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Clinical Guidance and Practical Recommendations for Probiotic Use in Patients With Irritable Bowel Syndrome, Functional Constipation, and *Clostridioides difficile* Infection Considering Sex-based Differences

Yong Sung Kim,[1,2] Seon-Young Park,[3] Seung Joo Kang,[4] Min Woo Lee,[5] Yonghoon Choi,[6] Byung Yong Kim,[7] Miyoung Choi,[8] Cheol Min Shin,[6] Young Sun Kim,[4] Nayoung Kim,[5,6]* and Moo In Park[9]*;
Gut Microbiota and Therapy Research Group of the Korean Society for Neurogastroenterology and Motility

[1]Digestive Disease Research Institute, School of Medicine, Wonkwang University, Iksan, Jeonlabuk-do, Korea; [2]Kim's GutEase Internal Medicine, Gunpo, Gyeonggi-do, Korea; [3]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea; [4]Department of Internal Medicine, Healthcare System Gangnam Center Seoul National University Hospital, Seoul, Korea; [5]Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; [6]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Korea; [7]Department of Food Science and Biotechnology, Konyang University, Nonsan, Chungcheongnam-do, Korea; [8]Division of Healthcare Research, National Evidence-based Healthcare Collaborating Agency, Seoul, Korea; and [9]Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Probiotics have gained increasing clinical attention as adjunctive treatment for lower gastrointestinal disorders. However, evidence supporting their therapeutic efficacy remains limited, particularly with regard to sex-related differences. This expert review provides evidence-based insights and practical recommendations for the use of probiotics in patients with irritable bowel syndrome (IBS), functional constipation (FC), and *Clostridioides difficile* infection (CDI), considering possible sex-related differences. Evidence from randomized controlled trials and meta-analyses indicates that probiotics can modestly improve global symptoms, abdominal pain, and bloating in IBS and enhance bowel movement frequency and stool consistency in FC. However, these effects are strain-specific and heterogeneous. Although clinical studies on probiotics in IBS have not confirmed significant sex-related differences, experimental animal studies using stress-induced IBS models have demonstrated sex-dependent responses to specific probiotic strains, supporting the biological plausibility of such differences. For CDI, the efficacy of probiotics in preventing primary or recurrent infections remains inconsistent across large trials, and current guidelines usually do not recommend their routine use. However, sex and age difference of immunology supports the clinical differences of CDI. Probiotics are generally considered safe for healthy individuals, although caution is advised in patients who are immunocompromised or critically ill. Clinicians should select probiotic products based on strain-specific clinical evidence, adequate viable doses, patient's characteristics, or patient's sex. In conclusion, probiotics might play a role as adjunctive therapy for IBS and FC, with variability in responses influenced by microbial, host, and potential sex-related factors. Further research is needed to establish optimized personalized probiotic strategies.

Keywords: *Clostridioides difficile*; Constipation; Irritable bowel syndrome; Probiotics; Sex

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***Correspondence:** Nayoung Kim and Moo In Park are equally responsible for this study.
Nayoung Kim, MD, PhD
Department of Internal Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Korea
Tel: + 82-31-787-7008, **E-mail:** nakim49@snu.ac.kr, nayoungkim49@empas.com

Moo In Park, MD, PhD
Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu 49267, Busan, Korea
Tel: +82-51-990-6719, **E-mail:** mipark@ns.kosinmed.or.kr

Yong Sung Kim, Seon-Young Park, and Seung Joo Kang are co-first authors and contributed equally to this paper.

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INTRODUCTION

For over a century, probiotics have been widely consumed as fermented beverages and supplements to promote gut health. Over the past 2 decades, research on gut microbiota has expanded rapidly, highlighting its pivotal role in human health, leading to the development of microbiome-based therapeutics, including probiotics. Nowadays, probiotics are commonly used for lower gastrointestinal (GI) disorders, such as irritable bowel syndrome (IBS) and functional constipation (FC), whereas their role in *Clostridioides difficile* infection (CDI) remains more controversial.[1-3] Despite multiple prior meta-analyses, considerable uncertainty remains, including which probiotic strains, doses, and intervention periods are necessary to meaningfully improve symptoms in IBS, FC, or CDI, warranting a focused synthesis of the most reliable and clinically relevant evidence. This considerable discrepancy could originate from the influence of complex environmental factors, ranging from diet to biological factors such as sex. As IBS and FC are more prevalent in women and gut microbiota exhibits well-established sex-specific differences, probiotics may exert sex-specific therapeutic effects. It is well known that sex hormones affect the gut microbiome, especially through the immune activity.[4] In addition, both estrogen and androgens are affected by gut microbiome, especially by β-glucuronidase-producing microbiome in the menopause and in old males.[5] Furthermore, there are biologically plausible mechanisms linking sex differences with gut microbiota composition, immune signaling, or visceral sensitivity.[4-6] However, few studies have explored whether probiotic efficacy varies by sex. This review summarizes the current concepts of probiotics and evaluates evidence supporting their use in patients with lower GI disorders, with a focus on potential sex-related differences.

SEARCH STRATEGY AND STUDY SELECTION

This review was conducted to summarize and interpret the current evidence on probiotics on IBS, FC, and CDI in terms of sex differences. A literature search was performed using MEDLINE, EMBASE, and Cochrane Central. Search terms for probiotics included combinations of keywords related to Probiotics, *Saccharomyces, Lactobacillus*, and *Bifidobacterium*. For IBS, the most recent systematic review about this topic published in 2023 was chosen as a key meta-analysis.[7] We individually reviewed the 82 trials included in a key meta-analysis and searched for newly published studies from January 2023 through April 2025, combining the term "irritable bowel syndrome" OR "IBS" in the 3 databases. To examine the effects of probiotics on FC, detailed literature searches were conducted combining the terms "functional constipation" OR "constipation" OR "FC" from January 2000 to April 2025. To analyze studies on the efficacy of probiotics in CDI, we searched for studies published between January 2000 and August 2025 using a similar search strategy. Search terms for CDI include "*Clostridium difficile* infection," "pseudomembranous colitis," and "CDI". Only articles published in English were considered. Original research articles (randomized controlled trials [RCTs] and observational studies), review articles including meta-analysis, and clinical guidelines relevant to the topic were included. Case reports and studies with limited clinical relevance were excluded. Additional articles were identified through manual screening of reference lists from key publications.

Since this article is a narrative review rather than a systematic review, the final article selection was based on the authors' qualitative assessment of relevance to clinical practice, methodological rigor of study findings, and contribution to the understanding of the sex-difference effect of probiotics. Findings were mainly synthesized narratively, with an emphasis on the effect of specific diseases, areas of agreement and controversy, and clinical implications. Among the selected studies, we specifically identified studies reporting outcomes separately for males and females or providing subgroup analyses relevant to sex-specific differences. These studies were separately categorized and described, and quantitative synthesis was attempted where possible.

