The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials[1–3]

Eirini Dimidi, Stephanos Christodoulides, Konstantinos C Fragkos, S Mark Scott, and Kevin Whelan

ABSTRACT

Background: Functional constipation is a prevalent, burdensome gastrointestinal disorder whose treatment remains challenging. Probiotics have been increasingly investigated in its management.

Objective: The aim was to investigate the effect of probiotics on gut transit time, stool output, and constipation symptoms in adults with functional constipation via a systematic review and meta-analysis of randomized controlled trials (RCTs).

Design: Studies were identified by searching 4 electronic databases, back-searching reference lists, contacting authors, and hand-searching abstracts. RCTs that reported administration of probiotics in adults with functional constipation were included. Two reviewers independently performed the screening, data extraction, and bias assessment. Outcome data were synthesized by using weighted mean differences (WMDs) or standardized mean differences (SMDs) with the use of a random-effects model.

Results: A total of 660 records were identified of which 14 were eligible (1182 patients). Overall, probiotics significantly reduced whole gut transit time by 12.4 h (95% CI: −22.3, −2.5 h) and increased stool frequency by 1.3 bowel movements/wk (95% CI: 0.7, 1.9 bowel movements/wk), and this was significant for *Bifidobacterium lactis* (WMD: 1.5 bowel movements/wk; 95% CI: 0.7, 2.3 bowel movements/wk) but not for *Lactobacillus casei* Shirota (WMD: −0.2 bowel movements/wk; 95% CI: −0.8, 0.9 bowel movements/wk). Probiotics improved stool consistency (SMD: +0.55; 95% CI: 0.27, 0.82), and this was significant for *B. lactis* (SMD: +0.46; 95% CI: 0.08, 0.85) but not for *L. casei* Shirota (SMD: +0.26; 95% CI: −0.30, 0.82). No serious adverse events were reported. Attrition and reporting bias were high, whereas selection bias was unclear due to inadequate reporting.

Conclusions: Probiotics may improve whole gut transit time, stool frequency, and stool consistency, with subgroup analysis indicating beneficial effects of *B. lactis* in particular. However, caution is needed with the interpretation of these data due to their high heterogeneity and risk of bias. Adequately powered RCTs are required to better determine the species or strains, doses, and duration of use of probiotics that are most efficacious. *Am J Clin Nutr* 2014;100:1075–84.

INTRODUCTION

Functional constipation is a symptom-based gastrointestinal disorder without an organic origin (eg, bowel obstruction). It has a prevalence of ∼14% in adults (1), representing a huge health care burden. In 2012, it was estimated that functional constipation accounted for 3.2 million visits to medical centers in the United States (2, 3), with annual treatment costs of $1912–$7522 per patient (4). During the same period, there were ∼17.4 million prescriptions for laxatives in England at a cost of £80 million (>US$130 million) (5). In addition to the economic costs, constipation greatly affects patients' quality of life, with a significant impairment of both mental and physical components (6, 7).

The management of functional constipation remains challenging. Bulking agents, osmotic laxatives, stimulant laxatives, and stool softeners are commonly used (8, 9). However, up to 47% of patients are not completely satisfied with such treatments, with the main reasons being treatment efficacy, inconsistent symptom response, and concerns with regard to safety, adverse effects, taste, inconvenience, and cost (10). Accordingly, patients with functional constipation commonly adopt self-management approaches, with 80% having tried over-the-counter products (10) such as foods believed to exert a laxative effect, "functional foods," and nutraceuticals (11).

Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit to the host (12). There are several potential mechanisms of action by which probiotics may benefit functional constipation (13). First, probiotics modify the gastrointestinal microbiota, which is known to be altered in constipation (14, 15). Second, probiotic metabolites may alter gut function, including sensation (16, 17) and motility (18, 19). Third, some probiotics increase the production of lactate and short-chain fatty acids, reducing luminal pH, which some researchers have proposed will enhance colonic peristalsis and shorten whole gut transit time (GTT)[4] (20, 21).

[1] From the Diabetes and Nutritional Sciences Division, School of Medicine, King's College London, London, United Kingdom (ED, SC, and KW); the Centre for Digestive Diseases, Neurogastroenterology Group and GI Physiology Unit, Queen Mary University of London, London, United Kingdom (ED, SC, and SMS); and the Division of Medicine, Centre for Gastroenterology and Clinical Nutrition, University College London, London, United Kingdom (KCF).

[2] This meta-analysis was undertaken as part of a PhD fellowship funded by Nestec Ltd. Nestec Ltd had no involvement in the design or implementation of the review, analysis and interpretation of the data, or review of the manuscript.

[3] Address reprint requests and correspondence to K Whelan, King's College London, Diabetes and Nutritional Sciences Division, 150 Stamford Street, London, SE1 9NH, London, United Kingdom. E-mail: kevin.whelan@kcl.ac.uk.

[4] Abbreviations used: GTT, gut transit time; RCT, randomized controlled trial; SMD, standardized mean difference; WMD, weighted mean difference.

Received April 1, 2014. Accepted for publication July 3, 2014.

First published online August 6, 2014; doi: 10.3945/ajcn.114.089151.

A number of studies investigated the effect of probiotics on symptoms or physiology (eg, GTT) in subjects with constipation. The aim was to investigate the effect of probiotics on GTT, stool output, and constipation symptoms in adults with functional constipation via a systematic review and meta-analysis of randomized controlled trials (RCTs). Our hypothesis was that probiotics would significantly shorten whole and regional GTT, increase stool frequency, and improve stool consistency.

SUBJECTS AND METHODS

This systematic review was carried out in line with the relevant criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (22) and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (23). The methods of the eligibility criteria, search, extraction, and analysis were specified in advance and documented in a protocol that was published in a prospective register of systematic reviews, PROSPERO (http://www.crd.york.ac.uk/PROSPERO; ref CRD42013004799). The eligibility criteria were developed by using a PICOS (Patient, Intervention, Comparators, Outcome, Study design) approach (24) and are detailed in **Table 1**. Briefly, the inclusion criteria were any RCT reporting the administration of a single or combination of live probiotics to patients with functional constipation that measured clinical or physiologic outcomes relevant to constipation.

Search strategy and study selection

Studies were identified through searching electronic databases, scanning reference lists of relevant articles, hand-searching of conference abstracts, contacting authors, and consultation with experts in the field. No limits were applied for language or publication date.

An electronic search of the published literature was conducted by using MEDLINE (http://ovidsp.ovid.com; 1946 to March 2014), EMBASE (http://ovidsp.ovid.com; 1946 to March 2014), Web of Science (http://isiknowledge.com; 1900 to March 2014), and the Cochrane Central Register of Controlled Trials (http://onlinelibrary.wiley.com/cochranelibrary/search; to 2013). Studies were searched by using the term "constipation," both as medical subject heading and free-text terms. The detailed search strategy can be found in Supplemental Material 1 under "Supplemental data" in the online issue and the search was last conducted in March 2014. A search of a clinical trials database (www.clinicaltrials.gov) was conducted to locate any completed, but unpublished studies.

