Supplementary Table 1. Selected Key Questions Raised by the Guideline Development Committee

Focus area	Indicator
Definition and epidemiology	KQ1: What is the definition of chronic constipation?
	KQ2: Does the prevalence of constipation increase with age?
	KQ3: Is the prevalence of constipation higher in females than in males?
Diagnosis	KQ4: Can the Bristol Stool Form scale be used to predict slow-transit constipation in patients with chronic constipation?
	KQ5: Is digital rectal examination useful for identifying secondary constipation due to organic causes in the anorectum?
	KQ6: Is digital rectal examination useful for screening for defecatory disorders?
	KQ7: Should colonoscopy be performed in patients with chronic constipation?
	KQ8: When should physiological testing be performed in chronic functional constipation?
	KQ9: Is the balloon expulsion test useful for screening for defecatory disorders?
	KQ10: Is anorectal manometry useful for diagnosing defecatory disorders in constipated patients?
	KQ11: Is defecography useful for diagnosing structural abnormalities of the pelvic floor or pelvic dyssynergia in patients with chronic constipation?
	KQ12: Is the colon transit time useful for differentiating defecatory disorders and slow-transit constipation in patients with chronic constipation?
Management	KQ13: Is dietary fiber effective as a treatment for chronic constipation?
	KQ14: Can exercise help relieve symptoms in adults with chronic constipation?
	KQ 15: Are bulking agents effective as a treatment for chronic constipation?
	KQ16: Are bulking agents safe as a treatment for chronic constipation?
	KQ17: Are magnesium salts effective as a treatment for chronic constipation?
	KQ18: Are magnesium salts safe as a treatment for chronic constipation?
	KQ19: Can non-absorbable carbohydrates help relieve symptoms in adults with chronic constipation?
	KQ20: Are non-absorbable carbohydrates safe for use in patients with chronic constipation?
	KQ21: Is polyethylene glycol effective as a treatment for chronic constipation?
	KQ22: Is long-term use of polyethylene glycol safe for patients with chronic constipation?
	KQ23: Can stimulants help relieve symptoms in adults with chronic constipation?
	KQ24: Are stimulant laxatives safe for patients with chronic constipation?
	KQ25: Can probiotics help relieve symptoms in adults with chronic constipation?
	KQ26: Can prucalopride help relieve symptoms in adults with chronic constipation?
	KQ27: Can lubiprostone help relieve symptoms in adults with chronic constipation?
	KQ28: Is linaclotide effective as a treatment for chronic constipation?
	KQ29: Is biofeedback therapy an effective treatment for patients with defecatory disorders?
	KQ30: Does biofeedback therapy exert a long-term effect on patients with defecatory disorders?
	KQ31: Is enema effective as a treatment for chronic constipation?
	KQ32: Is enema safe as a treatment for chronic constipation?
	KQ33: What is the treatment for medically intractable (non-responsive patients with slow-transit constipation?
	KQ34: Is surgical management effective in improving the symptoms in patients with the obstructive defecation syndrome?
	KQ35: Can sacral nerve stimulation help relieve symptoms in adults with chronic constipation?

KQ, key question.

Supplementary Table 2. Conflict of Interest Register

Name	Relevant employee experience	Relevant consultation experience	Personal ownership interest	Non-personal pecuniary interest	Relevant honorarium experience	Action required
Cho YS	None	None	None	None	None	None
Shin JE	None	None	None	None	None	None
Jung HK	None	None	None	None	None	None
Park SY	None	None	None	None	None	None
Lee YJ	None	None	None	None	None	None
Kang SJ	None	None	None	None	None	None
Song KH	None	None	None	None	None	None
Kim JW	None	None	None	None	None	None
Lim HC	None	None	None	None	None	None
Park HS	None	None	None	None	None	None
Kim SJ	None	None	None	None	None	None
Cha RR	None	None	None	None	None	None
Bang KB	None	None	None	None	None	None
Bang CS	None	None	None	None	None	None
Yim SK	None	None	None	None	None	None
Ryoo SB	None	None	None	None	None	None
Kye BH	None	None	None	None	None	None
Ji WB	None	None	None	None	None	None
Choi MY	None	None	None	None	None	None

Supplementary Table 3. Characteristics of the Comparison Studies Between Fiber Supplementation and Placebo

Study (yr)	Disease	Country	Number (C/T)	Age (mean)	Sex (M/F)	Duration (wk)	Treatment (C/T)
Chey et al,[94] 2021	CIC	USA	46/30	42.7 ± 15.94	7/69	4	Psyllium (12 g/day) Kiwifruit (2 g/day)
Wisten et al,[103] 2005	CIC	Sweden	10/10	74.9 ± 13.6	10/10	2	Control Mixed fiber (7.5 g)
Chan et al,[93] 2007	CIC	China	22/22	50.4 ± 12.72	13/42	4	Control Kiwifruit (2 g/day)
Maeta et al,[99] 2022	CIC	Japan	25/25	21	0/50	2	Control Mixed fiber (Okara)
Venancio et al,[102] 2018	CIC	USA	19/17	26.1 ± 7.32	11/25	4	Psyllium (5 g/day) Mango fruit (300 mg)
Attaluri et al,[91] 2011	CIC	USA	20/20	NR	3/37	6	Psyllium (11 g/day) Plum (100 mg)
Erdogan et al,[95] 2016	CIC	USA	40/32	42.9	6/66	4	Psyllium (5 g/day) Mixed fiber (SupraFiber)
Baek et al,[92] 2016	CIC	Korea	40/40	24.0 ± 4.1	9/71	8	Control Mixed fiber (*F. carica*)
Sairanen et al,[100] 2007	CIC	Finland	22/21	76	11/32	6	Control Prunes (12 g), Linseed (6 g)
Jung et al,[97] 2020	CIC	Korea	26/13	21.8 ± 2.0	0/39	4	Wheat diet Insoluble fiber (brown rice)
Badiali et al,[104] 1995	CIC	Italy	12/12	40.1 ± 11	2/22	8	Control Wheat bran (20 g)
Duncan et al,[105] 2018	CIC	Switzerland	39/80	46.8	8/111	4	Control Rye bread
Huh et al,[96] 2007	CIC	Korea	20/22	32.2 ± 6.9 31.2 ± 8.3	NR	4	Control Mixed fiber (7.5 g)
Kim et al,[98] 2006	CIC	Korea	36/73	24.0 ± 4.2 24.6 ± 5.66	NR	3	Control Mixed fiber (14 g)
Soltanian et al,[101] 2019	CIC, DM	Iran	27/50	58.0	NR	12	Control Flaxseed (10 g)

C/T, control/test; M, male; F, female; CIC, chronic idiopathic constipation; *F. carica*, *Ficus carica*; DM, diabetes mellitus; NR, not reported.

Supplementary Table 4. Studies Showing the Association Between Physical Activity and Constipation in Adults

Author (yr)	Study design	Definition of constipation	Results
Wilson,[113] 2020	Population-level, cross-sectional study in the USA, with 9963 adults	< 3 stools/wk BSFS 1 or 2	< 3 stools/wk in patients with no vigorous recreational activity (OR [95% CI], 1.82 [1.11-2.97]) and for patients with no moderate recreational activity (OR [95% CI], 1.41 [1.08-1.85]). Insignificant difference in multivariate models
Moezi et al,[20] 2018	Cross-sectional study in Southern Iran, with 9264 participants (age, 40-75 yr)	Based on the Rome IV criteria	Physical activity (OR, 0.56; 95% CI, 0.46-0.68)
Mazlyn et al,[112] 2013	Database generated via survey	Constipation severity score	Constipation severity score was associated with higher physical activity levels
Ragput et al,[116] 2014	Cross-sectional study in India	Based on the Rome IV criteria	Physical exercise ($P < 0.001$) Never, 40/129 (31.0%) Sometimes, 23/238 (9.6%) Habitual, 22/138 (15.9%)

BSFS, Bristol stool form scale.

Supplementary Table 5. Studies Showing the Effectiveness of Exercise in the Management of Constipation

Author (yr)	Study design	Patients	Intervention	Results
Nour-Eldein et al,[119] 2014	Pre-post intervention study	Twenty-three elderly patients with FC (≥ 60 yr) at a nursing home	Lifestyle modification, including education (3 separate sessions at intervals of 2 wk)	Improvement of the PAC-QOL and PAC-SYM scores
Speed et al,[S1] 2010	RCT, three-arm	A total of 154 patients with FC (age ≥ 55 yr)	Non-personalized dietary and lifestyle advice; personalized dietary and lifestyle advice, with reinforcement	No evidence of improvement of the PAC-QOL or PAC-SYM scores
Meshkinpour et al,[S2] 1998	Pre-post intervention study	Eight patients with constipation (SBM, less than 3/wk)	Four weeks of exercise using a treadmill	No benefit
Tanaway et al,[S3] 2017	RCT and pre-post intervention	A total of 125 obese women (age, 20-40 yr) with CC	Physical activity + routine care (n = 62). Routine care (n = 63). A 12-week program	Significant intragroup difference and inter-group difference Improvement of the PAC-QOL and PAC-SYM scores
Chin et al,[120] 2006	RCT and pre-post intervention	A total of 157 institutionalized participants (age, 64-94 yr)	Resistance training, 40-60 min, 2/wk (n = 40) Functional training (n = 41) Combined training (n = 45) Control (n = 31) 24-wk program	No effects of constipation symptoms or laxative use.
De Schryver et al,[121] 2005	Pre-post intervention	A total of 43 inactive patients (age > 45 yr)	Brisk walking for 30 min, ≥ 2/wk, 12-wk PA program	Significantly decreased number of fulfilled Rome criteria for constipation (2.7 to 1.5, $P < 0.05$) Significantly decreased rectosigmoid (17.5 to 9.6 hr) and total colon transit (79.2 to 58.4 hr, $P < 0.05$) time

FC, functional constipation; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; RCT, randomized controlled trial; SBM, spontaneous bowel movement.

