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META-ANALYSIS

Contemporary meta-analysis of short-term probiotic consumption on gastrointestinal transit

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Abstract

AIM: To determine the efficacy of probiotic supplementation on intestinal transit time (ITT) in adults and to identify factors that influence these outcomes.

METHODS: We conducted a systematic review of randomized controlled trials of probiotic supplementation that measured ITT in adults. Study quality was assessed using the Jadad scale. A random effects meta-analysis was performed with standardized mean difference (SMD) of ITT between probiotic and control groups as the primary outcome. Meta-regression and subgroup analyses examined the impact of moderator variables on SMD of ITT.

RESULTS: A total of 15 clinical trials with 17 treatment effects representing 675 subjects were included in this analysis. Probiotic supplementation was moderately efficacious in decreasing ITT compared to control, with an SMD of 0.38 (95%CI: 0.23-0.53, $P < 0.001$). Subgroup analyses demonstrated statistically greater reductions in ITT with probiotics in subjects with *vs* without constipation (SMD: 0.57 *vs* 0.22, $P < 0.01$) and in studies with high *vs* low study quality (SMD: 0.45 *vs* 0.00, $P = 0.01$). Constipation ($R^2 = 38\%$, $P < 0.01$), higher study quality ($R^2 = 31\%$, $P = 0.01$), older age ($R^2 = 27\%$, $P = 0.02$), higher percentage of female subjects ($R^2 = 26\%$, $P = 0.02$), and fewer probiotic strains ($R^2 = 20\%$, $P < 0.05$) were predictive of decreased ITT with probiotics in meta-regression. Medium to large treatment effects were identified with *B. lactis* HN019 (SMD: 0.67, $P < 0.001$) and *B. lactis* DN-173 010 (SMD: 0.54, $P < 0.01$) while other probiotic strains yielded negligible reductions in ITT relative to control.

CONCLUSION: Probiotic supplementation is moderately efficacious for reducing ITT in adults. Probiotics were most efficacious in constipated subjects, when evaluated in high-quality studies, and with certain probiotic strains.

Key words: Constipation; Gastrointestinal; Intestinal transit time; Meta-analysis; Probiotics

Core tip: We performed a contemporary systematic review and meta-analysis of randomized controlled trials to determine the effects of short-term probiotic supplementation on transit time in adults. Probiotic supplementation is moderately efficacious for reducing intestinal transit time in adults. Probiotics were most efficacious in constipated subjects, when evaluated in high-quality studies, and with certain probiotic strains.

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INTRODUCTION

The human colonic microbiota is a complex ecosystem involved in maintenance of health and physiological functions of the host. Disturbances within the microbiota may result in gastrointestinal disorders such as constipation, irritable bowel syndrome, or periodic bouts of irregularity. Functional gastrointestinal disorders are a highly prevalent group of persistent and recurring conditions with a prevalence of 69% in the general population[1]. Slow intestinal transit is a common manifestation of functional gastrointestinal disorders affecting the bowel[2] and may also occasionally affect otherwise healthy individuals. Although the benefits of reducing intestinal transit time (ITT) in patients with constipation are obvious, reductions in ITT are also considered a beneficial physiological effect in the non-diseased general population[3]. Over-the-counter and prescription medications intended to normalize intestinal transit are widely utilized although no known treatment is considered efficacious, safe, and cost effective[4]. Probiotics are live micro-organisms that confer a health benefit on the host when administered in adequate dosages[5] and have been extensively studied for enhancement of gastrointestinal health[6,7]. Previously, we performed the first systematic review and meta-analysis on the efficacy of probiotic supplementation on ITT in adults[8]. The purpose of this study was to update these findings with data from randomized controlled trials (RCTs) published over the 3-year period since our last review.

MATERIALS AND METHODS

Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[9]. We searched MEDLINE and EMBASE for RCTs of probiotic supplementation that reported ITT in adults by using a combination of relevant keywords. The details of the MEDLINE search strategy are listed in Table 1. The syntax for EMBASE was similar, but adapted as necessary. Additionally, manual searches were conducted using the Directory of Open Access Journals, Google Scholar, and the reference lists of included papers and other relevant meta-analyses. No date restrictions were applied to the searches. The final search was conducted in October 2015.

