
15. Lewis, S.J.; Heaton, K.W. Stool form scale as a useful guide to intestinal transit time. *Scand. J. Gastroenterol.* **1997**, *32*, 920–924. [CrossRef] [PubMed]
16. Clark, H.D.; Wells, G.A.; Huët, C.; McAlister, F.A.; Salmi, L.R.; Fergusson, D.; Laupacis, A. Assessing the Quality of Randomized Trials: Reliability of the Jadad Scale. *Control. Clin. Trials* **1999**, *20*, 448–452. [CrossRef]
17. RevMan. Available online: https://training.cochrane.org/online-learning/core-software/revman (accessed on 27 November 2023).
18. Lau, J.; Ioannidis, J.P.; Schmid, C.H. Quantitative synthesis in systematic reviews. *Ann. Intern. Med.* **1997**, *127*, 820–826. [CrossRef]
19. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials revisited. *Contemp. Clin. Trials* **2015**, *45*, 139–145. [CrossRef]
20. Akers, J.; Aguiar-Ibáñez, R.; Sari, A. *CRD's Guidance for Undertaking Reviews in Health Care*; University of York: Heslington, UK, 2009.
21. Silvi, S.; Verdenelli, M.C.; Cecchini, C.; Coman, M.M.; Bernabei, M.S.; Rosati, J.; De Leone, R.; Orpianesi, C.; Cresci, A. Probiotic-enriched foods and dietary supplement containing SYNBIO positively affects bowel habits in healthy adults: An assessment using standard statistical analysis and Support Vector Machines. *Int. J. Food Sci. Nutr.* **2014**, *65*, 994–1002. [CrossRef]
22. Cecchini, C.; Verdenelli, M.C.; Silvi, S.; Coman, M.M.; Orpianesi, C.; Pascucci, G.; Colizzi, V.; Cresci, A.; Filoni, R. Effects of synbiotics on house dust mite allergic symptoms: A baseline-controlled open-label study. *Int. J. Probiotics Prebiotics* **2016**, *11*, 117.
23. Coman, M.M.; Verdenelli, M.C.; Silvi, S.; Cecchini, C.; Gabbianelli, R.; Amadio, E.; Orpianesi, C.; Cresci, A. Knowledge and acceptance of functional foods: A preliminary study on influence of a synbiotic fermented milk on athlete health. *Int. J. Probiotics Prebiotics* **2017**, *12*, 33.
24. Coman, M.M.; Micioni Di Bonaventura, M.V.; Cifani, C.; Silvi, S.; Verdenelli, M.C. SYNBIO® Probiotic and Antioxidant Dietary Supplementation: Clinical Trial Evaluation of Potential Effects on Airline Flight Crew Members' Well-Being. *Microorganisms* **2023**, *11*, 924. [CrossRef] [PubMed]
25. Deng, X.; Shang, X.; Zhou, L.; Li, X.; Guo, K.; Xu, M.; Hou, L.; Hui, X.; Li, S. Efficacy and Safety of Probiotics in Geriatric Patients with Constipation: Systematic Review and Meta-Analysis. *J. Nutr. Health Aging* **2023**, *27*, 1140–1146. [CrossRef] [PubMed]
26. Ding, F.; Hu, M.; Ding, Y.; Meng, Y.; Zhao, Y. Efficacy in bowel movement and change of gut microbiota on adult functional constipation patients treated with probiotics-containing products: A systematic review and meta-analysis. *BMJ Open* **2024**, *14*, e074557. [CrossRef]
27. Wen, Y.; Li, J.; Long, Q.; Yue, C.-C.; He, B.; Tang, X.-G. The efficacy and safety of probiotics for patients with constipation-predominant irritable bowel syndrome: A systematic review and meta-analysis based on seventeen randomized controlled trials. *Int. J. Surg.* **2020**, *79*, 111–119. [CrossRef]
28. Johanson, J.F.; Kralstein, J. Chronic constipation: A survey of the patient perspective. *Aliment. Pharmacol. Ther.* **2007**, *25*, 599–608. [CrossRef]