Conference abstracts were identified via hand-searching from the following conferences: Digestive Diseases Week from 2000 to 2013 (*Gastroenterology*), the British Society of Gastroenterology from 2000 to 2013 (*Gut*), the American Society for Parenteral and Enteral Nutrition from 2000 to 2013 (*J Parent Enteral Nutr*), the European Society for Clinical Nutrition and Metabolism from 2002 to 2012 (*Clin Nutr*, *Clin Nutr Supp*, e-SPEN), the British Dietetic Association from 2002 to 2012 (*J Hum Nutr Diet*), the British Association for Parenteral and Enteral Nutrition from 2000 to 2013 (*Proc Nutr Soc*, e-SPEN), the Association of Coloproctology of Great Britain and Ireland from 2000 to 2013 (*Colorectal Dis*), and the Association of American Colon and Rectal Surgeons from 2000 to 2013 (*Dis Colon Rectum*). The reference lists of eligible articles or relevant review papers were screened for other eligible trials.

All citations were imported into a bibliographic database (EndNote X6; Thomson Reuters) for assessment of eligibility. The title and abstract of all identified articles were independently reviewed by 2 reviewers (ED and SC) in a blinded standardized manner. The corresponding author was contacted in case of inadequate information to assess eligibility or to identify relevant

TABLE 1
Inclusion and exclusion criteria and data extracted following the PICOS approach[1]

PICOS	Inclusion and exclusion criteria	Data extraction
Patient	Adult populations aged ≥18 y with functional chronic constipation defined by clinical symptoms, a physician's opinion, or the Rome I, II, or III criteria. Studies of IBS-C were excluded. No restrictions for age, sex, or ethnicity were applied. Community or outpatient setting included only.	Age, sex, location, type of constipation, method of diagnosis for constipation, setting, inclusion and exclusion criteria, number of patients in the intervention, and comparator group.
Intervention	Any species/strains/dose/treatment regimen of live probiotics. Probiotics may be administered in tablet, powder, capsule, softgel, or fortified food forms (as long as the control group is such that the effect of the probiotic alone can be isolated).	Single or combination of probiotics alone. Genus, species, and strain of the probiotic as found in the article. When strain was not available, genus and species alone were extracted. The dose and schedule of probiotic and duration of intervention period were also recorded.
Comparators	Trials were included if they used a placebo as a control. For trials in which the probiotic intervention was a fortified food, an acceptable comparator was taken to be the food without the probiotic(s).	Type and dose of comparator.
Outcome	Reports of the clinical outcomes of stool frequency, stool consistency, stool weight, gut transit time (whole and regional), other gastrointestinal symptoms (eg, bloating, pain), 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, fulfillment of intention-to-treat analysis, adequacy of randomization, and allocation concealment and blinding.

[1] IBS-C, constipation-predominant irritable bowel syndrome; PICOS, Patient, Intervention, Comparators, Outcome, Study design.

data. Disagreements between reviewers were resolved by a third researcher (KW).

Data extraction

A data extraction spreadsheet was developed, and 2 reviewers (ED and SC) independently extracted the data from eligible studies. The data extracted included the characteristics of trial participants, the intervention, the comparator group, the outcomes measured (GTT, stool output, constipation symptoms, adverse effects, and compliance), and the study design (Table 1). Disagreements were resolved by a third researcher (KW).

To measure study quality, the 2 reviewers independently assessed the adequacy of randomization and allocation concealment, blinding methods, implementation of the intention-to-treat analysis, complete outcome data, and selective data reporting. Judgment of bias relating to each domain was categorized as low, high, or unclear according to the criteria described in the Cochrane handbook (23).

Data synthesis and statistical analysis

Meta-analysis was performed where outcomes from at least 2 studies could be obtained by using standard statistical procedures in proprietary software (RevMan version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration; and Stata version 12.0; StataCorp). For an outcome measured using the same technique and reported using the same units (whole and regional GTT, stool frequency), a weighted mean difference (WMD) was calculated. However, where the same outcome was measured or reported differently, the standardized mean difference (SMD) was calculated (25). In crossover studies, the means and SDs or SEs of the intervention and control periods separately were used (26). Where necessary, SDs were calculated from SEs or 95% CIs. A random-effects model was used to produce a pooled estimate of the WMD or SMD. Subgroup analyses were performed where there were sufficient trials for a specific species (eg, *Bifidobacterium lactis)* or a specific strain (eg, *Lactobacillus casei* Shirota*)*. However, subgroup analysis is only discussed where $\geq$2 studies or intervention arms contributed to the WMD or SMD. Statistical heterogeneity was assessed by using the chi-square test and was quantified by using the I^2 statistic, with a value $>$50% considered to represent substantial heterogeneity (27–29). When heterogeneity was statistically high, possible explanations were investigated by using sensitivity analyses according to probiotic species or strain and criteria for diagnosis of functional constipation. Publication bias was assessed by using funnel plots, and evidence of asymmetry was assessed by using the Egger test (30). A P value of $<$0.05 was considered to show significance.

RESULTS

The initial electronic and manual search generated 660 nonduplicated records of which only 65 were considered potentially eligible after review of the title and abstract. To assess study eligibility, 6 articles were translated to English (4 Japanese, 1 Chinese, 1 German), and 14 authors were contacted for further information. Searching of a clinical trials database (clinicaltrials.gov) found 3 other completed studies that were potentially eligible; on review, one was excluded and the remaining 2 studies were found to be completed only within the past 2 mo. Contact was made with the principal investigators of these studies, but data were not obtained.

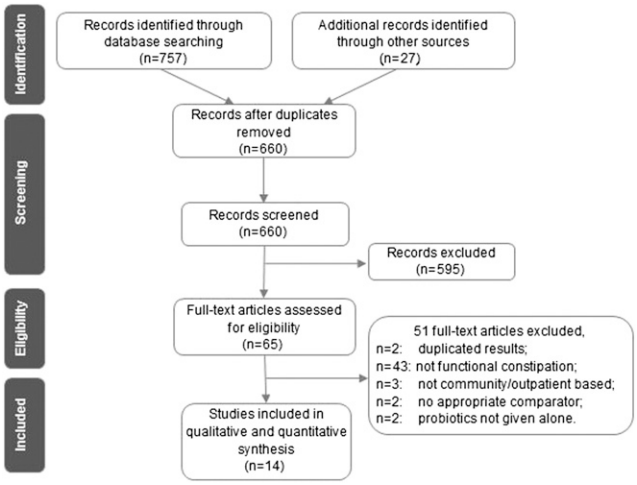

FIGURE 1. Flow diagram of studies evaluated in the systematic review.

After review of the full articles, 14 studies fulfilled the inclusion criteria (**Figure 1**). In total, 13 authors of the eligible studies were contacted for further information for data extraction, of which 5 replied.

Study characteristics

Thirteen of the 14 studies were full articles (20, 31–43), and one was available in abstract form only (39). Eleven studies were published in English, one in Japanese (41), one in Chinese (33), and one in German (35). There were 11 parallel-group RCTs (20, 31–33, 35–39, 42, 43) and 3 crossover RCTs (34, 40, 41). One study had a change-over design, with participants randomly assigned to receive probiotics or placebo for 4 wk, and then a change-over only in those whose symptoms had not improved (38). To minimize bias from the change-over effect, only data from the RCT component at week 4 were used.