Supplementary Table 6. Characteristics of the Comparison Studies Between Bulking Agent and Placebo

Study (yr)	Design	Duration	Agents	Patient	Number (C/T)	Result
Ashraf et al,[S4] 1995	Double-blind study	8 wk	Psyllium (5 g bid)	CC	11/11	1. Improved stool frequency, 3.8 vs 2.9 stools/wk 2. Improved stool consistency, 3.2 vs 3.8 3. Reduced pain during defecation, 2.0 vs 2.6
Fenn et al,[S5] 1986	Single-blind study	2 wk	Psyllium (3.6 g tid)	CC	97/104	Symptom relief (psyllium vs. placebo, 86.5% vs 47.4%)
Nunes et al,[S6] 2005	Double-blind study	2 wk	Psyllium (10 g/day)	CC	30/30	Symptom relief (psyllium vs placebo, 86.7% vs 30.0%)
Soltanian et al,[101] 2018	Single-blind trial	12 wk	Psyllium (10 g bid)	CC with DM	27/24	Improvement of the global constipation symptom score (psyllium vs placebo, 1.5 vs 0.5)
Sturtzel et al,[S7] 2010	Parallel intervention trial	12 wk	Oat-bran (6.6 g tid)	CC in elderly	15/15	Use of laxatives vs placebo, 59% reduction vs 8% increase
Baldiali et al,[104] 1995	Double-blind trial	2 wk	Wheat bran	CC	12/12	1. Improves bowel frequency (n/wk; bran vs placebo, 6.4 vs 5.1) 2. Reduction in the need for straining during defecation, bran vs placebo, 55.6% vs 28.6%

C/T, control/test; bid, twice a day; tid, 3 times a day; CC, chronic constipation; DM, diabetes mellitus.

Supplementary Table 7. Characteristics of the Comparison Studies Between Non-absorbable Carbohydrate and Placebo

Study (yr)	Definition	Criteria used to define response	Number of patients	Laxative used	Duration of therapy
Wesselius-De Casparis et al,[142] 1968	Need for regular laxative use	No requirement of additional laxatives during the treatment period	103	Lactulose (15 mL): 54 Placebo: 49	3 wk
Sanders et al,[141] 1978	Three or fewer BMs + another symptom	No increase in the bowel movement	42	Lactulose (30 mL): 19 Placebo: 23	2 wk
Kasugai et al,[143] 2019	Rome III (without excluding IBS-C)	Number of patients with constipation stratified by severity	250	Lactulose (13 g): 63 Lactulose (26 g): 63 Lactulose (39 g): 62 Placebo: 62	2 wk

BM, bowel movement; IBS-C, irritable bowel syndrome with constipation.

Supplementary Table 8. Characteristics of the Comparison Studies Between Polyethylene Glycol and Placebo

Study (yr)	Country	Diagnostic criteria used to define FC	Primary endpoints	Total number of patients	Sex ratio (M/F)	Duration	Intervention
Corazziari et al,[160] 1996	Italy (6 centers)	< 2 BMs (at least 12 mo) or the presence of 2 or more of the following: < 3 BMs/wk, straining during defecation, sense of incomplete evacuation, and hard stools in at least 25% of defecations	Bowel frequency, normalization of bowel frequency	48	11/37	8 wk	PEG 4000 (14.6 g)
Dipalma et al,[161] 2000	USA (4 centers)	≤ 2 stools during a 7-day qualification period	≥ 3 BMs/7 day	151	20/131	2 wk	PEG 3350 (17 g)
Corazziari et al,[162] 2000	Italy (4 centers)	< 2 BMs (at least 12 mo) or the presence of two or more of the following: < 3 BMs/wk, straining at defecation, sense of incomplete evacuation, and hard stools in at least 25% of defecations	Complete remission of constipation with ≥ 3 BMs/wk, no use of laxatives, no straining at defecation, a feeling of complete evacuation, and no hard/pellety stools	70	12/58	20 wk	PMF-100 (14.6 g twice daily). Dose reduction allowed
Dipalma et al,[164] 2007	USA (4 centers)	Rome II and medication that had a 3% or greater incidence of constipation	Beyond Rome II	100	26/74	4 weeks	MiralLax (17 g)
Dipalma et al,[165] 2007	USA (50 centers)	Modified Rome	0.50 or greater rate of successful treatment weeks 1. No use of rescue laxative 2. Satisfactory stool greater than or equal to 3 times/wk 3. One or fewer of the remaining three Rome-based symptom criteria a. Straining during more than 25% of defecations b. Lumpy or hard stools in more than 25% of defecations c. A sensation of incomplete evacuation in more than 25% of defecations	304	46/258	24 wk	MiralLax (17 g)
Nakajima et al,[166] 2019	Japan	Rome III	Change in the frequency of SBMs from baseline at week 2	156	24/132	2 wk	PEG 3350 (17 g)
MV Cleveland et al,[163] 2001	USA	≤ 3 BMs/wk	Bowel movement, constipation symptoms	23 (cross over)	1/22	2 wk	PEG-ELS (17 g)
T McGraw et al,[167] 2016	USA	Rome III	Inflammation of the oral mucosa	65	14/51	2 wk	PEG 3350 (17 g)

FC, functional constipation; M, male; F, female; BM, bowel movement; USA, United States of America; PEG, polyethylene glycol; SBM, spontaneous bowel movement; PEG-ELS, polyethylene glycol electrolyte lavage solution.

Supplementary Table 9. Characteristics of the Comparison Studies Between Probiotics and Placebo

Study (yr)	Patients	Probiotics	CFU	Number (T/C)	Duration	Outcome
Airaksinen et al,[184] 2019	FC, IBS-C	*Lactobacillus acidophilus, Lacticaseibacillus paracaseis, Bifidobacterium animalis*	> 1010	78/78	2 wk	Frequency, transit time
Bazzocchi et al,[185] 2014	FC	*Lactobacillus acidophilus, Lacticaseibacillus paracaseis, Bifidobacterium animalis*	2.4 × 1010	17/12	8 wk	Symptom, consistency, transit time
Cudmore et al,[186] 2017	FC	*Bifidobacterium bifidum, Lactobacillus rhamnosus, Lactobacillus acidophilus*	6 × 108	35/34	4 wk	Frequency, consistency, transit time
Del Piano et al,[187] 2010	Evacuation disorder	*Lactobacillus plantarum, Bifidobacterium animalis lactis*	5 × 109	220:80	30 day	Frequency, consistency, transit time
Dimidi et al,[188] 2019	FC	*Bifidobacterium lactis*	1.5 × 1010	37/38	4 wk	Frequency, consistency, transit time
Ding et al,[189] 2016	FC	*Bifidobacterium longum Lactobacillus acidophilus Enterococcus faecalis*	3 × 107	48/45	12 wk	Frequency, consistency, transit time
Fateh et al,[190] 2011	FC	*Bifidobacterium longum, Bifidobacterium breve Lactobacillus casei, Lacticaseibacillus rhamnosus, Streptococcus thermophilus*	108	31/29	4 wk	Frequency, symptoms
Favretto et al,[191] 2013	FC	*Bifidobacterium lactis* Bi-07	1010	15/15	30 day	Frequency
Ibarra et al,[192] 2018	FC	*Bifidobacterium animalis* HN019	109 and 1010	152:76	4 wk	Frequency, consistency, transit time
Krammer et al,[193] 2011	Slow-transit constipation	*Lactobacillus casei* Shirota	6.5 × 109	12/12	4 wk	Frequency, consistency, transit time
Lim et al,[194] 2018	FC	*Bifidobacterium lactis, Lactiplantibacillus plantarum*	1010	43/42	12 wk	Frequency, consistency, symptom
Magro et al,[195] 2014	Chronic constipation	*Bifidobacterium lactis, Lactobacillus acidophilus*	> 109	26/21	2 wk	Frequency, transit time
Martoni et al,[196] 2019	FC	*Lactobacillus acidophilus, Bifidobacterium animalis lactis, Bifidobacterium longum, Bifidobacterium bifidum*	1.5 × 1010	48/46	4 wk	Frequency, consistency
Mazlyn et al,[197] 2013	FC	*Lactobacillus casei* Shirota	3 × 1010	50/50	4 wk	Frequency, consistency
Ojetti et al,[198] 2014	FC	*Limosilactobacillus reuteri* DSM17938	108	20/20	4 wk	Frequency, symptom
Waitzberg et al,[199] 2013	FC	*Bifidobacterium lactis, Lacticaseibacillus paracasei, Lacticaseibacillus rhamnosus, Lactobacillus acidophilus*	< 109	49/50	30 day	Frequency, consistency, symptom
Waller et al,[200] 2011	< 3 BMs/wk	*Bifidobacterium animalis* HN019	1.7 × 1010 and 1.8 × 109	59:29	2 wk	Transit time, symptom
Yang et al,[201] 2008	< 3 BMs/wk	*Bifidobacterium lactis* DN173010	1.2 × 1010	63/63	2 wk	Frequency, consistency, symptom
Madempudi et al,[202] 2020	FC	*Bacillus coagulans*	2 × 1010	50/50	4 wk	Frequency, consistency
Wang et al,[203] 2021	FC	*Streptococcus thermophilus, Lactobacillus bulgaricus, Bifidobacterium animalis*	1010	23/21	4 wk	Frequency, consistency, symptom

Supplementary Table 9. Continued

Study (yr)	Patients	Probiotics	CFU	Number (T/C)	Duration	Outcome
Botelho et al,[204] 2020	FC	*Lactobacillus acidophilus, Lactobacillus casei, Lactococcus lactis, Bifidobacterium bifidum, Bifidobacterium lactis*	5 × 109	21/14	30 day	Frequency, consistency
Zhang et al,[205] 2021	FC and depression	*Lacticaseibacillus paracasei*	1010	38/31	9 wk	Symptom, microbiota
Ghafar et al,[206] 2020	FC	*Lactobacillus acdiphpilus, Lactobacillus casei, Lactococcus lactis, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium longum*	5 × 1010	36/36	7 day	Frequency, symptom
Araujo et al,[207] 2021	FC	*Lactobacillus acidophilus, Lactobacillus casei, Lactococcus lactis, Bifidobacterium lactis, Bifidobacterium bifidum*	109	25/20	30 day	Frequency, consistency, symptom
Kang et al,[208] 2021	FC	*Bacillus coagulans*	109	40/40	8 wk	Frequency, symptom

CFU, colony-forming units; T/C, test/control; FC, functional constipation defined by the Rome criteria; IBS-C, irritable bowel syndrome with constipation; BM, bowel movement.