RESULTS

Gut Dysbiosis and Clinical Evidence of Probiotics in Patients With Irritable Bowel Syndrome

IBS is a common disorder of gut–brain interaction that occurs in the absence of identifiable organic GI disease.[1] The global prevalence of IBS is estimated at 11.2%, with an incidence of 1.35% to 1.5%.[8] Notably, IBS shows a sex-based disparity, being more prevalent in females[9] and in younger individuals.[10]

The pathophysiology of IBS remains only partially understood,[11] and no treatment has been proven to alter the long-term natural course of the condition. Furthermore, a substantial proportion of patients either do not respond to or become dissatisfied with conventional therapy.[12,13]

Among the various proposed mechanisms, disturbances in the GI microbiota[14,15] have been implicated in IBS pathogenesis. Thus, modulation of the gut microbiota has emerged as a potential therapeutic approach.

Probiotics have been extensively investigated in patients with IBS, and their efficacy in alleviating symptoms has been supported by numerous clinical trials and meta-analyses. [7,16-19] Although mechanisms remain incompletely defined and human biomarkers, such as increased short-chain fatty acid (SCFA) production, decreased pro-inflammatory cytokines, and improved gut barrier function, are largely surrogates, probiotics may help alleviate IBS symptoms.[20-22]

A 2023 meta-analysis by Goodoory et al[7] examined the efficacy of probiotics in patients across all IBS subtypes. The analysis included 31 RCTs comprising 1,733 patients in the probiotic group and 1,636 in the control group. The meta-analyses suggested benefits for global symptoms (RR = 0.78; 95% CI, 0.71-0.87), abdominal pain (RR = 0.72; 95% CI, 0.64-0.82), and bloating (RR = 0.75; 95% CI, 0.64-0.88), albeit with high heterogeneity.

However, strain-specific effectiveness varied considerably, and substantial heterogeneity was observed across studies in terms of probiotic species, dosage, treatment duration, and outcome measures. *Escherichia* spp. showed moderate certainty evidence of improvement in global symptoms. *Lactobacillus* strains, including *Lactiplantibacillus plantarum* (formerly *Lactobacillus plantarum*) 299v,[23-27] demonstrated low certainty, similar to *Bifidobacterium* strains, with *B. infantis* 35624 showing some efficacy at specific doses.[28,29] Combinations of strains and *Bacillus* species also yielded low certainty, with some combinations showing promise in a limited number of trials. *Saccharomyces*, particularly *S. cerevisiae* I-3856, has also been associated with low-certainty evidence of reducing abdominal pain. In addition, the number of studies that have analyzed outcomes according to IBS subtypes is very limited, and most meta-analyses have reported results without stratification by subtype.[7,19] Overall, these findings should be interpreted with caution due to marked heterogeneity and strain-specific effects, which likely contribute to the lack of strain-level and subtype-specific recommendations in current clinical guidelines.[1,17,18,30]

Several studies reported the efficacy of probiotics in IBS regarding sex-specific treatment outcomes (Table 1).[31-37] Finally, 3 studies[32,34,35] were suitable for meta-analysis, and the results are presented in Figure 1. The analysis showed a favorable treatment effect of probiotics in female patients with IBS, and it was supported by another recent study by Mullish et al.[38] It reported a significant reduction of IBS symptom scores in female patients, along with improvements in bowel habits and reductions in anxiety, depression, and IBS-related behaviors. However, they did not reach statistical significance between sexes. Subgroup analyses based on individual species or strains were also not feasible. These findings urge the need for future studies focusing on sex-specific differences in the efficacy of probiotics in the treatment of IBS.

Gut Dysbiosis and Clinical Evidence Supporting Probiotics Use in Patients With Functional Constipation

In patients with FC, there is evidence of gut dysbiosis, characterized by a decrease in the abundance of *Bifidobacterium* spp., *Lactobacillus* spp., *Prevotella* spp., and butyrate-producing genera, and an increase in the abundance of *Coprococcus*, *Ruminococcus* spp., *Akkermansia*, and *Clostridium* spp.[39,40] Although the gut environment and microbiota composition may vary across different types of constipation, patients with FC generally show a reduced abundance of beneficial lactic acid- and butyric acid-producing bacteria, together with an increased prevalence of methanogenic archaea.[41] In contrast, overall microbial diversity shows inconsistent changes across studies, unlike other chronic GI disorders such as IBS or inflammatory bowel diseases (IBD), where a significant reduction in diversity is typically observed.[42]

Probiotics can produce SCFA through the fermentation of dietary fiber, and these SCFA can increase stool volume via osmotic effects and stimulate peristaltic movement via ENS stimulation.[43] Among the SCFA, butyrate maintains intestinal barrier integrity, prevents bacterial endotoxin and inflammatory responses, and reduces interference with intestinal motility.[44] Colon transit time is generally longer in females than that in males,[45] and slow-transit constipation is more frequently reported in females. The relative abundance of methanogenic microbes was significantly higher in patients with slow-transit constipation. Methane delays peristaltic conduction velocity by enhancing non-propulsive circular muscle contractions.[15,46] Some probiotics can restore gut microbial homeostasis and reduce methanogenic populations. These mechanisms may partly explain the greater therapeutic effects of probiotics in female patients.

Probiotics therapy exerts multifactorial effects that can alleviate symptoms of constipation by modulating the gut environment, epithelial immune response, and the neuroendocrine regulation of intestinal motility and secretory activity.[47,48] Commonly used probiotics include

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Table 1. Studies Reporting Sex Differences in the Efficacy of Probiotics in Irritable Bowel Syndrome

Year	Country	Patients	Probiotics[a]	CFU	Total		Treatment group		Control group		Duration	Primary outcome	Results
					Male	Female	Male	Female		Female			
Enck 2008[31]	Germany	N/A	*E. coli* DSM 17252, *E. faecalis* DSM 16440	1.35×10^8-4.05×10^8	150	147	77	72	73	75	8 weeks	Global symptoms and abdominal pain	NNT: males 2.49 (1.76-4.22), females 3.98 (2.55-9.13)
Enck 2009[32]	Germany	N/A	*E. coli* DSM 17252	6.8×10^7-2.0×10^8	151	147	76	72	75	75	8 weeks	Global symptoms and abdominal pain	Responder rate: males 22.6% vs 7.2%, females 15.5% vs 2.5%
Ludidi 2014[33]	The Netherlands	Rome III	*L. casei* W56, *L. salivarius* W57, *L. lactis* W58, *L. acidophilus* NCFM, *L. rhamnosus* W71	5.0×10^9	13	27	6	15	7	12	6 weeks	Abdominal pain (visceral perception)	MSS: males −1.18 (−1.80 to −0.25) vs 0.93 (−3.87 to 1.43), females −0.06 (−3.77 to 1.64) vs −1.49 (−7.42 to −0.32)
Mack 2022[34]	Germany	Rome III	*E. coli* DSM 17252, *E. faecalis* DSM 16440	1.3×10^8-3.9×10^8	187	197	56	131	63	134	26 weeks	Global symptoms and abdominal pain	IBS-GAI: males 16.1% vs 17.2%, females 18.0% vs 13.1%
Quigley 2023[35]	US, UK/Ireland	Rome IV	*B. hydrogenotrophica*	2.0×10^{10}-2.0×10^{11}	96	269	50	127	46	142	8 weeks	Bowel habit and abdominal pain	Overall response: males 19.1% vs 20.0%, females 26.0% vs 16.7%
Preston 2018[36]	US, Canada	Rome III	*L. acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2	1.0×10^{11}	45	68	16	21	29	47	12 weeks	Global symptoms and abdominal pain	Improvement in QOL; IBS-D only in males
Chang 2024[37]	South Korea	Rome III	*B. longum* IDCC 4101, *B. bifidum* IDCC 4201, *B. lactis* IDCC 4301, *B. breve* IDCC 4401, *E. faecium* IDCC 2102, *L. rhamnosus* IDCC 3201, *L. acidophilus* IDCC 3302, *L. casei* IDCC 3451, *L. plantarum* IDCC 3501, *L. helveticus* IDCC 3801	1.0×10^{10}	39	53	26	21	13	32	4 weeks	Global symptoms	Overall IBS symptom relief: males 3.54 ± 0.42 vs 2.69 ± 0.44, females 3.48 ± 0.32 vs 2.40 ± 0.28

[a]Studies listing multiple probiotic strains represent multi-strain probiotic formulations.