Participants and intervention

The 14 studies recruited 1182 participants. However, one study investigated 2 different probiotic interventions (*Bifidobacterium breve/Lactobacillus plantarum* compared with *B. lactis* compared with placebo) (31), and one study investigated the same probiotic in 2 doses (*B. lactis* 17.2×10^9 CFU/d compared with *B. lactis* 1.8×10^9 CFU/d compared with placebo) (20), and these different intervention groups were considered as separate studies, resulting in a total of 16 separate interventions in the meta-analysis. Seven interventions were *B. lactis* alone (20, 31–34, 41, 43), 4 were *L. casei* Shirota (32, 35–37), and one each were *Escherichia coli* Nissle (38), *Lactobacillus reuteri* (39), *Lactobacillus paracasei* (40), and *B. breve/L. plantarum* (31). Of these, the doses ranged from 10^8 to 3×10^{10} CFU/d and the treatment period varied from 2 to 8 wk. The probiotics were provided in yogurt, fermented milk, beverages, sachets, capsules, or probiotic-fortified foods (**Table 2**).

Outcomes

The outcomes of each meta-analysis are reported in **Table 3**. No study reported a global dichotomous outcome variable for satisfactory relief of constipation.

TABLE 2
Characteristics of randomized controlled trials of probiotics compared with placebo/comparator in functional constipation[1]

		Patients			Probiotics				
Study, year (ref)	*n*	Age[2]	Women	Constipation definition	Genus, species, and strain	Dose	Form	Duration	Comparator
		y	%						
Favretto et al, 2013 (32)	30	Probiotics: 38 Placebo: 41	100	Rome III criteria for functional constipation	*Bifidobacterium lactis* BI-07	10^8 CFU/d	Cheese	30 d	Cheese without probiotics
Yang et al, 2008 (43)	126	Probiotics: 46 Control: 46	100	<3 stools/wk, increased stool hardness	*B. lactis* DN 173 010	1.25×10^{10} CFU/d	Fermented milk	2 wk	Acidified milk without probiotics
He et al, 2009 (33)	159	Probiotics: 47 Control: 47	NR	<3 stools/wk	*B. lactis* DN-173 010	1.25×10^{10} CFU/d	Yogurt	2 wk	Yogurt
Ishizuka et al, 2012 (34)	17	Range: 20–23	100	NR	*B. lactis* GCL2505	1×10^{10} CFU/d	Milk-like drink	2 wk	Milk-like drink
Takii et al, 2012 (41)	62	43	76	2–5 stools/wk	*B. lactis* GCL2505	$>1 \times 10^7$ CFU/g	Yogurt	2 wk	Yogurt without the probiotic
Waller et al, 2011 (20)	88	High probiotics: 43	63	Stool consistency rated as type 2–4 on Bristol stool form scale and 1–3 stools/wk	*B. lactis* HN019	17.2×10^9 CFU/d or	Capsules	14 d	Capsules with rice maltodextrin
		Low probiotics: 44 Placebo: 45				1.8×10^9 CFU/d			
Del Piano et al, 2010 (31)	300	Range: 24–71	50	Presence of evacuation disorder and hard stools	Group B: *Lactobacillus plantarum* LMG P-21021 and *Bifidobacterium breve* DSM 16604	Group B: 2.5×10^9 CFU/d of each strain	Sachets	30 d	3 g Maltodextrin in a half glass of water
					Group C: *B. lactis* LMG P-21384	Group C: 5×10^9 CFU/d			
Mollenbrink and Bruckschen, 1994 (38)	70	Probiotics: 45 Control: 48	77	≤2 stools/wk	*Escherichia coli* Nissle 1917	1×10^{11} CFU/d	Capsules	8 wk	Capsules without probiotic
Koebnick et al, 2003 (35)	70	Range: 18–70	54	NR	*Lactobacillus casei* Shirota	6.5×10^9 CFU/d	Beverage	4 wk	Beverage without probiotics
Krammer et al, 2011 (36)	24	50	100	Colonic transit time >72 h	*L. casei* Shirota	6.5×10^9 CFU/d	Fermented milk	4 wk	Milk drink without probiotics
Mazlyn et al, 2013 (37)	90	Probiotics: 32 y Control: 32	87	Rome II criteria for functional constipation	*L. casei* Shirota	3×10^{10} CFU/d	Fermented milk	4 wk	Fermented milk without probiotics
Tilley et al, 2014 (42)	106	Probiotics: 39 Placebo: 41	83	≤4 stools/wk and hard or lumpy stools in at least 25% of defecations	*L. casei* Shirota	6.5×10^9 CFU/d	Fermented milk	4 wk	Fermented milk without probiotics
Ojetti et al, 2013 (39)	20	35	60	Rome III criteria for functional constipation	*Lactobacillus reuteri* DSM 17938	2×10^8 CFU/d	Tablets	4 wk	Tablets
Riezzo et al, 2012 (40)	20	39	85	Rome III criteria for functional constipation	*Lactobacillus paracasei* IMPC 2.1 (LMGP22043)	2×10^{10} CFU/d	Artichokes	15 d	Artichokes without probiotics

[1] NR, not reported; ref, reference.
[2] Values for age are means unless otherwise stated.

TABLE 3
Statistical analysis for the outcomes reported in ≥2 randomized controlled trials and included in the meta-analysis[1]

Outcomes	No. of studies in meta-analysis (ref nos.)	Patients	Results: Meta-analysis overall estimate (95% CI)	Results: *P*	Heterogeneity: Chi-square test	Heterogeneity: *P*	Heterogeneity: I^2
		n					%
Whole GTT	2 (20, 36)	141	WMD: −12.4 h (−20.3, −2.5 h)	0.01	2.61	0.27	23
Right GTT	2 (20, 36)	141	WMD: −4.9 h (−10.5, 0.8 h)	0.09	3.50	0.17	43
Left GTT	2 (20, 36)	141	WMD: −4.9 h (−10.2, 0.3 h)	0.07	1.47	0.48	0
Rectosigmoid GTT	2 (20, 36)	141	WMD: −4.0 h (−7.6, −0.4 h)	0.03	2.19	0.33	9
Stool frequency	10 (31–34, 37–39, 41–43)	1060	WMD: 1.3 BM/wk (0.7, 1.9 BM/wk)	<0.00001	100.81	<0.00001	90
Stool consistency	10 (31, 33, 35, 37, 38, 40–43)	1003	SMD: 0.55 (0.27, 0.82)	0.0001	44.49	<0.00001	80
Stool quantity	3 (34, 37, 41)	169	SMD: 0.23 (−0.08, 0.54)	0.14	2.79	0.25	28
Bloating	4 (31, 35, 37)	460	SMD: −0.77 (−1.46, −0.07)	0.03	42.66	<0.0001	93
Flatulence	3 (20, 35)	158	SMD: −0.34 (−0.7, 0.02)	0.07	3.01	0.22	34
Incomplete evacuation	6 (31, 32, 37, 40, 41)	502	SMD: −0.77 (−1.14, −0.39)	<0.0001	22.49	0.0004	78
Hard stools	5 (32, 35, 37, 38, 40)	280	SMD: −0.74 (−1.19, −0.28)	0.001	10.14	0.04	61
Ease of expulsion	4 (31, 32, 41)	392	SMD: 0.81 (0.15, 1.48)	0.02	51.61	<0.0001	94

[1] Data were meta-analyzed by using a random-effects model and are presented as WMDs or SMDs as appropriate. Statistical heterogeneity was assessed by using the chi-square test and quantified by using the I^2 statistic. BM, bowel movements; GTT, gut transit time; ref nos., reference numbers; SMD, standardized mean difference; WMD, weighted mean difference.