Supplementary Table 10. Characteristics of the Comparison Studies Between Prucalopride and Placebo

Study (yr)	Country	Number of patients	Age (mean)	Sex (M/F)	Duration (wk)	Treatment protocol
Krogh et al,[218] 2002	Denmark	22	37.0	16/6	4	1 mg vs placebo
						2 mg vs placebo
Camilleri et al,[214] 2008	USA, Belgium	620	48.3	45/371	12	2 mg vs placebo
						4 mg vs placebo
Camilleri et al,[219] 2009	USA	89	82.9	24/65	4	0.5 mg vs placebo
						1 mg vs placebo
Quigley et al,[213] 2009	Ireland	641	47.9	86/555	12	2 mg vs placebo
						4 mg vs placebo
Tack et al,[215] 2009	Belgium	713	43.9	66/650	12	2 mg vs placebo
						4 mg vs placebo
Müller-Lissner et al,[217] 2010	Germany	303	76.0	92/211	4	1 mg vs placebo
						2 mg vs placebo
						4 mg vs placebo
Ke et al,[216] 2012	China, Korea	501	41.6	51/450	12	2 mg vs placebo
Piessevaux et al,[220] 2015	Europe	361	48.9	53/308	24	2 mg vs placebo
Yiannakou et al,[221] 2015	Europe	370	58.5	NR	12	2 mg vs placebo

M, male; F, female; USA, United States of America; NR, not reported.

Supplementary Table 11. Characteristics of the Comparison Studies Between Lubiprostone and Placebo

Study (yr)	Disease	Country	Number (T/C)	Age (mean)	Sex (M/F)	Duration (wk)	Treatment
Johanson et al,[229] 2007	CIC	USA	94/33	48.8	10/84	3	Control/24 μg qd/24 μg bid/24 μg tid
Johanson et al,[230] 2008	CIC	USA	120/122	48.0 ± 12.3	13/107	4	Control/24 μg bid
Barish et al,[231] 2010	CIC	USA	119/118	46.2 ± 12.1	15/104	4	Control/24 μg bid
Fukudo et al,[232] 2011	CIC	Japan	128/42	39.9	13/115	3	Control/8 μg bid/16 μg bid/24 μg bid
Fukudo et al,[233] 2015	CIC	Japan	62/62	42.7 ± 16.4	6/56	4	Control/24 μg bid
Christie et al,[234] 2017	CIC and DM	USA	37/39	56.9 ± 9.1	14/23	8	Control/24 μg bid

T/C, test/control; M, male; F, female; CIC, chronic idiopathic constipation; USA, United States of America; qd, once a day; bid, twice a day; DM, diabetes mellitus.

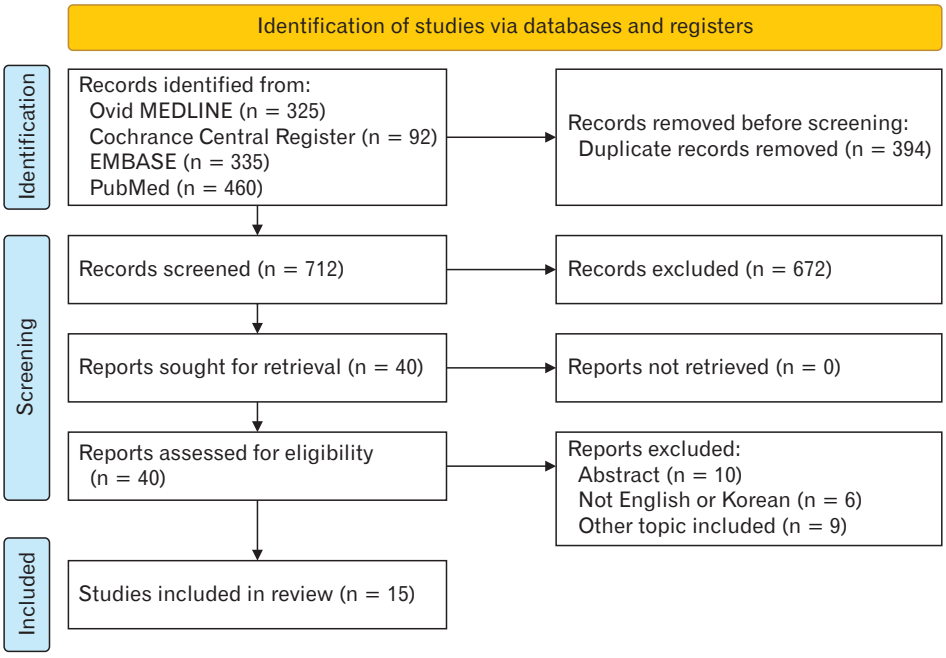
Supplementary Table 12. Characteristics of the Comparison Studies Between Linaclotide and Placebo

Study (yr)	Study population	Treatment	Control	Endpoint
Fukudo et al,[248] 2019	CIC (Rome III and < 3 SBMs/wk)	Once daily Linaclotide 500 μg (0.5 mg) for 4 wk	Placebo for 4 wk	≥ 3 CSBMs and an increase of ≥ 1 CSBM/wk from the baseline at 4 wk or ≥ 3 SBMs and an increase of ≥ 1 SBM/wk from the baseline at 4 wk
Schoenfeld et al,[247] 2018	CIC (Rome III and < 3 SBMs/wk)	Once daily Linaclotide 72 μg or 145 μg for 12 wk	Placebo for 12 wk	≥ 3 CSBMs and an increase of ≥ 1 CSBM/wk from the baseline in the same week for ≥ 9 wk of the 12-wk treatment period
Lacy et al,[246] 2015	CIC (Rome II, < 3 SBMs/wk, and average abdominal bloating scores of more than 5 during the 14-day period)	Once daily Linaclotide 145 μg or 290 μg for 12 wk	Placebo for 12 wk	≥ 3 CSBMs/wk and an increase of ≥ 1 CSBM/wk from the baseline at 12 wk ≥ 3 CSBMs/wk at 4 and 12 wk, an increase of ≥ 1 CSBM/wk from the baseline at 12 wk
Lembo (2011 trial 303) et al,[245] 2011	CIC (Rome II and < 3 SBMs/wk)	Once daily Linaclotide 145 μg or 290 μg for 12 wk	Placebo for 12 wk	≥ 3 CSBMs and an increase of ≥ 1 CSBM/wk from the baseline in the same week for ≥ 9 wk of the 12-wk treatment period
Lembo (2011 trial 01) et al,[236] 2011	CIC (Rome II and < 3 SBMs/wk)	Once daily Linaclotide 145 μg or 290 μg for 12 wk	Placebo for 12 wk	≥ 3 CSBMs and an increase of ≥ 1 CSBM/wk from the baseline in the same week for ≥ 9 wk of the 12-wk treatment period

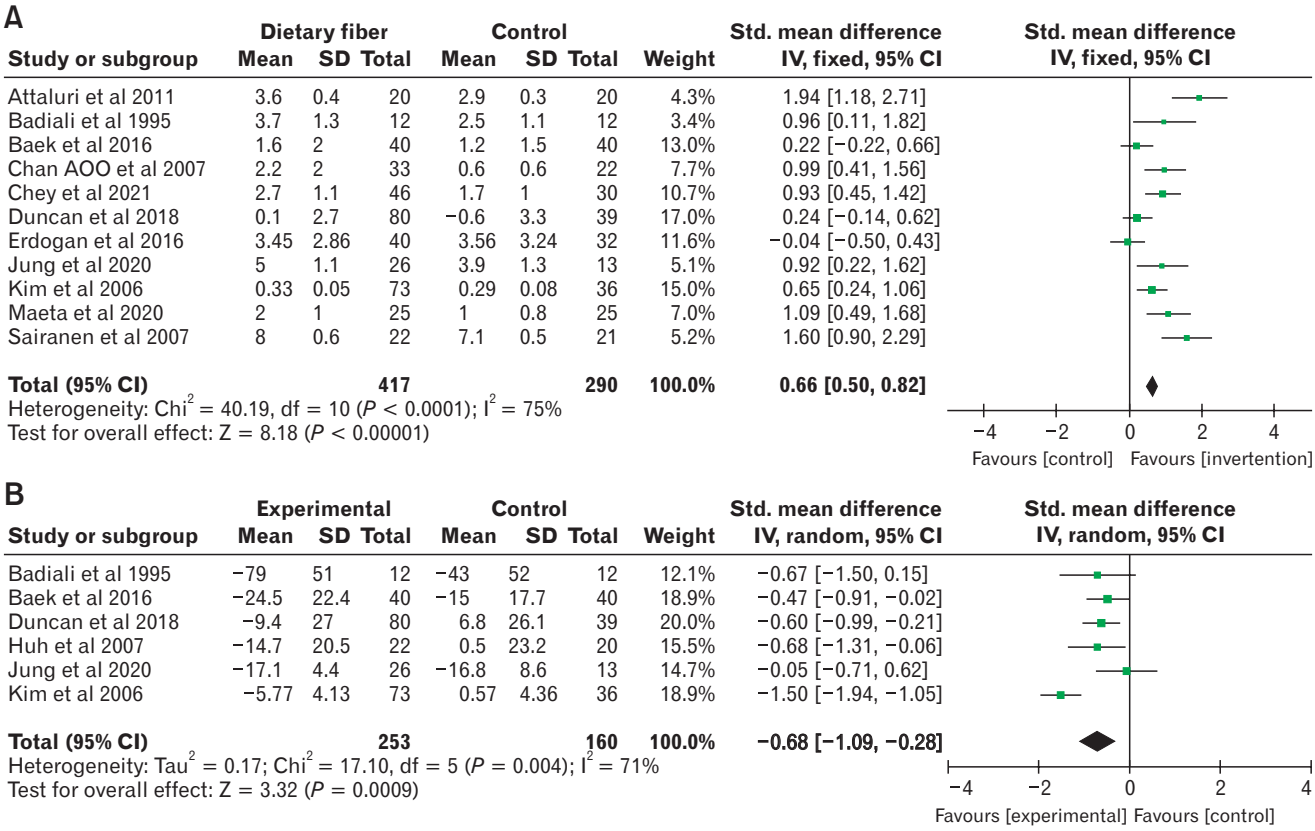
CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement.