CFU, colony-forming unit; NA, not applicable; NNT, number needed to treat; MSS, mean symptom score; IBS-GA, irritable bowel syndrome-global assessment of improvement; QOL, quality of life; IBS-D, diarrhea-predominant irritable bowel syndrome.

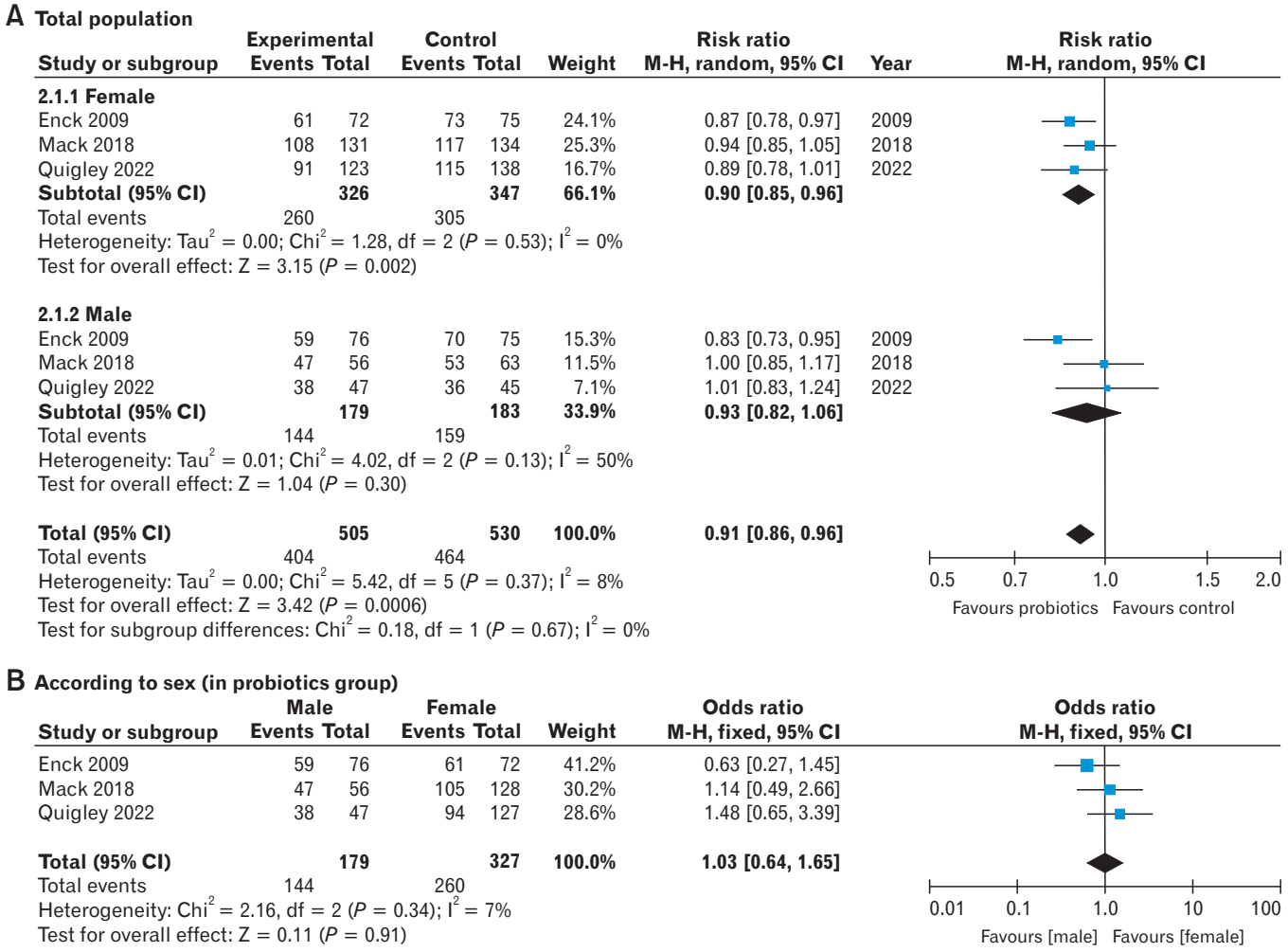

Figure 1. Meta-analysis of studies reporting sex differences in the efficacy of probiotics in irritable bowel syndrome. (A) Total population. (B) According to sex (in probiotics group). M-H, Mantel-Haenszel.

Bifidobacterium and *Lactobacillus* species, but the most effective strains for FC are still controversial.[49] Table 2 shows the RCTs investigating the effect of probiotics in patients with FC.[50-74] A total of 25 studies were included in this review and meta-analysis. These studies used various probiotic strains and colony-forming units (CFUs) and included a relatively small number of patients. The most frequently used species was *Bifidobacterium*, which was followed by *Lactobacillus*. Overall, probiotics significantly increased spontaneous bowel movement (SBM) per week by 0.67 (95% CI, 0.22-1.12) at 4 weeks after ingestion (Fig. 2). However, heterogeneity among the studies was very high (I^2 = 96%), possibly due to differences in probiotic strains and dosages as well as differences in the severity of symptoms and patient characteristics. When the data were analyzed by species, neither a significant increase in SBM per week nor a significant difference among species was observed. Probiotics also improved stool consistency, as measured using the Bristol stool form scale (BSFS). Probiotics slightly increased BSFS by 0.31 (95% CI, 0.01-0.61) at 4 weeks (Fig. 3). Similar to the changes in SBM, analysis by species showed that only synbiotics significantly improved stool consistency. Although several studies suggest potential symptomatic improvements, the heterogeneity and generally low quality of evidence limit confidence in the therapeutic value of probiotics in FC. In a recently published network meta-analysis, when probiotics were classified by strain, no single strain showed a significant increase in stool frequency compared to placebo.[75] Three studies included only female patients.[52,54,74] In a study including 100 women experiencing constipation diagnosed according to the Rome III criteria, patients treated with 6 g of synbiotics (fructooligosaccharides with *Lactobacillus* and *Bifidobacterium* spp.) daily achieved a higher bowel frequency and stool consistency score compared

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Table 2. Characteristics of Studies Using Probiotics in Patients With Constipation