GTT

Two studies measured whole and regional GTT by using a standard radio-opaque marker technique (20, 36). However, one study consisted of 2 intervention groups (compared with one placebo group) and these were treated as separate studies in the meta-analysis (20), resulting in 3 separate studies in the meta-analysis.

Overall, probiotics significantly reduced whole GTT by 12.4 h (95% CI: −22.3, −2.5 h; $P = 0.01$) (**Figure 2**). There was no significant heterogeneity between studies ($I^2 = 23\%$, $P = 0.27$). In the subgroup analysis, *B. lactis* did not significantly decrease whole GTT (WMD: 13.5 h; 95% CI: −33.1, 6.1 h; $P = 0.12$), although these data were derived from 2 intervention groups of the same study.

With regard to rectosigmoid transit time, overall there was a significant effect in favor of probiotics reducing transit time through this region by 4.0 h (95% CI: −7.6, −0.4 h; $P = 0.03$); specifically this related to *B. lactis*, which significantly reduced transit time by 4.8 h (95% CI: −9.0, −0.5 h; $P = 0.03$). However, there was no significant effect on right (WMD: −4.9 h; 95% CI: −10.5, 0.8 h; $P = 0.09$) or left (WMD: −4.9 h; 95% CI: −10.2, 0.3 h; $P = 0.07$) colonic transit times for probiotics overall, nor were there species-specific or strain-specific effects. There was no significant heterogeneity found in the regional transit times (Supplemental Figure 1 under "Supplemental data" in the online issue).

Stool output

Stool frequency was measured in all 14 studies; however, only 10 of these were included in the meta-analysis (31–34, 37–39, 41–43). The remaining 4 studies were not included because 2 did not report data in a suitable form for meta-analysis (35, 36) and 2 did not measure stool frequency in bowel movements per unit of time (instead measuring it as "reduced frequency of defecation" and "irregular bowel movements on a scale from 1 to 100") (40, 43).

Overall, probiotics significantly increased stool frequency by 1.3 (95% CI: 0.7, 1.9) bowel movements/wk ($P < 0.0001$) compared with placebo (**Figure 3**), but there was significant

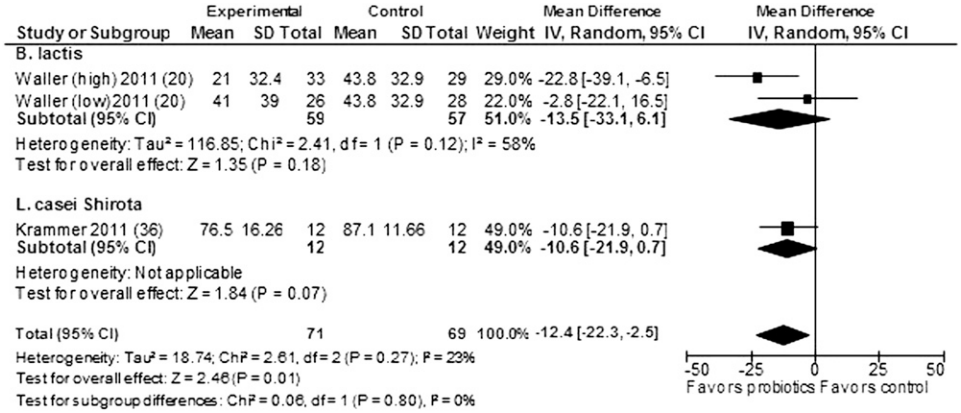

FIGURE 2. Forest plot of randomized controlled trials in adults with functional constipation comparing probiotics with placebo/comparator. Weighted mean differences (95% CIs) for whole gut transit time are shown. B., *Bifidobacterium*; IV, inverse variance; L., *Lactobacillus*.

heterogeneity ($I^2 = 90\%$, $P < 0.00001$). There was no significant funnel plot asymmetry (Egger test = 1.44; 95% CI: −2.02, 9.10; $P = 0.183$), suggesting no evidence of publication bias or other small study effects (Supplemental Figure 2 under "Supplemental data" in the online issue). Subgroup analysis showed that *B. lactis* resulted in significantly higher stool frequency (WMD: +1.5 bowel movements/wk; 95% CI: 0.7, 2.3 bowel movements/wk; $P = 0.0003$); however, significant heterogeneity persisted ($I^2 = 92\%$, $P < 0.00001$). *L. casei* Shirota did not significantly affect stool frequency (WMD: −0.2 bowel movements/wk; 95% CI: −0.8, 0.9 bowel movements/wk; $P = 0.5$), and no heterogeneity was detected ($I^2 = 0\%$, $P = 0.83$).

Although stool consistency was measured in 11 studies (31, 33, 35–43), 2 did not present the data, and these were not obtained on request (36, 39). The method of measuring stool consistency varied among the studies, including the Bristol Stool Form Scale or modified versions of it, and therefore the SMD was calculated. Overall, probiotics led to statistically improved stool consistency compared with placebo (SMD: +0.55; 95% CI: 0.27, 0.82; $P = 0.0001$), which meant that stools were becoming less hard/more soft, but there was significant heterogeneity ($I^2 = 80\%$, $P < 0.00001$) (**Figure 4**). There was no funnel plot asymmetry (Egger test = 0.57; 95% CI: −4.87, 8.09; $P = 0.583$), suggesting no evidence of publication bias or other small study effects (Supplemental Figure 3 under "Supplemental data" in the online issue). Subgroup analysis showed significant improvement in stool consistency for studies of *B. lactis* (SMD: +0.46; 95% CI: 0.08, 0.85; $P = 0.02$), but heterogeneity remained significantly high ($I^2 = 81\%$, $P = 0.001$). *L. casei* Shirota did not significantly improve stool consistency (SMD: +0.26; 95% CI: −0.30, 0.82; $P = 0.36$), but heterogeneity was again significant ($I^2 = 80\%$, $P = 0.006$).

Stool weight was not directly measured in any study. However, stool quantity was estimated in 3 studies through comparison of stool size to that of a medium-sized egg (34, 37) or a table tennis ball (41). Overall, probiotics did not significantly affect estimated stool quantity (SMD: 0.23; 95% CI: −0.08, 0.54; $P = 0.14$) and there was no significant heterogeneity ($I^2 = 28\%$, $P = 0.25$). *B. lactis* did not significantly affect estimated stool quantity (SMD: 0.38; 95% CI: −0.13, 0.89; $P = 0.14$), and no heterogeneity was detected ($I^2 = 46\%$, $P = 0.17$).

Bloating and flatulence

Bloating was reported in 4 trials (31, 35, 37, 41), but one did not present any data (41). Bloating was significantly lower after probiotic consumption compared with placebo (SMD: −0.77; 95% CI: −1.46, −0.07; $P = 0.03$), but significant heterogeneity was observed ($I^2 = 93\%$, $P < 0.00001$). Subgroup analysis indicated that *L. casei* Shirota did not affect bloating (SMD: −0.12; 95% CI: −0.43, 0.19; $P = 0.44$), and no heterogeneity was detected ($I^2 = 0\%$, $P = 0.61$).