Supplementary Table 13. Main Outcomes of the Comparison Studies Between Linaclotide and Placebo

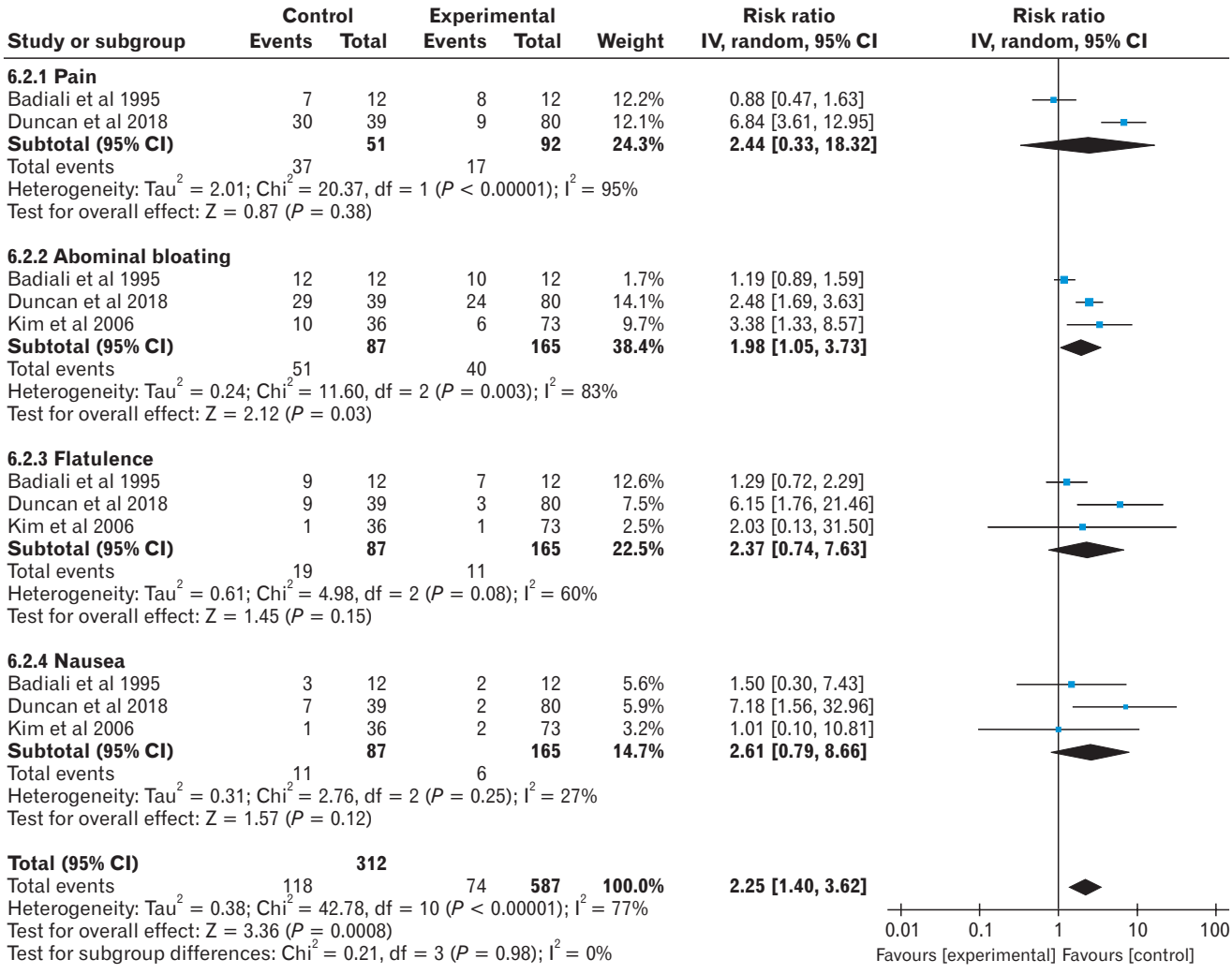
Study (yr)	Symptomatic improvement	Adverse events
Fukudo et al,[248] 2019	42/92 (500 μg), 11/89 (placebo) at 4 wk	26/92 (linaclotide), 13/90 (placebo) (diarrhea was most common) (12/92, 1/90)
Schoenfeld et al,[247] 2018	55/411 (72 μg), 51/411 (145 μg), 19/401 (placebo) at 12 wk	At least 1 AE, 143/411 (72 μg), 145/411 (145 μg), 107/401 (placebo) (diarrhea was most common) (79/411, 91/144, 28/401)
Lacy et al,[246] 2015	24/153 (145 μg), 26/159 (290 μg), 13/171 (placebo) for at least 9 of the 12 wk of treatment	At least 1 AE, 75/153 (145 μg), 76/160 (290 μg), 65/173 (placebo) (diarrhea was most common) (9/153, 27/160, 4/173)
Lembo (2011 trial 303) et al,[245] 2011	46/217 (145 μg), 42/216 (290 μg), 7/209 (placebo) for at least 9 of the 12 wk of treatment	At least 1 AE, 260/430 (145 μg), 235/422 (290 μg), 221/424 (placebo) (diarrhea was most common) (69/430, 60/422, 20/424)
Lembo (2011 trial 01) et al,[236] 2011	34/213 (145 μg), 43/202 (290 μg), 13/215 (placebo) for at least 9 of the 12 wk of treatment	At least 1 AE, 260/430 (145 μg), 235/422 (290 μg), 221/424 (placebo) (diarrhea was most common) (69/430, 60/422, 20/424)



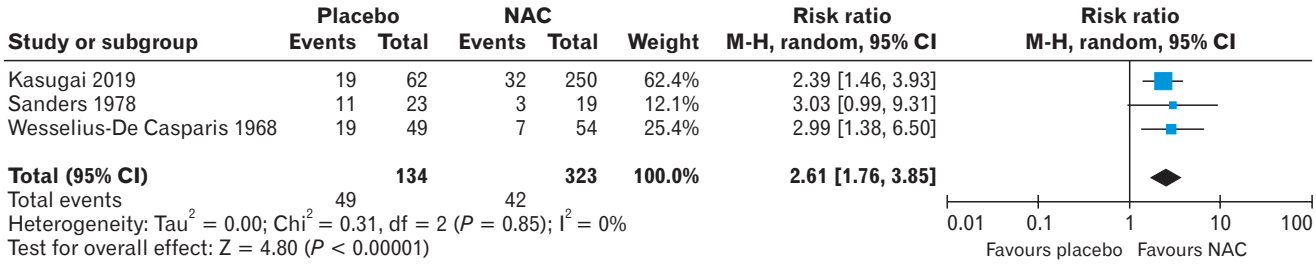
Supplementary Figure 1. Flow chart of the literature screening process and results of the efficacy of fiber supplementation in patients with chronic constipation.