Year	Country	Patients	Probiotics[a]	CFU	Treatment group:control group	Duration	Outcome
del Piano 2008[50]	Italy	Evacuation disorder	*L. plantarum* *B. animalis lactis*	5.0×10^9	80:110:110[b]	30 days	Increase in number of weekly evacuations in probiotics group
Fateh 2011[51]	Iran	FC (Rome III)	*B. longum, B. breve, L. casei, L. rhamnosus, S. thermophilus*, FOS	1.0×10^8	31:29	4 weeks	Increase in stool frequency in men receiving probiotics
Favretto 2013[52]	Brazil	FC (Rome III)	*B. lactis* Bi-07	1.0×10^8	15:15	30 days	Increase in stool frequency in women receiving probiotics
Mazlyn 2013[53]	Malaysia	FC (Rome III)	*L. casei* Shirota	3.0×10^{10}	50:50	4 weeks	Probiotics did not alleviate constipation severity, stool frequency, and consistency.
Waitzberg 2013[54]	Brazil	FC (Rome III)	*B. lactis, L. paracasei, L. rhamnosus, L. acidophilus*, and FOS	$< 10^9$	49:50	30 days	Synbiotics improved stool frequency and consistency in constipated women.
Ojetti 2014[55]	Italy	FC (Rome III)	*L. reuteri* DSM17938	1.0×10^8	20:20	4 weeks	Probiotics increased stool frequency. No difference in stool consistency.
Ding 2016[56]	China	FC (Rome III)	*B. longum, L. acidophilus, E faecalis*, soluble fiber (Pectin)	3.0×10^7	48:45	12 weeks	Synbiotic exhibited increased stool Frequency and improved stool consistency and constipation-related symptoms.
Cudmore 2017[57]	Ireland	FC (Rome III)	*B. bifidum, L. rhamnosus, L. acidophilus*, psyllium/inulin	6.0×10^8	35:34	4 weeks	Synbiotics did not significantly improve stool frequency.
Ibarra 2018[58]	France	FC (Rome III)	*B. animalis* HN019	1.0×10^9 /10^{10}	76:76:76[c]	4 weeks	No difference in stool frequency and consistency between the probiotics and placebo groups.
Lim 2018[59]	Malaysia	FC (Rome III)	*B. lactis* BB12, *L. plantarum* LP01, inulin-oligofructose	1.0×10^{10}	43:42	12 weeks	No difference in stool frequency and consistency between the probiotics and placebo groups.
Dimidi 2019[60]	United Kingdom	FC (Rome III)	*B. lactis*	1.5×10^{10}	37:38	4 weeks	There were also no improvements in stool output, symptoms, or quality of life between probiotics and placebo groups.
Martoni 2019[61]	Canada	FC (Rome III)	*L. acidophilus, B. animalis lactis, B. longum, B. bifidum*	1.5×10^{10}	48:46	4 weeks	No difference in stool frequency and consistency between the probiotics and placebo groups.
Botelho 2020[62]	Brazil	FC (Rome IV)	*L. acidophilus, L. casei, L. lactis, B. bifidum, B. lactis*	5.0×10^9	21:14	30 days	Probiotics improved constipation-related symptoms.
Madempudi 2020[63]	India	FC (Rome III)	*B. coagulans* Unique IS2	2.0×10^{10}	50:50	4 weeks	Probiotics improved stool frequency and consistency.
Kang 2021[64]	South Korea	FC (Rome III)	*B. coagulans* SNZ1969	1.0×10^9	40:40	8 weeks	Probiotics improved stool frequency and colon transit time.
Wang 2021[65]	China	FC (Rome III)	*S. thermophilus, L. bulgaricus, B. animalis*	1.0×10^{10}	23:21	4 weeks	Probiotics improved constipation-related symptoms.
Mitelmao 2022[66]	Brazil	FC (Rome IV)	Multiple combination of *Lactobacillus* and *Bifidobacterium*	8.0×10^9	51:51	30 days	Probiotics improved stool frequency and consistency.
Takeda 2022[67]	Japan	FC (Rome IV) and elderly (> 65)	*B. longum* BB536	5.0×10^{10}	39:41	4 weeks	Probiotics improved stool frequency in elderly patients.
Wang 2022[68]	China	FC (Rome IV)	*B. bifidum* CCFM16	2.0×10^9	53:50	4 weeks	Probiotics improved stool consistency.
Lai 2023[69]	China	FC (Rome IV)	*B. animalis subsp lactis* HN019, *L. rhamnosus* HN0001		50:50	4 weeks	Probiotics improved stool consistency and constipation-related symptoms, but did not increase stool frequency.
Ma 2023[70]	China	FC (Rome IV)	*L. plantarum* P9	1.0×10^{11}	78:85	4,6 weeks	Probiotics significantly improved stool frequency and symptoms.
Cheng 2024[71]	China	FC (Rome IV)	*B. animalis subsp lactis* HN019	7.0×10^9	112:117	8 weeks	No difference in stool frequency in probiotics and placebo groups.
Salo 2024[72]	Spain	Constipation	*B. animalis subsp lactis* BLa80	2.0×10^9	23:23	4,8 weeks	Probiotics improved stool frequency.
Jin 2025[73]	South Korea	Constipation	Multiple combination of *Lactobacillus* and *Bifidobacterium*	2.0×10^9	33:37	4,8 weeks	Probiotics significantly improved stool frequency, consistency and symptoms.
Roos 2025[74]	Sweden	Constipation	*L. gasseri*	1.0×10^9	20:20	4 weeks	Probiotics improved constipation-related symptoms in women.

[a]Studies listing multiple probiotic strains represent multi-strain probiotic formulations.

[b]80 subjects with placebo, 110 subjects with mixed *L. plantarum* LP01 and *B. breve* BR03, and 110 subjects with *B. animalis* subsp. *lactis* BS01.

[c]76 subjects with placebo, 76 subjects with the low dose group, and 76 subjects with the high dose group.

CFU, colony-forming unit; FC, functional constipation; FOS, fructo-oligosaccharide.