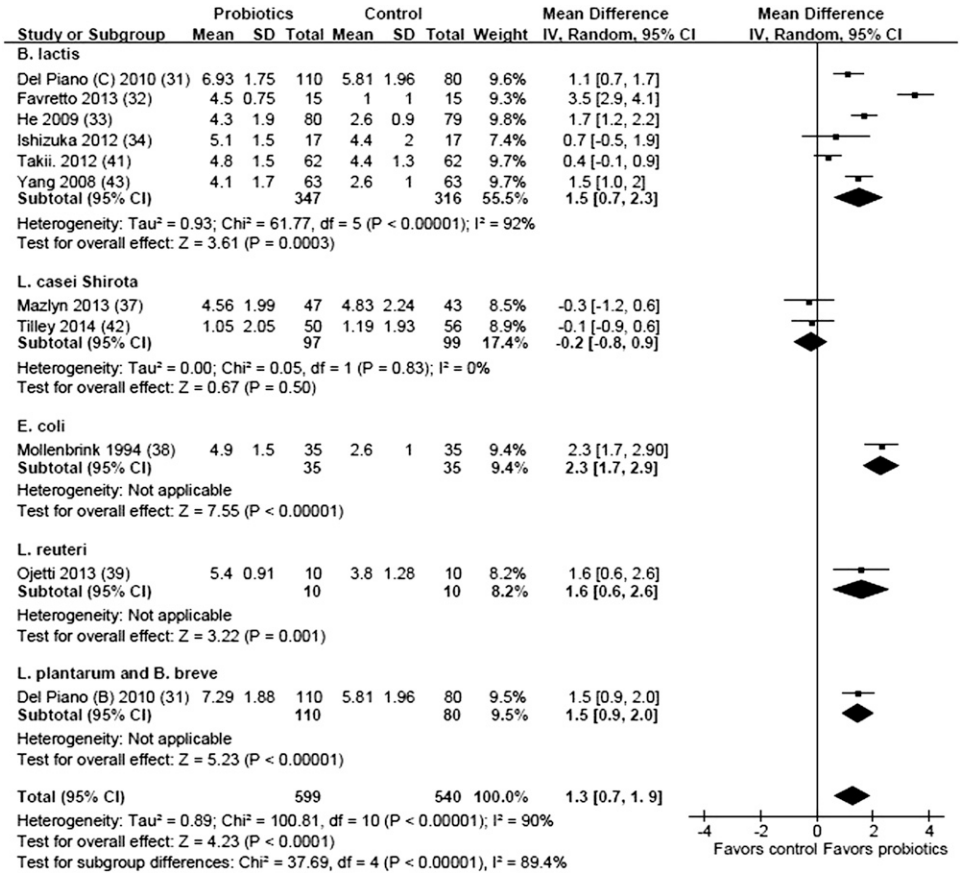

FIGURE 3. Forest plot of randomized controlled trials in adults with functional constipation comparing probiotics with placebo/comparator. Weighted mean differences (95% CIs) for stool frequency with the use of a random-effects model are shown. B., *Bifidobacterium*; E., *Escherichia*; IV, inverse variance; L., *Lactobacillus*.

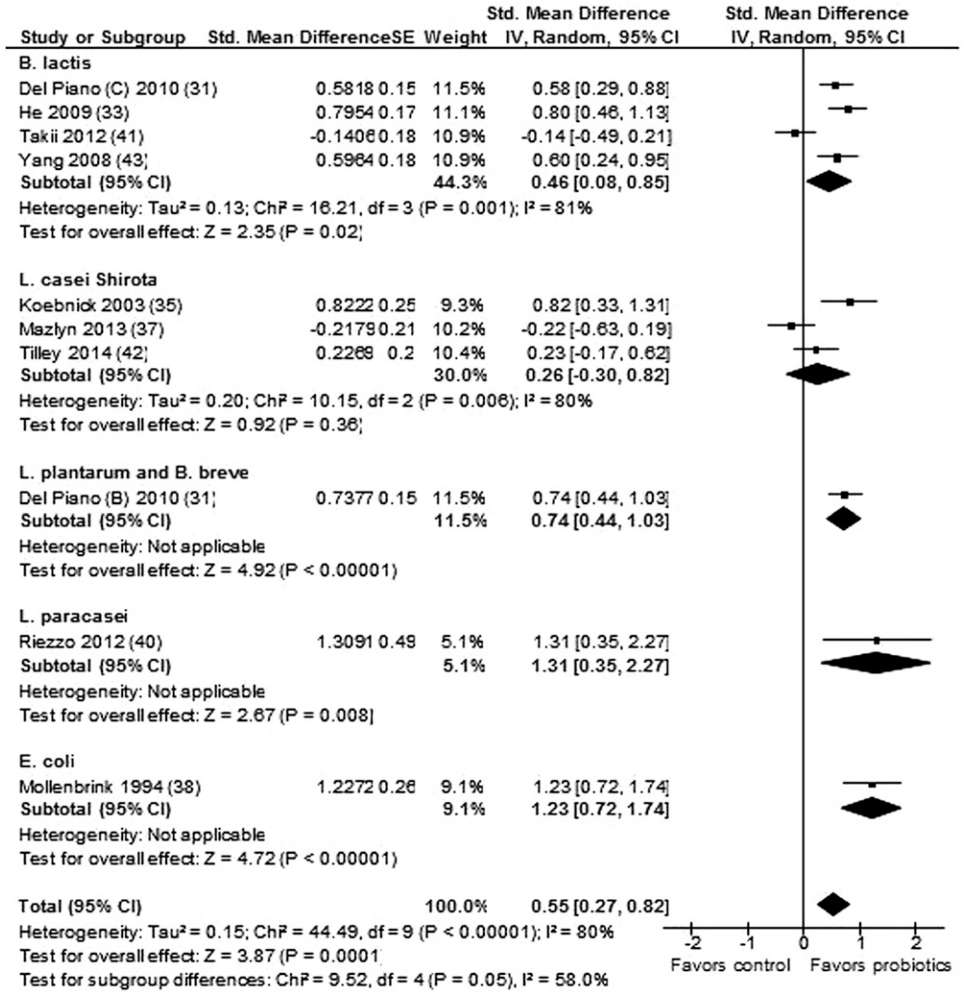

FIGURE 4. Forest plot of randomized controlled trials in adults with functional constipation comparing probiotics with placebo/comparator. Standardized mean differences (95% CIs) for stool consistency with the use of a random-effects model are shown. B., *Bifidobacterium*; E., *Escherichia*; IV, inverse variance; L., *Lactobacillus*; Std., standardized.

Flatulence was measured in 2 studies (20, 35). Overall, probiotics did not significantly reduce flatulence (SMD: −0.34; 95% CI: −0.70, 0.02; $P = 0.07$) and no heterogeneity was detected ($I^2 = 34\%$, $P = 0.22$). *B. lactis* significantly reduced flatulence (SMD: −0.53; 95% CI: −0.90, −0.16; $P = 0.005$), and no heterogeneity was detected ($I^2 = 0\%$, $P = 0.93$), although these data are from 2 intervention groups of the same study.