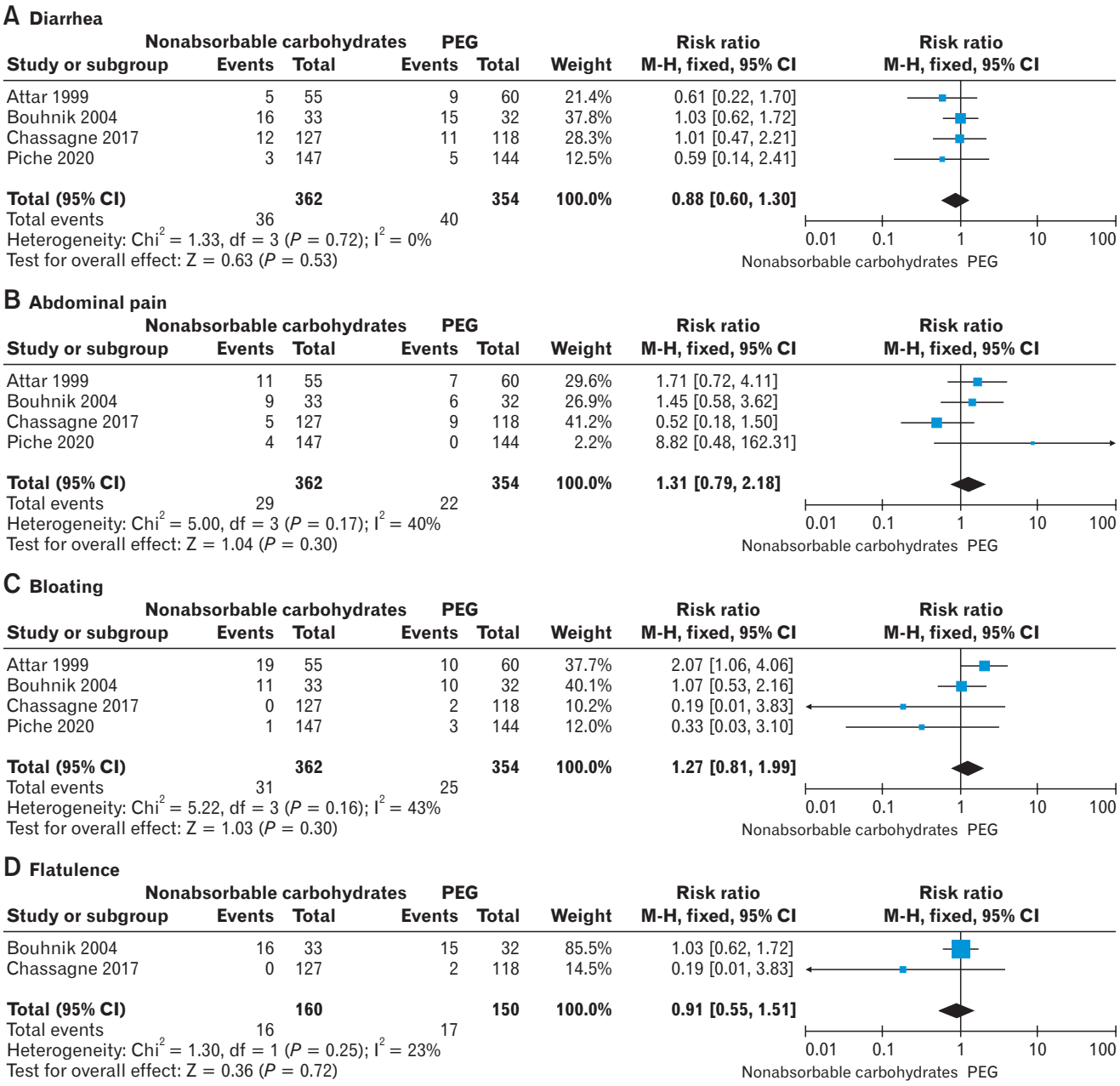
Supplementary Figure 2. Efficacy of fiber supplementation versus placebo in the treatment of chronic constipation (A) Forrest plot of spontaneous bowel movement changes during the first 4 weeks. (B) Forrest plot of changes in the colon transit time during the first 4-8 weeks.



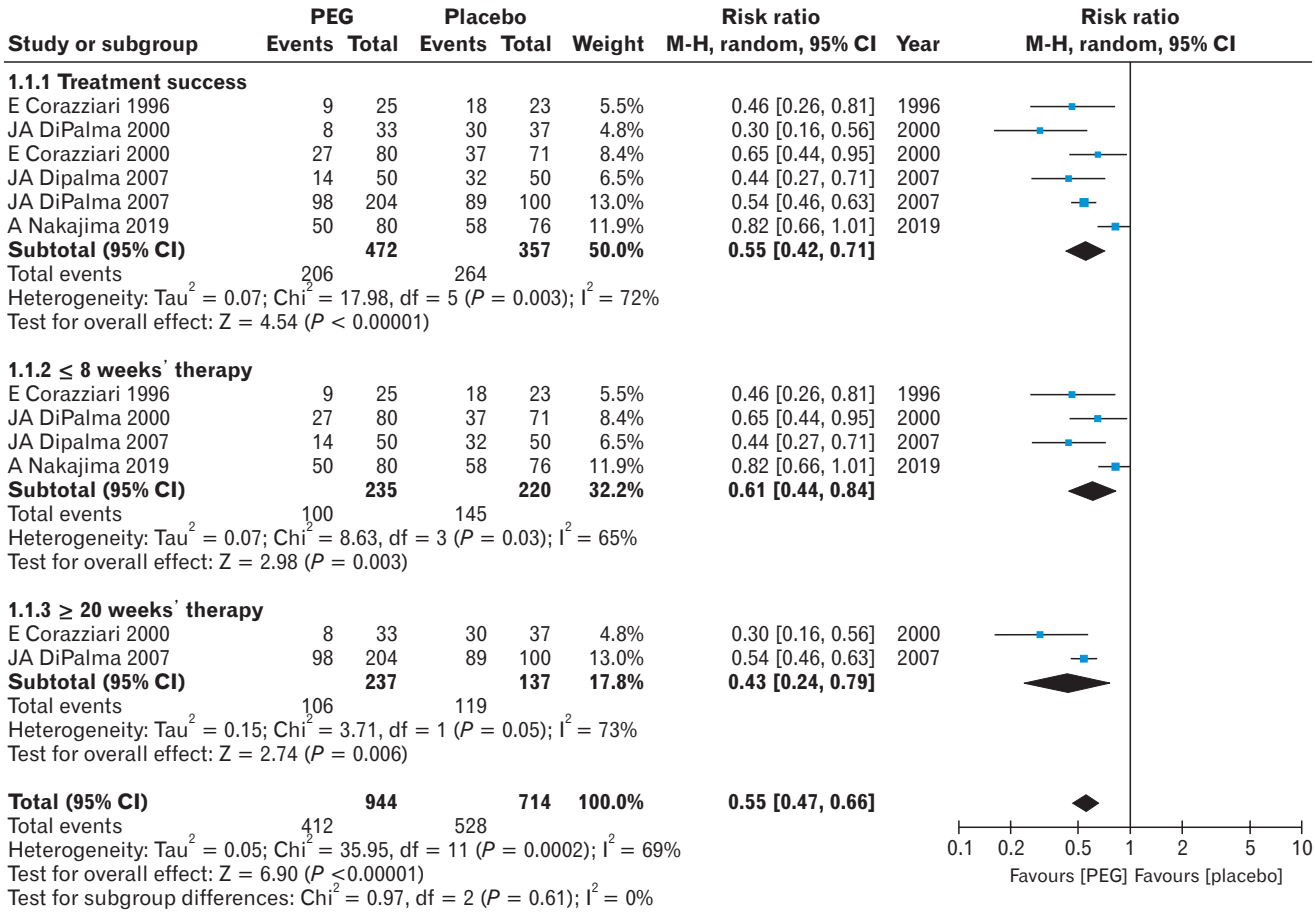
Supplementary Figure 3. Forrest plot for patients with adverse events in the fiber and placebo groups.



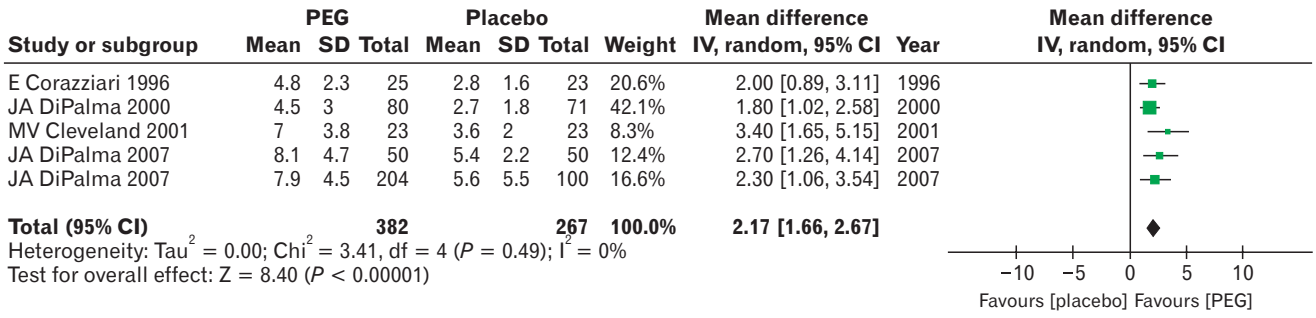
Supplementary Figure 4. Forrest plot of the efficacy of non-absorbable carbohydrates (NAC) versus placebo in the treatment of chronic constipation (treatment failure). M-H, Mantel-Haenszel.



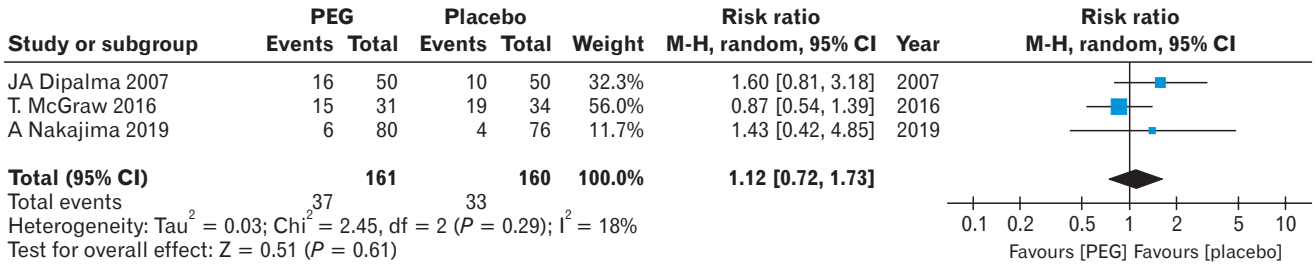
Supplementary Figure 5. Forrest plot for patients with adverse events between the non-absorbable carbohydrate and polyethylene glycol (PEG) groups. M-H, Mantel-Haenszel.