29. Jeong, J.J.; Ganesan, R.; Jin, Y.J.; Park, H.J.; Min, B.H.; Jeong, M.K.; Yoon, S.J.; Choi, M.R.; Choi, J.; Moon, J.H.; et al. Multi-strain probiotics alleviate loperamide-induced constipation by adjusting the microbiome, serotonin, and short-chain fatty acids in rats. *Front. Microbiol.* **2023**, *14*, 1174968. [CrossRef]
30. Chen, Z.; Peng, Y.; Shi, Q.; Chen, Y.; Cao, L.; Jia, J.; Liu, C.; Zhang, J. Prevalence and Risk Factors of Functional Constipation According to the Rome Criteria in China: A Systematic Review and Meta-Analysis. *Front. Med.* **2022**, *9*, 815156. [CrossRef]
31. Dimidi, E.; Mark Scott, S.; Whelan, K. Probiotics and constipation: Mechanisms of action, evidence for effectiveness and utilisation by patients and healthcare professionals. *Proc. Nutr. Soc.* **2020**, *79*, 147–157. [CrossRef]
32. He, Y.; Zhu, L.; Chen, J.; Tang, X.; Pan, M.; Yuan, W.; Wang, H. Efficacy of Probiotic Compounds in Relieving Constipation and Their Colonization in Gut Microbiota. *Molecules* **2022**, *27*, 666. [CrossRef]
33. Dimidi, E.; Christodoulides, S.; Scott, S.M.; Whelan, K. Mechanisms of Action of Probiotics and the Gastrointestinal Microbiota on Gut Motility and Constipation. *Adv. Nutr.* **2017**, *8*, 484–494. [CrossRef]
34. Salminen, S.; Salminen, E. Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. *Scand. J. Gastroenterol. Suppl.* **1997**, *222*, 45–48. [CrossRef] [PubMed]
35. Yan, J.; Wu, M.; Zhao, W.; Kwok, L.-Y.; Zhang, W. Effects of probiotics and its fermented milk on constipation: A systematic review. *Food Sci. Hum. Wellness* **2023**, *12*, 2124–2134. [CrossRef]
36. Gu, Y.; Chen, H.; Li, X.; Li, D.; Sun, Y.; Yang, L.; Ma, Y.; Chan, E.C. Lactobacillus paracasei IMC 502 ameliorates type 2 diabetes by mediating gut microbiota–SCFA–hormone/inflammation pathway in mice. *J. Sci. Food Agric.* **2023**, *103*, 2949–2959. [CrossRef] [PubMed]
37. Salvesi, C.; Silvi, S.; Fiorini, D.; Alessandroni, L.; Sagratini, G.; Palermo, F.A.; De Leone, R.; Egidi, N.; Cifani, C.; Di Bonaventura, M.V.M.; et al. Six-Month Synbio® Administration Affects Nutritional and Inflammatory Parameters of Older Adults Included in the PROBIOSENIOR Project. *Microorganisms* **2023**, *11*, 801. [CrossRef]
38. Salvesi, C.; Silvi, S.; Fiorini, D.; Scortichini, S.; Sagratini, G.; Palermo, F.A.; De Leone, R.; Egidi, N.; Fatone, L.; Cifani, C.; et al. Impact of a probiotic diet on well-being of healthy senior: THE PROBIOSENIOR PROJECT. *J. Appl. Microbiol.* **2022**, *133*, 2941–2953. [CrossRef]

39. Wang, G.; Yang, S.; Sun, S.; Si, Q.; Wang, L.; Zhang, Q.; Wu, G.; Zhao, J.; Zhang, H.; Chen, W. Lactobacillus rhamnosus Strains Relieve Loperamide-Induced Constipation via Different Pathways Independent of Short-Chain Fatty Acids. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 423. [CrossRef]
40. Bharucha, A.E.; Lacy, B.E. Mechanisms, Evaluation, and Management of Chronic Constipation. *Gastroenterology* **2020**, *158*, 1232–1249.e3. [CrossRef]
41. Araújo, M.M.; Botelho, P.B. Probiotics, prebiotics, and synbiotics in chronic constipation: Outstanding aspects to be considered for the current evidence. *Front. Nutr.* **2022**, *9*, 935830. [CrossRef]