Constipation-related symptoms

Many studies reported the impact of probiotics on a range of constipation symptoms. Data from 5 studies indicated that probiotics significantly reduced the frequency of the sensation of incomplete evacuation (SMD: −0.77; 95% CI: −1.14, −0.39; $P < 0.0001$), but significant heterogeneity was detected ($I^2 = 78\%$, $P = 0.0004$) (31, 32, 37, 40, 41). Analysis of the 3 studies of *B. lactis* showed no significant impact on the frequency of the sensation of incomplete evacuation (SMD: −0.65; 95% CI: −1.34, 0.05; $P = 0.07$), but heterogeneity was significant ($I^2 = 88\%$, $P = 0.0003$).

Five studies asked participants to report the "occurrence of hard stools" with the use of an explicit symptom question (instead of, or in addition to, prospectively recording stool consistency by using a stool chart). These indicated that probiotics significantly reduced the occurrence of hard stools (SMD: −0.74; 95% CI: −1.19, −0.28; $P = 0.001$), but significant heterogeneity was detected ($I^2 = 61\%$, $P = 0.04$) (32, 35, 37, 38, 40). Strain-specific analysis of 2 studies of *L. casei* Shirota showed no significant impact on the occurrence of hard stools (SMD: −0.52; 95% CI: −1.08, 0.04; $P = 0.07$), and heterogeneity was not significant ($I^2 = 67\%$, $P = 0.08$).

Data from 3 studies (including one with 2 intervention arms) indicated that probiotics significantly improved the ease of stool expulsion (SMD: 0.81; 95% CI: 0.15, 1.48; $P = 0.02$), but heterogeneity was also significant ($I^2 = 94\%$, $P < 0.00001$) (31, 32, 41). Analysis of the 3 studies of *B. lactis* showed no significant impact on the ease of stool expulsion (SMD: 0.80; 95% CI: −0.17, 1.77; $P = 0.11$), and heterogeneity remained high ($I^2 = 96$, $P < 0.00001$).

Three studies reported the need for manually assisted defecation (36, 37, 40), 2 studies reported frequency of unsuccessful evacuatory attempts (36, 37), and 2 studies reported painful evacuation (31, 36); however, data were only reported or were attainable for a maximum of one study and therefore meta-analysis was not possible. Frequency of laxative use (37) and

length of time per evacuatory attempt (36) were each reported in one study only.

Adverse events and compliance

Five of the 6 studies that measured adverse events reported that none occurred in either the probiotic or the placebo group (20, 31, 39, 40, 43). One study reported minor adverse events in both probiotic and placebo groups (37). In one study, it was reported that both the probiotic and placebo study products were "well tolerated" (43), whereas in another study 91% of participants in the probiotic group and 80% in the placebo group rated the product as "good" or "very good" (35). Compliance was reported in only 2 studies, both of which reported >95% compliance with the probiotic (37, 40).

Study quality

The 14 studies had variable methodologic quality (Supplemental Figure 4 under "Supplemental data" in the online issue). There was low risk of bias with regard to the detection and performance bias, because 9 of the 14 studies had a double-blind design, and one had a triple-blind design. There were high risks of attrition bias, lack of intention-to-treat analysis, and selective reporting. None of the included trials were at low risk of bias across all domains.

DISCUSSION

Our hypothesis was that probiotics would significantly shorten whole and regional GTT, increase stool frequency, and improve stool consistency. The results of this study indicate that, overall, probiotics positively affected all of these measures. Several other cardinal symptoms of constipation also significantly improved (ie, bloating, sensation of incomplete evacuation, occurrence of hard stools, ease of stool expulsion). Meta-analysis also showed species-specific effects for *B. lactis* on rectosigmoid transit time, stool frequency and consistency, and flatulence, but not on whole GTT, right and left GTT, stool quantity, sense of incomplete evacuation, or ease of stool expulsion. No effect of *L. casei* Shirota was detected for stool frequency and consistency, bloating, or the passage of hard stools.

Probiotics were shown to significantly decrease whole GTT by half a day. However, these results are based on only 2 studies (3 intervention arms), one of which consisted of 2 different doses of the same probiotic. Nevertheless, a recent meta-analysis also showed a significant decrease in GTT, albeit in a mixed population of healthy people and those with constipation and constipation-predominant irritable bowel syndrome (44). Normal whole GTT is considered to be 30–40 h, with an upper limit of normal of ~72 h (45, 46). Hence, a decrease of 12.4 h could help normalize delayed transit. Mechanistically, an animal study showed that the modified gut microbial composition observed after a dietary intervention may result from a "microbiota-dependent" or "microbiota-independent" effect of the intervention on GTT (47). Probiotics may increase colonic short-chain fatty acids (21), which stimulate contractile colonic responses in rats (48). However, this contradicts recent findings of human studies (49, 50), and therefore the contribution of each mechanism of probiotics on GTT and constipation is unclear.

Stool frequency significantly increased by probiotics, specifically by *B. lactis* but not *L. casei* Shirota, although there was heterogeneity in these findings. Normal stool frequency ranges from 3 to 21 bowel movements/wk (51, 52) and an increase of 1.3 bowel movements/wk through probiotic consumption could normalize bowel frequency in adults with functional constipation. A recent meta-analysis showed that osmotic and stimulant laxatives increased stool frequency by 2.5 bowel movements/wk in patients with functional constipation (53). The findings of our current study show that probiotics have at least half of the efficacy of laxatives in increasing stool frequency, which was particularly evident for *B. lactis*.

Probiotics improved stool consistency with a species-specific effect of *B. lactis* but not a strain-specific effect of *L. casei* Shirota. There is a moderate negative correlation between whole GTT and stool form in constipation, and our findings of both shorter GTT in conjunction with improved consistency were therefore expected (54).

Bloating was significantly lower after probiotics, although when *L. casei* Shirota was isolated, there was no significant improvement. Bloating is common in constipation, with one survey reporting a prevalence of 57%, and it significantly affects quality of life (10). Importantly, constipated women reported that laxatives provided insufficient relief of bloating in constipation (55).

Overall, probiotics were well tolerated with a low risk of adverse events, which agrees with a recent report on the safety of probiotics (56). However, adverse events were reported in only half of the studies, a common deficiency in clinical trial reporting (57). Probiotics were also associated with high rates of compliance.

This meta-analysis provides clinically important information. People with constipation have an impaired quality of life (6, 7), and this is negatively correlated with symptom severity (58). The treatment of constipation may improve quality of life (6, 7), although this was not an outcome in this meta-analysis.

Many people with constipation do not present to medical care centers and use self-management approaches (55). Almost half of patients taking over-the-counter or prescription laxatives are not satisfied with the relief they provide (10), suggesting a large unmet need for alternatives to drug treatment. Accessibility to widely available, nonprescription management approaches allows for greater self-management, which could reduce the financial burden of constipation to medical providers. However, the results are based on short-term administration of probiotics, because no RCTs have been published investigating long-term use.