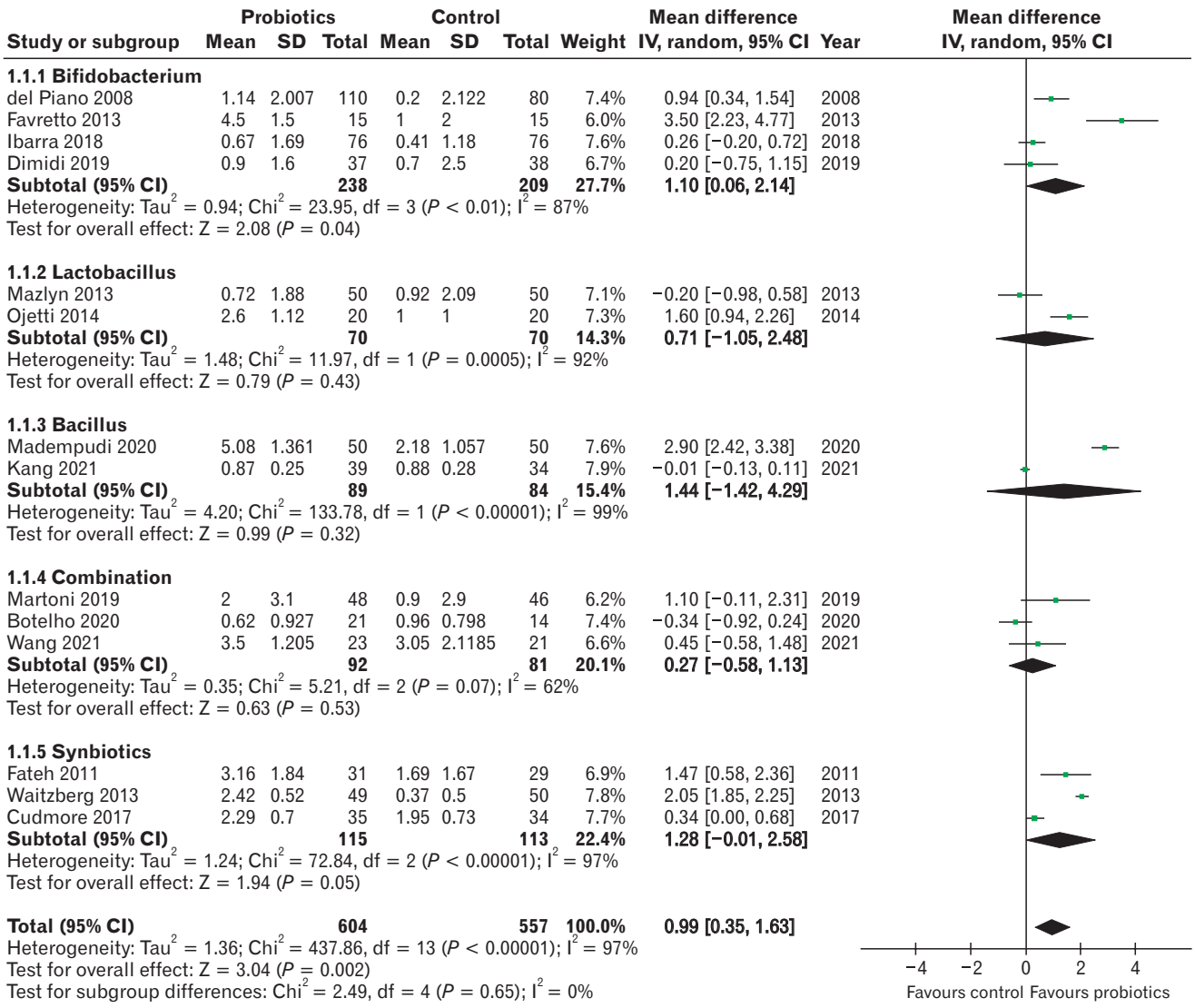
Supplementary Figure 6. Forrest plot of the efficacy of polyethylene glycol (PEG) versus placebo in the treatment of chronic constipation (treatment success and treatment success by the duration of treatment). M-H, Mantel-Haenszel.



Supplementary Figure 7. Forrest plot of the efficacy of polyethylene glycol (PEG) versus placebo in the treatment of chronic constipation (stool frequency).



Supplementary Figure 8. Forrest plot of the efficacy of polyethylene glycol (PEG) versus placebo in the treatment of chronic constipation (adverse event). M-H, Mantel-Haenszel.



Supplementary Figure 9. Change in spontaneous bowel movements per week at 4 weeks in the probiotic and placebo groups.

Summary of findings:

Probiotics compared to Placebo for Constipation

Patient or population: Constipation
Setting:
Intervention: Probiotics
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI) Risk with Placebo	Risk with Probiotics	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Change of SBM per week at 4 weeks	The mean change of SBM per week at 4weeks was **1.16**/week	MD **0.99**/**week higher** (0.35 higher to 1.63 higher)	-	1161 (14 RCTs)	⨁⨁◯◯ Low[a,b]	
Change of SBM per week at 2 weeks	The mean change of SBM per week at 2 weeks was **0.27**/week	MD **0.79**/**week higher** (0.27 higher to 1.3 higher)	-	402 (4 RCTs)	⨁⨁◯◯ Low[a,c]	
Change of SBM per week at 8-12 weeks	The mean change of SBM per week at 8-12 weeks was **1.07**/week	MD **0.95**/**week higher** (0.17 higher to 1.73 higher)	-	251 (3 RCTs)	⨁⨁⨁◯ Moderate[c]	
Consistency	-	SMD **0.48 SD higher** (0.05 higher to 0.9 higher)	-	875 (9 RCTs)	⨁⨁◯◯ Low[b,c]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

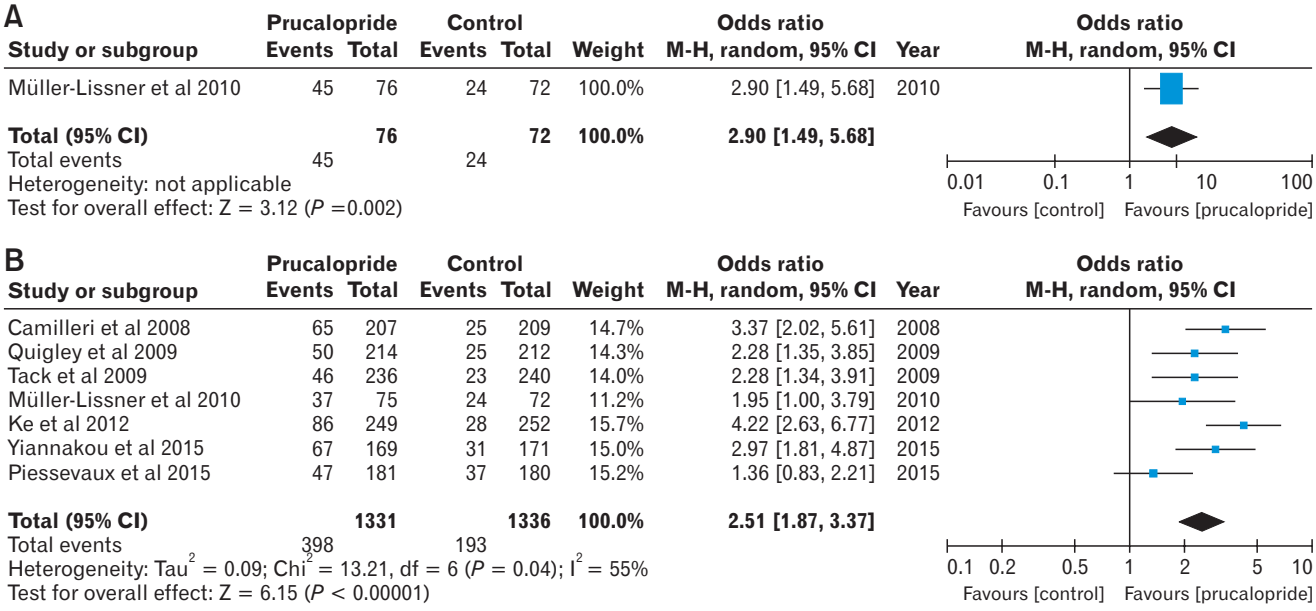
CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