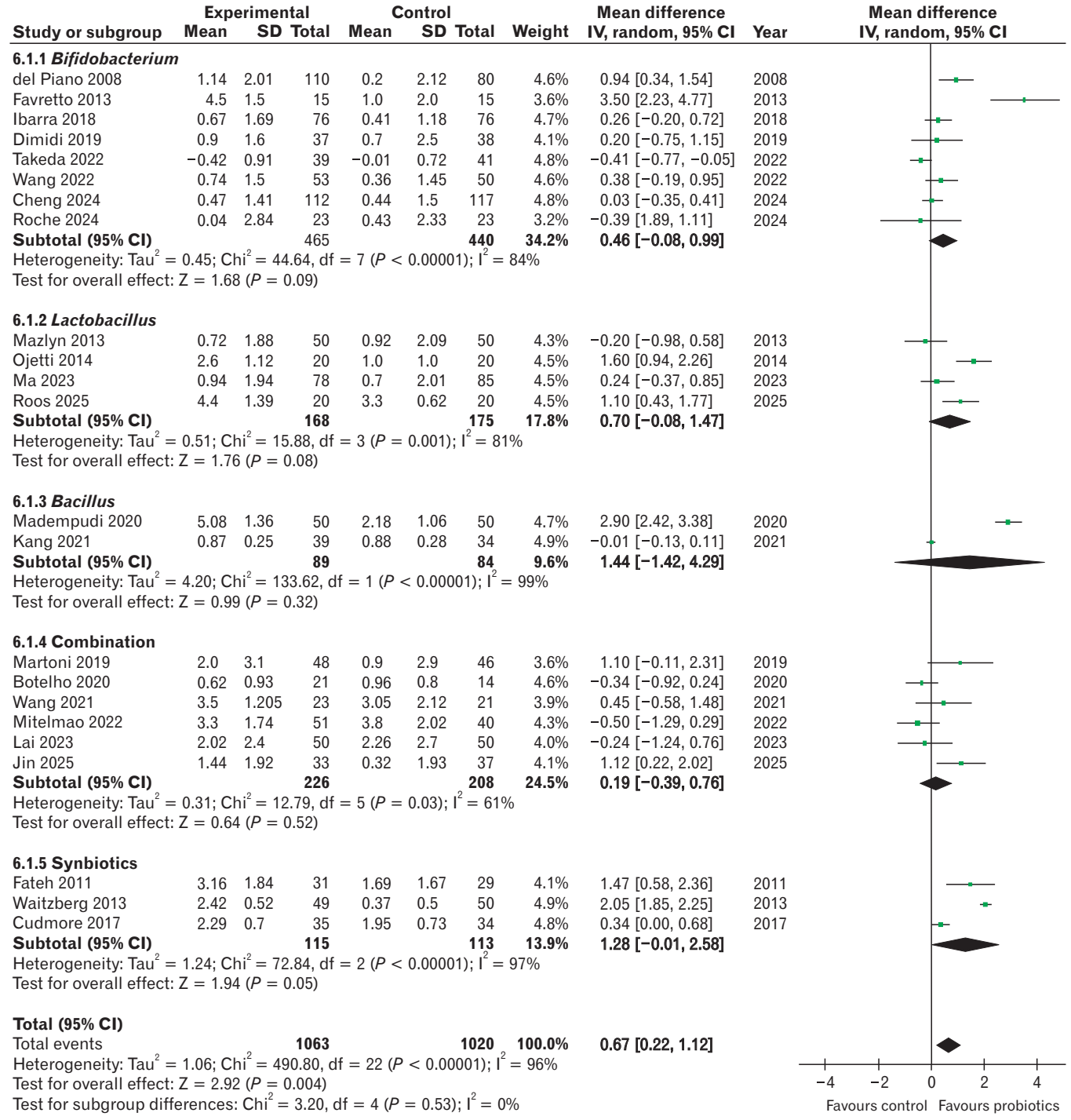

Figure 2. Change of spontaneous bowel movement by species.

with those of placebo.[54] In another study recruiting 40 women with constipation, SBM increased from 5.0 ± 0.9 to 9.4 ± 1.6 with *Lactobacillus gasseri*, while the placebo response was 4.2 ± 0.5 to 7.5 ± 0.7.[74] In studies limited to females, changes in SBM and consistency showed significantly greater (SBM change per week 2.06 [95% CI, 1.14-2.99] BSFS change 3.5 [95% CI, 2.87-4.13]) compared with studies including both sexes.

Use of Probiotics in *Clostridioides difficile* Infection: Current Evidence

CDI is a major cause of healthcare-associated infec-

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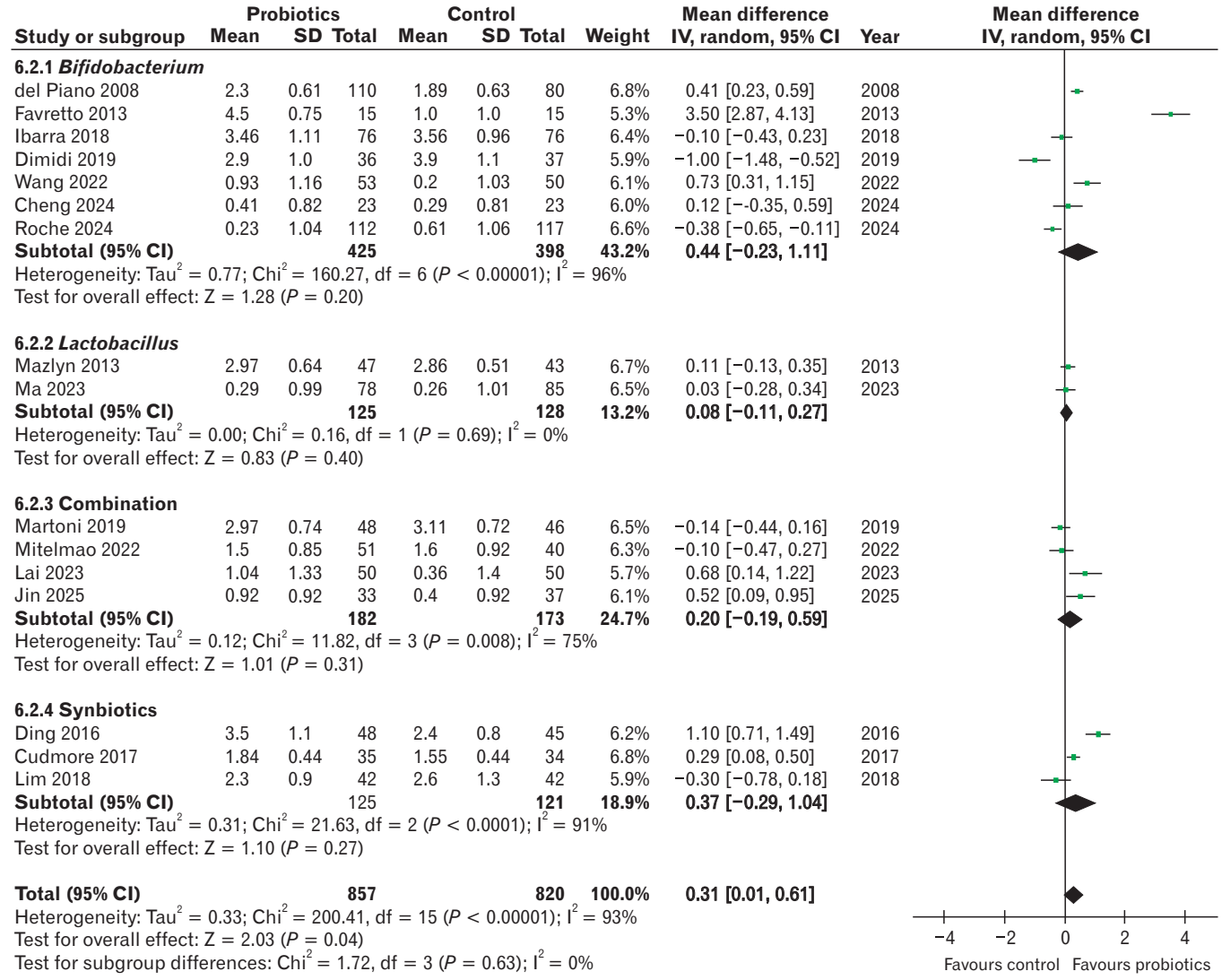

Figure 3. Change of stool consistency (Bristol stool form scale) by species.

tious diarrhea, and its global burden has been increasing, particularly among individuals aged 70 years and older.[76] Several studies have explored the role of probiotics in preventing CDI (Supplementary Table).[77-90] Among them, the most representative clinical trials are the PLACIDE trial[79] for primary prevention and the PICO trial[86] for secondary prevention. However, they failed to demonstrate significant effects largely due to the low incidence of CDI[79] or the absence of differences between groups,[86] respectively. Furthermore, there is a distinct lack of reproducibility in the following trials, including a single and multicenter studies.[91,92]

While, a 2017 Cochrane review and meta-analyses showed significant effects of probiotics on CDI prevention, several concerns remain.[93,94] The 2017 Cochrane analysis reported a relative risk reduction of 60% in the incidence of *Clostridioides difficile*-Associated Diarrhea, concluding that the short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated.[93] However, most studies included in this analysis were judged to be at high risk of bias, and the benefit of probiotics was observed only in trials enrolling participants with a baseline CDI risk greater than 5% in post hoc subgroup analyses, and only a subset of the included studies demonstrated a protective effect, warranting cautious interpretation. Meta-analyses often pool diverse genera into a single entity, thereby obscuring unique biological mechanisms and introducing significant bias; this represents an additional important limitation.