Although this meta-analysis included only functional constipation in adults, the findings might be applicable to adults with constipation-predominant irritable bowel syndrome, because the 2 are increasingly believed to belong to the same spectrum (59, 60). However, the Rome Foundation still characterizes them as separate disorders and therefore only functional constipation was examined in this review (61). In addition, a small number of studies were undertaken in children with functional constipation, with discordant results reported for the impact of probiotics on symptoms (62) and stool frequency (63). Reviews concluded that there is currently insufficient evidence for the effectiveness of probiotics in managing constipation in children (13, 64).

Strengths and limitations

This meta-analysis was undertaken with the use of a robust design. Effort was made to search various sources to minimize publication bias, and no language restrictions were applied. Only RCTs were included, and investigators sought additional information from authors, although few provided the requested information. There was no evidence of funnel plot asymmetry and search of a clinical trials database did not identify historic unpublished trials. Although a previous systematic review in this area has been published, the final search date was >5 y ago, only 3 RCTs were included, and there was no meta-analysis (13).

There was significant heterogeneity in many of the reported outcomes, indicating variation between the studies in the estimates of the effect of probiotics on the measured outcomes. This could be explained by the different probiotics used, although significant heterogeneity was sometimes found between studies of the same probiotic species or strain. Therefore, small sample sizes and differences in the methods used to measure outcomes are also likely contributing to heterogeneity. None of the included trials were at low risk of bias across all domains. Hence, pooling data from studies that used poor methodology could potentially overestimate the overall effect size of probiotics.

Controversy remains over whether RCTs of probiotics should undergo meta-analysis due to the varying microbiological and physiologic characteristics of different species and strains. In support of this approach, synthesizing RCTs allows the detection of patterns that would otherwise not be identified, particularly because many trials are small with nonsignificant findings. We were able to perform subgroup meta-analyses for *B. lactis* and *L. casei* Shirota for certain outcomes. Studies that investigated a range of other probiotics were identified, some of which showed significant effects for some outcomes. However, these were not discussed because it was not appropriate to consider findings based on single studies only. Further studies that use these underinvestigated probiotics are warranted.

Conclusions

This meta-analysis provides evidence that, overall, probiotics improve whole GTT, stool frequency, and stool consistency; however, specific probiotics improved only some of these outcomes. Furthermore, the interpretation is challenging due to high heterogeneity and risk of bias of individual studies. The results provide cautious optimism for the recommendation of specific probiotic species or strains in the management of functional constipation. Further adequately powered RCTs with the use of standardized outcome measures are needed to determine which species/strains, doses, and duration of probiotics are efficacious in functional constipation.

We thank Etsuro Yazaki, Chung Lee, and Rainer Simmering for their assistance with the translation of foreign language articles. We also thank Denis Guyonnet, Arthur Ouwehand, Hiroshi Takii, Linda Thomas, and Thais Rodrigues Moreira for providing extra information on their studies.

The authors' responsibilities were as follows—ED and KW: designed the study; ED and SC: performed eligibility screening and data extraction; ED and KCF: analyzed the data; KCF: performed the statistical analysis; ED, SMS, and KW: interpreted the data; ED: wrote the initial manuscript; SC, KCF, KW, and SMS: critically revised the manuscript; and KW: is the guarantor. ED and SC received PhD funding from Nestec Ltd. SMS and KW received grant funding from Nestec Ltd. None of the authors declared a conflict of interest.

REFERENCES

1. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol 2011;106:1582–91.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 2009;136:376–86.
3. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143(5):1179–87, e1–3.
4. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. J Manag Care Pharm 2013;19:755–64.
5. Prescribing and Primary Care Services; Health and Social Care Information Centre. Prescriptions dispensed in the community. Leeds, United Kingdom: Health and Social Care Information Centre, 2013.
6. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther 2010;31:938–49.
7. Wald A, Scarpignato C, Kamm MA, Mueller-Lissner S, Helfrich I, Schuijt C, Bubeck J, Limoni C, Petrini O. The burden of constipation on quality of life: results of a multinational survey. Aliment Pharmacol Ther 2007;26:227–36.
8. American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. Am J Gastroenterol 2005;100(suppl 1):S1–4.
9. Basilisco G, Coletta M. Chronic constipation: a critical review. Dig Liver Dis 2013;45:886–93.
10. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. Aliment Pharmacol Ther 2007;25:599–608.
11. Müller-Lissner SA, Kaatz V, Brandt W, Keller J, Layer P. The perceived effect of various foods and beverages on stool consistency. Eur J Gastroenterol Hepatol 2005;17:109–12.
12. Food and Agriculture Organization of the United Nations and WHO Working Group. Guidelines for the evaluation of probiotics in food. Geneva, Switzerland: FAO/WHO, 2002.
13. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. World J Gastroenterol 2010;16:69–75.
14. Khalif IL, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. Dig Liver Dis 2005;37:838–49.
15. Zoppi G, Cinquetti M, Luciano A, Benini A, Muner A, Bertazzoni Minelli E. The intestinal ecosystem in chronic functional constipation. Acta Paediatr 1998;87:836–41.
16. Ait-Belgnaoui A, Han W, Lamine F, Eutamene H, Fioramonti J, Bueno L, Theodorou V. Lactobacillus farciminis treatment suppresses stress induced visceral hypersensitivity: a possible action through interaction with epithelial cell cytoskeleton contraction. Gut 2006;55:1090–4.
17. Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, et al. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. Nat Med 2007;13:35–7.
18. Bueno L, de Ponti F, Fried M, Kullak-Ublick GA, Kwiatek MA, Pohl D, Quigley EM, Tack J, Talley NJ. Serotonergic and non-serotonergic targets in the pharmacotherapy of visceral hypersensitivity. Neurogastroenterol Motil 2007;19(suppl):89–119.
19. Quigley EM. Bacteria: a new player in gastrointestinal motility disorders–infections, bacterial overgrowth, and probiotics. Gastroenterol Clin North Am 2007;36:735–48.
20. Waller PA, Gopal PK, Leyer GJ, Ouwehand AC, Reifer C, Stewart ME, Miller LE. Dose-response effect of Bifidobacterium lactis HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. Scand J Gastroenterol 2011;46:1057–64.
21. Salminen S, Salminen E. Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. Scand J Gastroenterol Suppl 1997;222:45–8.
22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–94.
23. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0 [updated March 2011]. The Cochrane