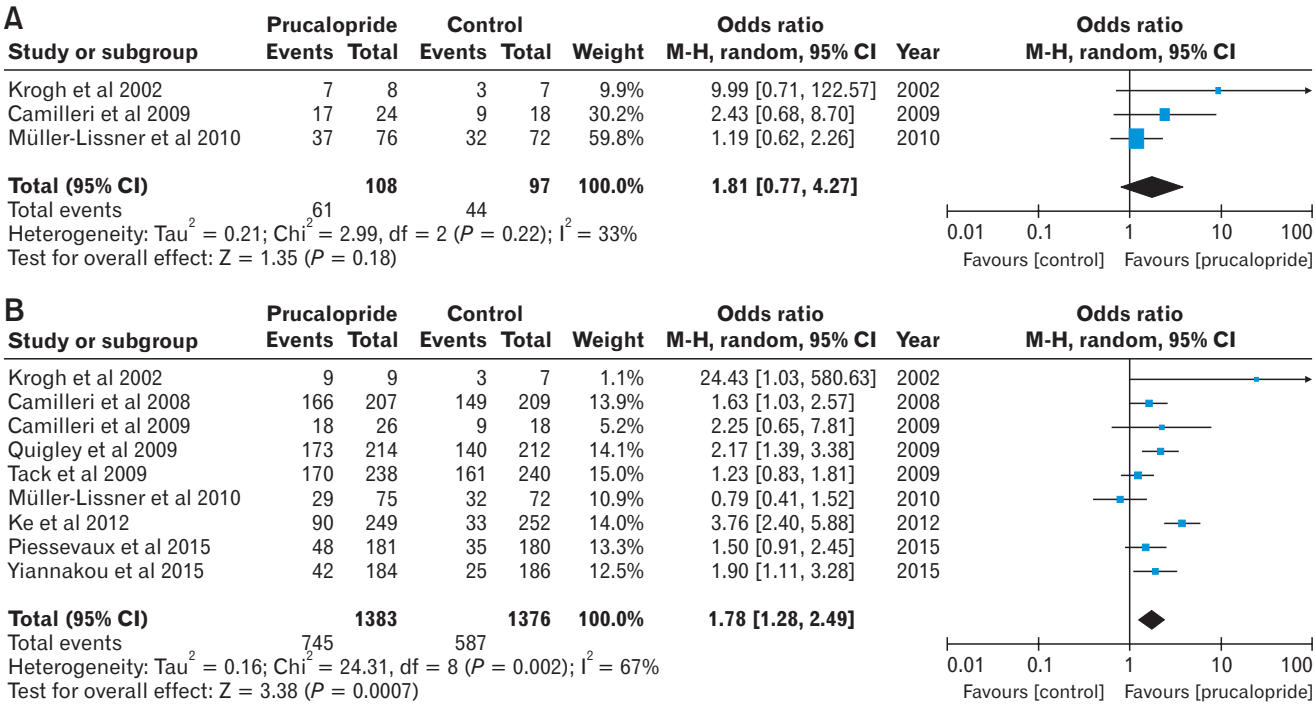
Explanations

a. High risk of bias
b. Inconsistent results
c. Low number of patients

Supplementary Figure 10. Summary of findings: probiotics compared to placebo for constipation.



Supplementary Figure 11. Forrest plot for patients with > 3 spontaneous bowel movements per week. (A) 1 mg prucalopride versus placebo. (B) 2 mg prucalopride versus placebo. M-H, Mantel-Haenszel.



Supplementary Figure 12. Forrest plot for patients with adverse events. (A) 1 mg prucalopride versus placebo. (B) 2 mg prucalopride versus placebo. M-H, Mantel-Haenszel.

Summary of findings:

Prucalopride compared to Placebo for [health problem]

Patient or population: [health problem]

Setting:

Intervention: Prucalopride

Comparison: Placebo

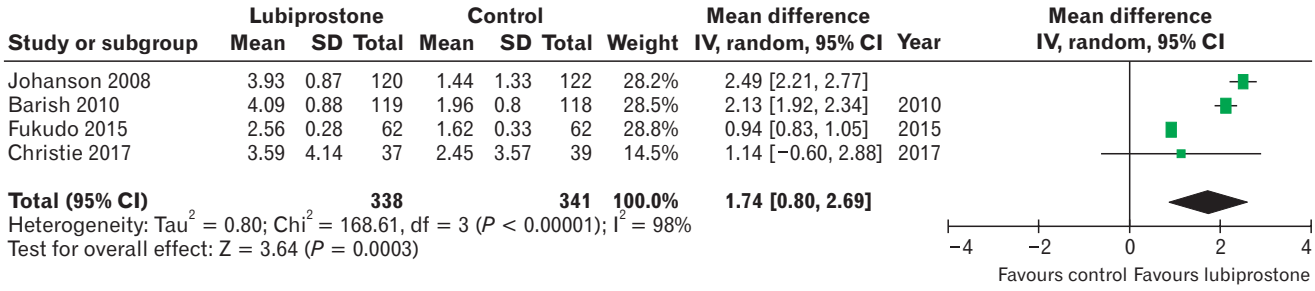
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Prucalopride				
Patients with >3 SCBM per week (Prucalopride 1mg vs Placebo)	333 per 1,000	**592 per 1,000** (427 to 740)	**OR 2.90** (1.49 to 5.68)	148 (1 RCT)	⊕⊕⊕⊕ High	
Patients with >3 SCBM per week (Prucalopride 2mg vs Placebo)	144 per 1,000	**298 per 1,000** (240 to 363)	**OR 2.51** (1.87 to 3.37)	2667 (7 RCTs)	⊕⊕⊕⊕ High	
Occurrence of adverse event (Prucalopride 1mg vs Placebo)	454 per 1,000	**600 per 1,000** (390 to 780)	**OR 1.81** (0.77 to 4.27)	205 (3 RCTs)	⊕⊕⊕⊕ High	
Occurrence of adverse evenet (Prucalopride 2mg vs Placebo)	485 per 1,000	**631 per 1,000** (564 to 693)	**OR 1.81** (1.37 to 2.39)	3694 (9 RCTs)	⊕⊕⊕⊕ High	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

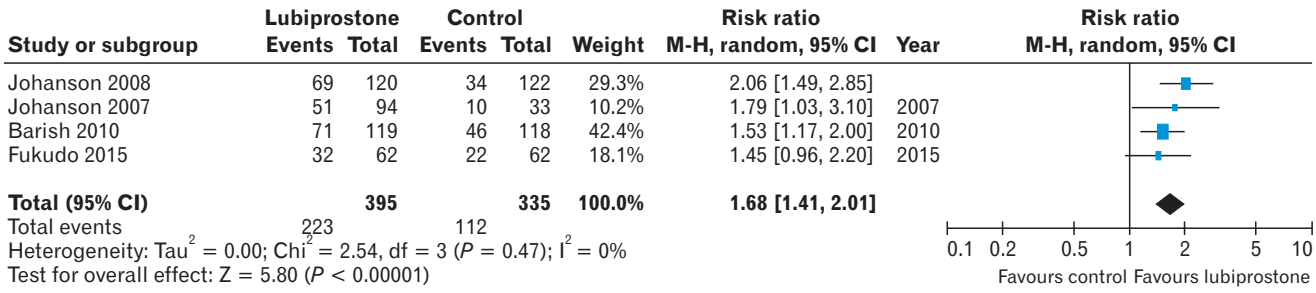
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Supplementary Figure 13. Summary of findings: prucalopride compared to placebo for chronic idiopathic constipation.



Supplementary Figure 14. Change in spontaneous bowel movements per week at 4 weeks in the lubiprostone and placebo groups.



Supplementary Figure 15. Patients with > 3 spontaneous bowel movements per week at 4 weeks in the lubiprostone and placebo groups. M-H, Mantel-Haenszel.

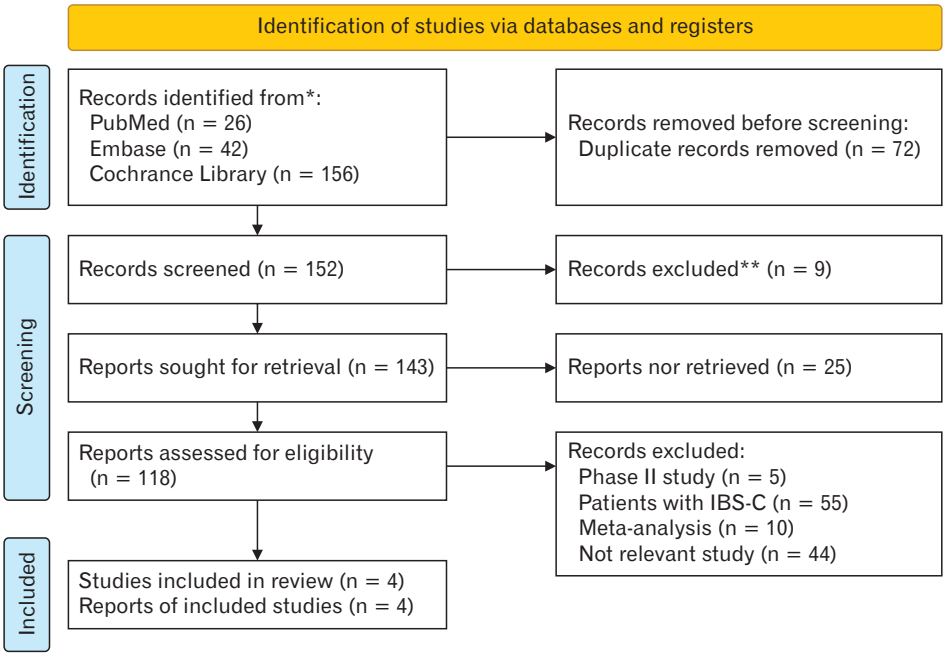
Outcomes	Anticipated absolute effects* (95% CI) Risk with Placebo	Risk with Lubiprostone	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Change of SBM per week at 4 weeks	The mean change of SBM per week at 4 weeks was **1.87** /week	MD **1.74 /week higher** (0.8 higher to 2.69 higher)	-	679 (4 RCTs)	⨁⨁⨁⨁ High	
Patients with >3 SBM/week at 4 weeks	334 per 1,000	**562 per 1,000** (471 to 672)	**RR 1.68** (1.41 to 2.01)	730 (4 RCTs)	⨁⨁⨁⨁ High	
Patients with SBM within 24 hours	321 per 1,000	**587 per 1,000** (494 to 693)	**RR 1.83** (1.54 to 2.16)	900 (5 RCTs)	⨁⨁⨁⨁ High	
Overall adverse event	167 per 1,000	**428 per 1,000** (334 to 550)	**RR 2.56** (2.00 to 3.29)	900 (5 RCTs)	⨁⨁⨁⨁ High	
Serious adverse event	39 per 1,000	**51 per 1,000** (24 to 109)	**RR 1.30** (0.61 to 2.78)	658 (4 RCTs)	⨁⨁⨁⨁ High	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