Accordingly, several guidelines do not recommend the

routine use of probiotics for CDI prevention. The reasons cited include, first, the lack of clear and consistent evidence supporting probiotic efficacy and cost-effectiveness. As discussed above, both primary and secondary prevention trials failed to demonstrate significant benefits. Second, substantial heterogeneity and uncertainty surrounding probiotic products have been highlighted, including inconsistencies and deviations from product label information; frequent misidentification, misclassification, or nonviability of strains; contamination; and diminished functional properties.[95] These uncertainties have led current guidelines to adopt cautious or even opposing positions regarding the routine use of probiotics.[95-97] Safety concerns have also been raised, as many patients at risk for CDI are critically ill or immunocompromised, in whom probiotic administration may be inappropriate.[95-97] This concern is further supported by microbiome studies suggesting that probiotics may impede normal recolonization of the colon following antibiotic exposure.[95]

From a sex-based perspective, females exhibit higher CDI incidence and recurrence rates. In contrast, males show increased mortality and prolonged hospitalization.[98,99] These observations suggest that sex may influence susceptibility and prognosis. Emerging data suggest that sex-related factors, such as gut microbiota composition and immunity, may play a role.[100] In particular, females generally exhibit higher circulating concentrations of immunoglobulin (Ig) M but lower IgA levels than males, which may contribute to reduced mucosal defense against *C. difficile* and potentially explain the higher incidence or recurrence of CDI observed in females.[101,102] Given the aforementioned sex differences, it is conceivable that the efficacy of probiotics may also vary between the sexes. However, to date, evidence regarding the sex-specific efficacy of probiotics remains unclear. Therefore, future clinical trials on probiotics should be carefully designed to account for these biological differences, which may ultimately refine preventive strategies and enable more personalized approaches for CDI management.

DISCUSSION

Hormonal Differences, Microbiome Variability, and Therapeutic Response

Gut microbiota is known to contribute to GI diseases such as IBS, IBD, and colon cancer. Although the exact etiology remains elusive, there is growing evidence regarding the effect of gut microbiome on gut motility, inflammation, and immune responses.[6,103] Recently, sex and gender differences in GI diseases and their relation to gut microbiome have been suggested.[5,6,103,104] Furthermore, the metabolism of estrogen and androgen was reported to be related to the gut microbiome. As gut microbiome is involved in the excretion and circulation process of sex hormones, the concept of "microgenderome" indicating the role of sex hormones on the gut microbiome has been suggested. Estrogen and testosterone have been shown to directly affect the gut microbiome and immune cells. β-estradiol affects the transformation of dendritic cells to produce IL-12 and IFN-γ.[105] This, in turn, activates pathways for pro-inflammatory cytokines. Estradiol prolongs the survival of B cells and activates polyclonal B cells.[105] The resulting pro-inflammatory environment with altered intestinal gut permeability causes the migration of gut microbiota into the lamina propria, which again promotes inflammation processes.[105] In males, testosterone shows an inhibitory effect on T-cell proliferation. In contrast to estradiol, testosterone does not alter the intestinal barrier.[105] Gut microbiota play key roles in modulating the brain-gut axis and intestinal barrier.[106-108] SCFAs are the most abundant and important microbial end-products. They are inflammation modulators that regulate gut motility and wound-healing.[109] They have also been found as a link between the microbiome-gut-brain axis.[110-112] Interestingly, the sex difference in butyrate-producing gut microbiota has been reported.[100] In addition, a recent study has shown that male and female rat gut microbiomes have different profiles of SCFAs when an oligofructose-containing diet is administered to both.[113] In females, oligofructose supplementation increased the abundance of Bacteroidetes, while no difference was found in males. Furthermore, fecal butyrate, liver IgA, IL-6, and cecal IL-6 levels were increased in males but IL-10 levels were higher in females.[113] Interestingly, native Africans had remarkably higher abundance in the butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Clostridium* cluster IV, and *Clostridium* cluster XIVa. In contrast, *Bacteroides* was the dominant in African Americans.[114] Bacteroides-Prevotella group showed higher levels in men than in women.[115] Regarding the therapeutic response of probiotics depending on sex, administration of a probiotic mixture of 5 *Lactobacillus* strains to lupus-prone mice improved renal function and showed anti-inflammatory effects in female and castrated male mice, but not in gonadally intact males, suggesting a sex difference in probiotic administration.[116] However, the majority of studies were performed in animals so far.

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Do the Effects of Probiotics Differ by Sex? Evidence From Preclinical Models

The biological effects of probiotics are influenced by strain-specific properties and host factors, including sex-related differences in physiology, immunity, and microbiota composition. In disorders with clear sex disparities like IBS, it is plausible that therapeutic responses also vary by sex.[117] However, clinical evidence remains inconclusive due to heterogeneous study designs and the underrepresentation of sex-based analyses. Conversely, controlled animal models have revealed distinct sex-dependent responses to probiotics, although preclinical studies specifically designed to assess these effects remain limited (Table 3).

In stress-induced GI disease models, such as the repeated water avoidance stress (rWAS) model, female rodents typically exhibit heightened vulnerability, characterized by greater visceral hypersensitivity, mast cell infiltration, and exaggerated mucosal cytokine expression compared to males. Research using the rWAS model demonstrated that oral administration of *Companilactobacillus farciminis* (formerly *Lactobacillus farciminis*) or *Bifidobacterium longum* BBH016 for 10 days significantly reduced visceral hypersensitivity and colonic microinflammation exclusively in female rats.[118,119] In contrast, *Roseburia faecis* BBH024 and R22-12-24 exerted more pronounced anti-inflammatory effects in male rats, attenuating fecal output and improving functional mi-

Table 3. Summary of Preclinical Studies Investigating Sex-dependent Effects of Probiotics