Collaboration, 2011. Available from: www.cochrane-handbook.org (cited December 2013).
24. Moher D, Tricco AC. Issues related to the conduct of systematic reviews: a focus on the nutrition field. Am J Clin Nutr 2008;88:1191–9.
25. Lipsey MW, Wilson DB. Practical meta-analysis. Thousand Oaks, CA; Sage, 2001.
26. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol 2002;31:140–9.
27. Bowden J, Tierney JF, Copas AJ, Burdett S. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. BMC Med Res Methodol 2011;11:41.
28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
29. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
31. Del Piano M, Carmagnola S, Anderloni A, Andorno S, Ballare M, Balzarini M, Montino F, Orsello M, Pagliarulo M, Sartori M, et al. The use of probiotics in healthy volunteers with evacuation disorders and hard stools a double-blind, randomized, placebo-controlled study. J Clin Gastroenterol 2010;44:S30–4.
32. Favretto DC, Pontin B, Moreira TR. Effect of the consumption of a cheese enriched with probiotic organisms (Bifidobacterium lactis bi-07) in improving symptoms of constipation. Arq Gastroenterol 2013; 50:196–201.
33. He M, Hu G, Yang Y. Effect of probiotic yogurt containing Bifidobacterium animalis strain DN-173 010 on symptoms of constipation. Chin J Gastroenterol 2009;14:287–9.
34. Ishizuka A, Tomizuka K, Aoki R, Nishijima T, Saito Y, Inoue R, Ushida K, Mawatari T, Ikeda T. Effects of administration of Bifidobacterium animalis subsp. lactis GCL2505 on defecation frequency and bifidobacterial microbiota composition in humans. J Biosci Bioeng 2012;113:587–91.
35. Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. Can J Gastroenterol 2003;17:655–9.
36. Krammer HJ, von Seggern H, Schaumburg J, Neumer F. Effect of Lactobacillus casei Shirota on colonic transit time in patients with chronic constipation. Coloproctology 2011;33:109–13.
37. Mazlyn MM, Nagarajah LH, Fatimah A, Norimah AK, Goh KL. Effects of a probiotic fermented milk on functional constipation: a randomized, double-blind, placebo-controlled study. J Gastroenterol Hepatol 2013;28:1141–7.
38. Mollenbrink M, Bruckschen E. [Treatment of chronic constipation with physiologic Escherichia coli bacteria. Results of a clinical study of the effectiveness and tolerance of microbiological therapy with the E. coli Nissle 1917 strain (Mutaflor).] Med Klin 1994;89:587–93 (in German).
39. Ojetti V, Ianiro G, Tortora A, Bruno G, Laterza L, Gigante G, Ponziani FR, Gammarita G, Gasbarrini A. Lactobacillus reuteri (DSM 17938) for the treatment of functional constipation in adult patients: a double-blind, randomised, placebo-controlled trial. Dig Liver Dis 2013;45:S132 (abstr).
40. Riezzo G, Orlando A, D'Attoma B, Guerra V, Valerio F, Lavermicocca P, De Candia S, Russo F. Randomised clinical trial: efficacy of Lactobacillus paracasei-enriched artichokes in the treatment of patients with functional constipation—a double-blind, controlled, crossover study. Aliment Pharmacol Ther 2012;35:441–50.
41. Takii H, Nishijima T, Takami K, Tanaka Y, Inugami M, Mawatari T, Sugimura H, Aoki R. Effects of fermented milk containing Bifidobacterium animalis subsp. lactis GCL2505 on improvement of defecation, fecal properties, and intestinal microflora. Jpn Pharmacol Ther 2012;40:657–65.
42. Tilley L, Keppens K, Kushiro A, Takada T, Sakai T, Vaneechoutte M, Degeest B. A probiotic fermented milk drink containing Lactobacillus Casei strain Shirota improves stool consistency of subjects with hard stools. Int J Probiotics Prebiotics 2014;9:23–30.
43. Yang YX, He M, Hu G, Wei J, Pages P, Yang XH, Bourdu-Naturel S. Effect of a fermented milk containing Bifidobacterium lactis DN-173010 on Chinese constipated women. World J Gastroenterol 2008; 14:6237–43.
44. Miller LE, Ouwehand AC. Probiotic supplementation decreases intestinal transit time: meta-analysis of randomized controlled trials. World J Gastroenterol 2013;19:4718–25.
45. Kim ER, Rhee PL. How to interpret a functional or motility test—colon transit study. J Neurogastroenterol Motil 2012;18:94–9.
46. Southwell BR, Clarke MC, Sutcliffe J, Hutson JM. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. Pediatr Surg Int 2009;25:559–72.
47. Kashyap PC, Marcobal A, Ursell LK, Larauche M, Duboc H, Earle KA, Sonnenburg ED, Ferreyra JA, Higginbottom SK, Million M, et al. Complex interactions among diet, gastrointestinal transit, and gut microbiota in humanized mice. Gastroenterology 2013;144:967–77.
48. Yajima T. Contractile effect of short-chain fatty acids on the isolated colon of the rat. J Physiol 1985;368:667–78.
49. Gorbatchef C, Jouet P, Coffin B, Flourie B, Lemann M, Franchisseur C, Jian R, Rambaud JC. Effects of short-chain fatty acids on the phasic and tonic motor activity in the unprepared colon of healthy humans. Gastroenterology 1998;114(4):A756.
50. Jouët P, Moussata D, Duboc H, Boschetti G, Attar A, Gorbatchef C, Sabate JM, Coffin B, Flourie B. Effect of short-chain fatty acids and acidification on the phasic and tonic motor activity of the human colon. Neurogastroenterol Motil 2013;25:943–9.
51. Connell AM, Hilton C, Irvine G, Lennard-Jones JE, Misiewicz JJ. Variation of bowel habit in two population samples. BMJ 1965;2:1095–9.
52. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut 1992;33:818–24.
53. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60:209–18.
54. Saad RJ, Rao SS, Koch KL, Kuo B, Parkman HP, McCallum RW, Sitrin MD, Wilding GE, Semler JR, Chey WD. Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. Am J Gastroenterol 2010;105:403–11.
55. Emmanuel A, Quigley E, Simrén M, Feng Y, Müller-Lissner S, Urbain D, Tack J, Bredenoord A, Sabaté J, Yiannakou Y, et al. Factors affecting satisfaction with treatment in European women with chronic constipation: an Internet survey. United European Gastroenterol J 2013;1:375–84.
56. Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JNV, Suttorp MJ, Johnsen B, Shanman R, Slusser W, Fu N, et al. Safety of probiotics to reduce risk and prevent or treat disease. Evidence Report/Technology Assessment No. 200. (Prepared by the Southern California Evidence-based Practice Center under contract 290-2007-10062-I.) Rockville, MD: Agency for Healthcare Research and Quality, April 2011. (AHRQ publication 11-E007.) Available from: www.ahrq.gov/clinic/tp/probiotictp.htm (cited December 2013).
57. Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med 2009;169:1737–9.
58. Glia A, Lindberg G. Quality of life in patients with different types of functional constipation. Scand J Gastroenterol 1997;32:1083–9.
59. Shekhar C, Monaghan PJ, Morris J, Issa B, Whorwell PJ, Keevil B, Houghton LA. Rome III functional constipation and irritable bowel syndrome with constipation are similar disorders within a spectrum of sensitization, regulated by serotonin. Gastroenterology 2013;145:749–57.
60. Wong RK, Palsson OS, Turner MJ, Levy RL, Feld AD, von Korff M, Whitehead WE. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. Am J Gastroenterol 2010;105:2228–34.
61. Irvine EJ, Whitehead WE, Chey WD, Matsueda K, Shaw M, Talley NJ, Veldhuyzen van Zanten SJ; Design of Treatment Trials Committee. Design of treatment trials for functional gastrointestinal disorders. Gastroenterology 2006;130:1538–51.
62. Banaszkiewicz A, Szajewska H. Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. J Pediatr 2005;146:364–9.
63. Bu LN, Chang MH, Ni YH, Chen HL, Cheng CC. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. Pediatr Int 2007;49:485–90.
64. Vandenplas Y, Benninga M. Probiotics and functional gastrointestinal disorders in children. J Pediatr Gastroenterol Nutr 2009;48(suppl 2):S107–9.