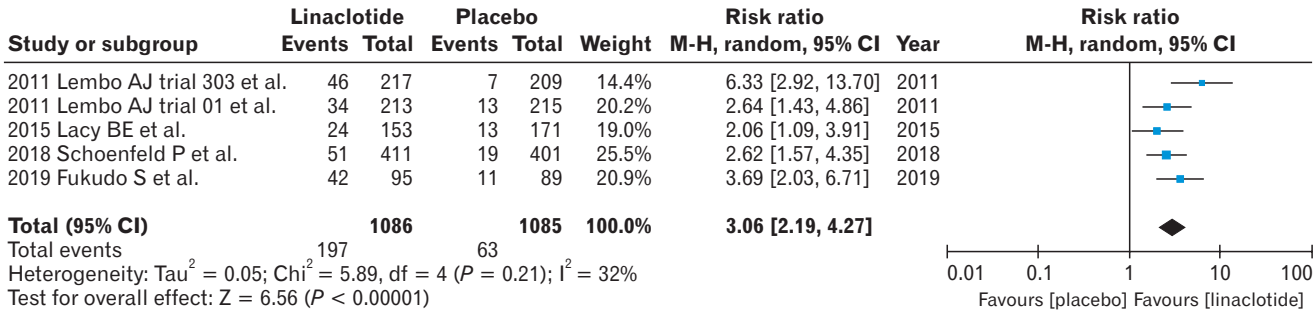
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

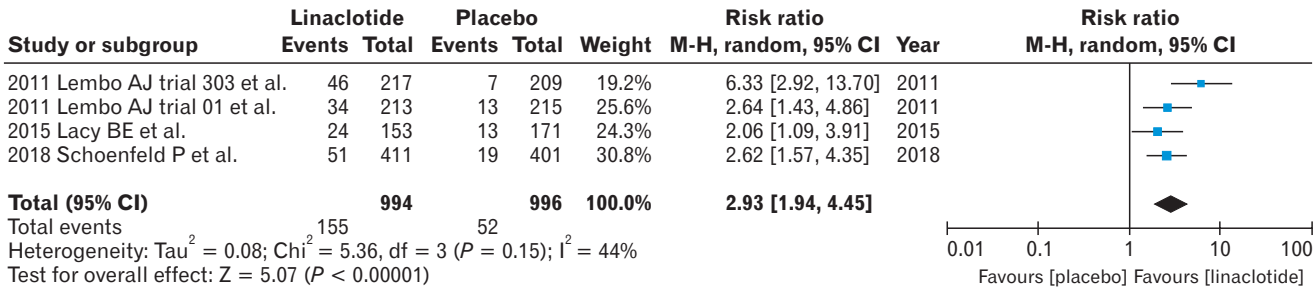
Supplementary Figure 16. Summary of findings: lubiprostone compared to placebo for chronic idiopathic constipation.



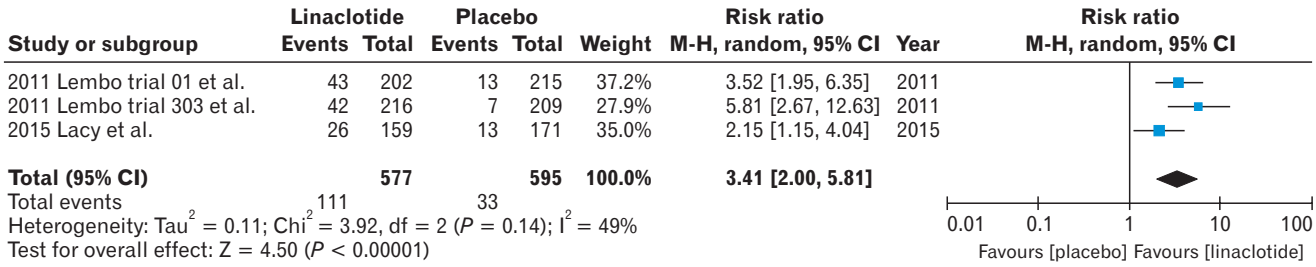
Supplementary Figure 17. Flow chart of the literature screening process and results of the efficacy of linaclotide in patients with chronic constipation.



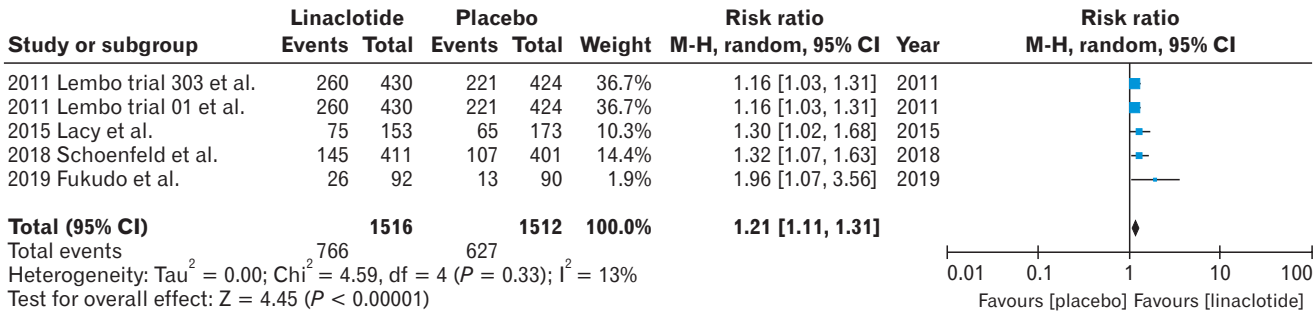
Supplementary Figure 18. Efficacy of linaclotide versus placebo in the treatment of chronic constipation (overall pooled analysis).



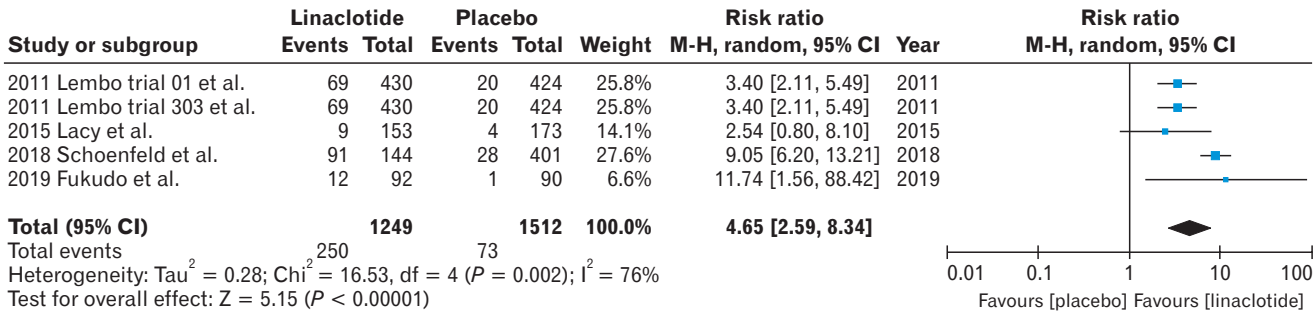
Supplementary Figure 19. Efficacy of linaclotide versus placebo in the treatment of chronic constipation (subgroup analysis with linaclotide 145 μg). M-H, Mantel-Haenszel.



Supplementary Figure 20. Efficacy of linaclotide versus placebo in the treatment of chronic constipation (subgroup analysis with linaclotide 290 μg). M-H, Mantel-Haenszel.



Supplementary Figure 21. Rate of adverse events related to linaclotide versus placebo in the treatment of chronic constipation. M-H, Mantel-Haenszel.



Supplementary Figure 22. Rate of diarrhea related to linaclotide versus placebo in the treatment of chronic constipation. M-H, Mantel-Haenszel.

Linaclotide compared to placebo for chronic constipation

Patient or population: patients with chronic constipation
Settings: RCT
Intervention: Linaclotide
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Linaclotide				
Clinical improvement	**58 per 1000**	**178 per 1000** (127 to 248)	**RR 3.06** (2.19 to 4.27)	2171 (5 studies)	⊕⊕⊕⊕ **high**	
Adverse events	**415 per 1000**	**502 per 1000** (460 to 543)	**RR 1.21** (1.11 to 1.31)	3028 (5 studies)	⊕⊕⊕⊕ **high**	
Diarrhea a/w linaclotide treatment	**48 per 1000**	**225 per 1000** (125 to 403)	**RR 4.65** (2.59 to 8.34)	2761 (5 studies)	⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Supplementary Figure 23. Summary of findings: linaclotide compared to placebo for chronic idiopathic constipation.

Supplementary References

S1. Speed C, Heaven B, Adamson A, et al. LIFELAX - diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people: randomised controlled trial. Health Technol Assess 2010;14:1-251.

S2. Meshkinpour H, Selod S, Movahedi H, Nami N, James N, Wilson A. Effects of regular exercise in management of chronic idiopathic constipation. Dig Dis Sci 1998;43:2379-2383.

S3. Tantawy SA, Kamel DM, Abdelbasset WK, Elgohary HM. Effects of a proposed physical activity and diet control to manage constipation in middle-aged obese women. Diabetes Metab Syndr Obes 2017;10:513-519.

S4. Ashraf W, Park F, Lof J, Quigley EM. Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. Aliment Pharmacol Ther 1995;9:639-647.

S5. Fenn GC, Wilkinson PD, Lee CE, Akbar FA. A general practice study of the efficacy of Regulan in functional constipation. Br J Clin Pract 1986;40:192-197.

S6. Nunes FP, Nunes CP, Levis E, et al. A double-blind trial of a celandin, aloevera and psyllium laxative preparation in adult patients with constipation. Rev Bras Med 2005;62:352-357.

S7. Sturtzel B, Mikulits C, Gisinger C, Elmadfa I. Use of fiber instead of laxative treatment in a geriatric hospital to improve the wellbeing of seniors. J Nutr Health Aging 2009;13:136-139.