Year	Animal, model	Probiotics	CFU/day/rat	Experimental design	Sex-dependent results
Lee 2017[118]	Wistar rats rWAS (1 hr/day for 10 days)	*C. farciminis*	1.0×10^{11} 10 day during rWAS	3 groups (no-stress, rWAS, rWAS + *C. farciminis*)	• Female: rWAS → ↑FPO, visceral analgesia, ↑mast cells and proinflammatory cytokines; Probiotics → ↓mast cells, ↓IFNγ, ↓TNFα, ↓IL-6, ↓PRSS1-3 • Male: rWAS → mild ↑FPO, no analgesia; Probiotics → no reduction in inflammation, ↑IL-1β, ↑IL-17
Choi 2024[119]	Wistar rats rWAS (1 hr/day for 10 days)	*B. longum* BBH016	1.0×10^{9} 10 day during rWAS	3 groups (control, rWAS, rWAS + *B. longum*)	• Females: rWAS → ↑FPO, ↑mast cells, dysbiosis; Probiotics → ↓FPO, ↓mast cells, mitigated dysbiosis • Males: rWAS → ↑FPO; Probiotics → no significant effect
Choi 2023[120]	Wistar rats rWAS (1 hr/day × 10 days)	*R. faecis* BBH024 and R22-12-24	1.0×10^{9} 10 day during rWAS	3 groups (control, rWAS, WAS + *R. faecis*)	• Female: rWAS → ↑FPO, ↑mast cells; probiotics → ↓FPO, ↑IL-6 • Male: rWAS → ↑FPO, ↑mast cells, ↑IL-6; Probiotics → ↓FPO, ↓mast cells, ↓IL-6
Choi 2023[121]	Fischer-344 rats, HFD (8 weeks)	*C. butyricum* IDCC 1301, Biovita	Low 1×10^{7} Medium 1×10^{8} High 1×10^{9} 8 wk during HFD	5 groups (control, Biovita, *C. butyricum* at low/medium/high concentrations)	• Female: HFD → ↓TJPs, ↑MPO, ↓butyrate, ↓IL-6; Probiotics → ↑TJPs, ↑IL-6 • Male: HFD → ↑TJPs, ↑TNF-α, ↑MPO, ↓butyrate; Probiotics → ↓TNF-α, ↓ MPO, ↑IL-10, ↑butyrate
Choi 2024[122]	Fischer-344 rats, HFD (8 weeks)	*C. butyricum* IDCC 1301, Biovita	Low 1×10^{7} Medium 1×10^{8} High 1×10^{9} 8 wk during HFD	5 groups (control, Biovita, *C. butyricum* at low/medium/high dose)	• Female: HFD → ↓α-diversity, ↓Ruminococcaceae, ↑Lachnospiraceae, ↑*A. muciniphila,* altered carbohydrate/energy metabolism; Probiotics → ↑Ruminococcaceae, ↓*A. muciniphila* • Male: HFD → ↓Ruminococcaceae, ↑*A. muciniphila*, ↓energy metabolism, altered carbohydrate/energy metabolism; Probiotics → ↑Lachnospiraceae, ↓*A. muciniphila*, recovered carbohydrate/energy metabolism
He 2019[123]	BALB/c mice, Healthy	*L. reuteri* DMSZ 8533	Low 1.0×10^{8} High 1.0×10^{10} 28 day	3 groups (control, *L. reuteri* at low/high dose)	• Females: ↑ *Helicobacter* ↓Actinobacteria • Males: ↓ Bacteroides, ↓*Prevotella*, ↑ *Clostridium* IV
Singh 2025[124]	C57BL/6 mice, POE	VSL#3	4.5×10^{11} Late gestation ~ postnatal day 21	2 groups (POE only, POE + VSL#3)	• Females: POE → ↓α-diversity, analgesia; Maternal probiotics → partial, transient normalization of analgesia • Males: POE → ↑α-diversity, hyperalgesia; Maternal probiotics → robust normalization of hyperalgesia

CFU, colony-forming unit; rWAS, repeated water avoidance stress; FPO, fecal pellet output; HFD, high fat diet; TJP, tight junction protein; POE, prenatal opioid exposure; PRSS, mucosal serine protease gene
Biovita contains *C. butyricum* 1301, *L. sporogenes* IDCC 1201, and *Bacillus subtilis* IDCC 1101.

crobial pathways.[120] Similar sex-dependent responses have been observed in metabolic and immune contexts beyond IBS models. In rats fed a high-fat diet, *Clostridium butyricum* IDCC 1301 supplementation mitigated intestinal inflammation and improved barrier function in a sex-dependent manner. The anti-inflammatory and barrier-protective effects were more pronounced in males, whereas females exhibited distinct alterations in bile acid profiles and inflammatory markers.[121] Furthermore, *C. butyricum* IDCC 1301 reshaped the gut microbiota differently between sexes, increasing butyrate-producing taxa predominantly in males while downregulating *Akkermansia muciniphila* more markedly in females.[122] These findings indicate that stress-induced gut dysfunction elicits sex-specific inflammatory and microbial responses, which are differentially modulated depending on both the probiotic strain and the host sex.

Independent studies in immune and neurobehavioral models have reported similar sex-dependent differences. Administration of *Limosilactobacillus reuteri* (formerly *Lactobacillus reuteri*) DMSZ 8533 in mice produced distinct shifts in microbial composition and cytokine levels between males and females.[123] Moreover, in offspring prenatally exposed to opioids, VSL#3 treatment ameliorated gut dysbiosis and nociceptive alterations in a sex-dependent manner, attenuating pain sensitivity in males and normalizing microbial profiles in females.[124] Collectively, these findings highlight that sex-specific probiotic effects influence the microbial and neuroimmune axes governing stress, metabolism, and pain.

Accumulating preclinical evidence suggests that the effects of probiotics vary by sex, likely due to differences in the hormonal milieu, immune activation, and baseline microbiota. These experimental findings underscore the necessity of considering sex as a critical biological variable to advance personalized microbiome-based interventions.

Bridging the Gap: Clinical Reality and Potential for Sex-Specific Probiotic Therapy

Based on the clinical evidence reviewed, probiotics demonstrate a modest but significant potential in managing lower GI disorders. In patients with IBS, specific strains can alleviate global symptoms, particularly abdominal pain and bloating. For FC, certain probiotics and synbiotics enhance bowel movement frequency and stool consistency. Regarding CDI, while their routine use for primary prevention remains controversial, they may offer benefits in specific high-risk populations. However, translating these findings into routine clinical practice remains challenging due to marked heterogeneity in study designs, probiotic strains, doses, and treatment durations. Also, most clinical trials utilize heterogeneous formulations, which preclude a clear understanding of strain-specific effects and complicate the development of standardized guidelines.

A particularly notable discrepancy exists between preclinical and clinical findings regarding sex-based differences. While controlled experimental settings in animal models have revealed distinct and robust sex-dependent responses to specific probiotics, clinical trials in humans have yet to confirm these clear disparities. The lack of significant sex-specific evidence in clinical settings often stems from underpowered studies, post-hoc analyses, or an underrepresentation of male or female populations. Therefore, at present, it is difficult to provide definitive clinical recommendations for selecting specific probiotic strains based on a patient's sex. Such considerations should instead be prioritized as a critical biological variable in future research and RCTs. Given this current lack of definitive evidence, clinicians must adopt a personalized and individualized approach, selecting strains based on predominant symptoms and underlying pathophysiology. Consequently, clinicians should possess a fundamental understanding of the practical and safety aspects of probiotics—including quality, stability, and patient-specific risk profiles—to ensure standardized and safe interventions despite individual variability.

What Should Clinicians Consider When Using Probiotics?

Although the use of probiotics in clinical practice has increased significantly, clinicians still face challenges owing to product variability, ambiguous labeling, and a lack of standardized prescription guidelines. Below, we discuss the factors that clinicians should consider when prescribing probiotics, including dosage, stability, formulation, and patient-specific factors.

Indications based on dosage and formulation

Physicians must verify probiotics' shelf stability and CFU retention via manufacturer documentation. While a minimum of 1.0×10^9 CFU/day is generally required for clinical benefits,[125-127] regulatory requirements vary (Korea: 1.0×10^8 CFU; EU/Canada: 1.0×10^9 CFU or higher; USA: 1.0×10^8 to 10^{11} CFU per day).[128,129] Dosage should align with strain-specific evidence from clinical trials, as higher doses do not always enhance efficacy.[130] To ensure viability through the expiration date, manufacturers often include an "overage" during production.[131] Solid formulations (capsules, powders) are generally more sta-

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ble than fluid suspensions.[132] Recent advancements like microencapsulation and nanotechnology further optimize site-specific delivery.[133]

Timing of probiotic administration

Survival and colonization are influenced by meal timing, circadian rhythms, and concomitant medications. Gastric acidity during fasting reduces bacterial survival; thus, taking probiotics with or shortly after meals—especially those containing fat—improves transit viability.[134] Although animal studies suggest diurnal variations in host-microbe interactions, human evidence is insufficient to recommend a specific time of day.[135] Meta-analyses of conditions such as IBS, infectious diarrhea, and IBD suggest that consistent daily intake is more important than exact timing.[2,136] Adherence is a strong predictor of probiotic efficacy, regardless of whether they are taken in the morning or evening. When used with antibiotics, a 2-3-hour interval is recommended to prevent direct inactivation.

Host factors influencing the efficacy of probiotics

Probiotic outcomes are significantly shaped by inter-individual variability across several key factors. The gut microbiota plays a critical role, as baseline diversity and "colonization resistance" are primary determinants of successful engraftment.[137] Genetic polymorphisms in innate immune receptors (eg, Toll-like receptors and nucleotide-binding oligomerization domain-containing protein 2) influence host–microbe interactions and may alter probiotic efficacy in modulating mucosal immunity.[138] Age also influences efficacy, with immature immune systems in infants and aging systems in the elderly offering distinct colonization potentials.[139,140] Furthermore, dietary habits impact survival and persistence, as fats enhance viability during gastric transit while fibers serve as prebiotic substrates.[141]

Finally, a patient's immune status and concurrent medications, such as PPIs or immunosuppressants, can further alter the survival and functional responses of administered probiotics.[142,143]

Safety of probiotics

Probiotics generally have a favorable safety profile, with mild GI side effects (bloating, flatulence) being most common.[144,145] However, safety data varies widely depending on the strains and formulations used, and most trials have methodological limitations, such as inadequate reporting of adverse events and insufficient follow-up to assess long-term risks.[146] Real-world data (Food and Drug Administration Adverse Event Reporting System 2005-2023) show an extremely low incidence of serious adverse events.[147] However, owing to sex-based differences, unclear labeling, and a small number of adverse events, these results may not reflect the true biological differences. Thus, the results should be interpreted with caution, and future studies should ensure proper sex-based stratification, larger sample sizes, and long-term monitoring. Rare risks such as translocation (bacteremia/fungemia) exist for high-risk groups (eg, intensive care unit patients, those with central venous catheters, or severe immunosuppression).[148-150] The increased mortality in the PROPATRIA trial was later attributed to specific metabolic factors rather than probiotic pathogenicity.[148] In addition, contamination or mislabeling during manufacturing and distribution may occasionally lead to exposure to unintended or pathogenic organisms.[146,151-153] Therefore, recognizing the potential signals of probiotic-related adverse reactions remains essential in clinical practice.[144,146,152,153] It should be emphasized that the risks described above are very rare and occur only under specific conditions.[154]

Gaps in Evidence and Future Research Direction

Need for strain-specific, adequately powered randomized controlled trials

Although probiotics are discussed as a homogeneous therapeutic category, accumulating evidence clearly indicates that their clinical effects are highly strain-specific. Most RCTs in IBS and FC have evaluated heterogeneous probiotic formulations, frequently combining multiple strains with different mechanisms of action, doses, and viability profiles. This heterogeneity substantially limits the interpretability and reproducibility of results and precludes robust subgroup analyses, including sex-stratified efficacy assessments. In addition, many trials are underpowered to detect clinically meaningful effects, particularly when stratified by sex. Given that probiotic responses may differ not only by disease phenotype but also by host sex, future RCTs should be designed with sufficient sample sizes to allow strain-specific and sex-based analyses.

Need for standardized and clinically meaningful outcome measures

Another major limitation of the current evidence is the lack of standardized clinical endpoints. Studies evaluating probiotics in IBS, FC, and CDI have employed a wide range of outcome measures, including global symptom

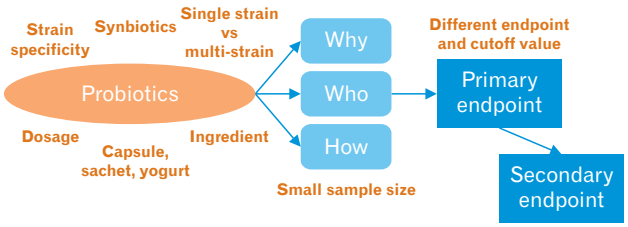

Figure 4. Factors contributing to heterogeneity in probiotic clinical trials.

improvement, individual symptom scores, stool frequency, stool consistency, quality-of-life scales, and various composite endpoints. This variability contributes to substantial heterogeneity in meta-analyses and complicates comparisons across the studies. Future studies should adopt harmonized and validated outcome measures.

Underrepresentation and imbalance of males and females in clinical studies

Despite the well-documented sex differences in the prevalence, pathophysiology, and clinical expression of IBS, FC, and CDI, most probiotic trials have not been designed to examine sex as a biological variable. Many studies include disproportionately female or male populations without justification. In some trials, sex-specific analyses are exploratory or post hoc, limiting their valid interpretation. This imbalance not only reduces statistical power but also risks masking clinically relevant differences in efficacy and safety. To advance personalized probiotic therapy, future clinical trials should ensure balanced recruitment of males and females, prespecify sex-based subgroup analyses, and transparently report sex-disaggregated results.

Need for mechanistic validation of sex-based hypotheses

Preclinical studies have provided compelling evidence that probiotic effects on gut inflammation, visceral sensitivity, immune responses, and microbial composition can differ markedly between males and females. These findings support the biological plausibility of sex-dependent probiotic efficacy. However, mechanistic validation in human studies remains limited. Most clinical trials rely on symptom-based outcomes without integrating mechanistic biomarkers, such as microbial functional profiles, immune signatures, epithelial barrier markers, or hormone–microbiota interactions. Future research should bridge this translational gap by incorporating mechanistic endpoints into well-designed clinical trials.

CONCLUSIONS

Currently available data remain inconsistent owing to variability in strains, dosages, and study designs in managing IBS, FC, and CDI (Fig. 4). However, bowel habits and symptom burden improved in selected patients, and animal studies provided clear evidence for sex differences. Given that IBS and FC show a clear female predominance, sex-related biological mechanisms warrant further consideration. Substantial systematic efforts are required to clarify the mechanistic and clinical effects of probiotics in terms of sex, which will contribute to the development of optimized and personalized probiotic strategies.

SUPPLEMENTARY MATERIAL

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm25221.

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