Table 1 MEDLINE search strategy

Therapeutic search terms
Probiotic
Synbiotic
Lactobacill
Bifidobacteri
Yogurt (yoghurt)
Fermented milk
Main outcome search terms
Gastrointestinal
Transit
Gut
Motility
Colonic
Constipation
Irritable bowel
Combination terms
or/1-6
or/7-13
and/14-15

Study selection

Two researchers independently selected studies for inclusion in the review. Disagreements were resolved by consensus. Titles and abstracts were initially screened to exclude manuscripts published in non-English journals. Next, review articles, commentaries, letters, and case reports were excluded. Lastly, we excluded studies of subjects where ITT reduction was undesirable or uninterpretable (*e.g.*, diarrhea or mixed IBS subtypes). Full-text of the remaining manuscripts was then retrieved and reviewed. Publications that failed to report ITT or that described non-randomized, non-controlled, or otherwise irrelevant studies were also excluded.

Data extraction

Data were extracted from eligible peer-reviewed articles by one author and then verified by a second author. Data extraction discrepancies between the two researchers were resolved by consensus. The following variables were recorded in a pre-designed database: general manuscript information (author, institution name and location, journal, year, volume, page numbers), study design characteristics (study quality, study design, sample size, method of ITT assessment,

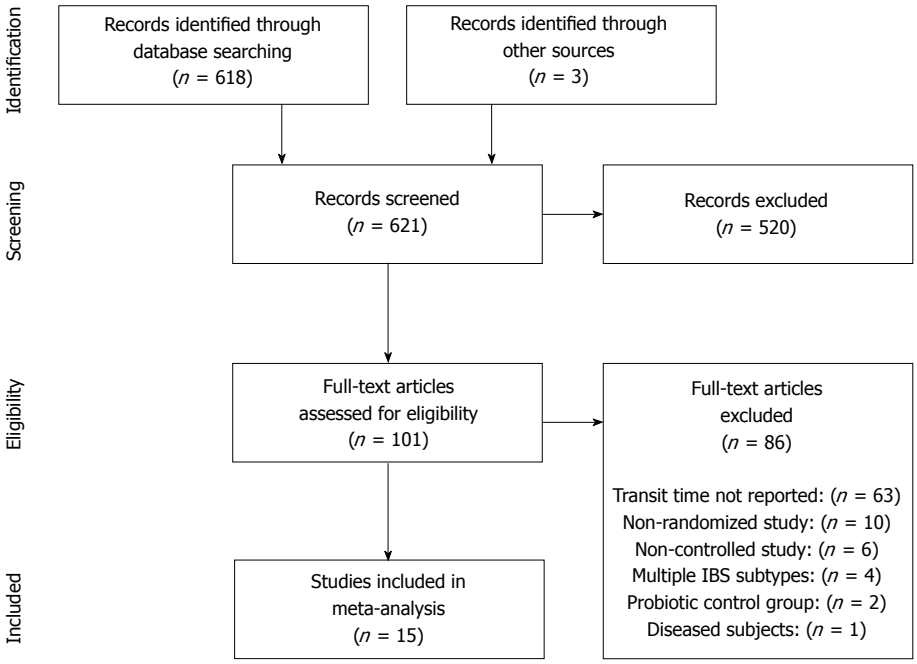

Figure 1 PRISMA flow diagram.

probiotic strain, daily dosage, product delivery method, and treatment duration), subject characteristics (age, gender, body mass index, and condition), and ITT summary statistics necessary for meta-analysis.

Quality assessment

The Jadad scale was used to assess RCT study quality[10]. Studies were scored according to the presence of three key methodological features: randomization, blinding and subject accountability. Randomization was scored from 0 to 2, blinding was scored from 0 to 2, and subject accountability was scored 0 or 1. RCTs with a score of 3 to 5 were classified as high quality; studies with a score of 0 to 2 were classified as low quality.

Statistical analysis

A random effects meta-analysis model was selected *a priori* based on the assumption that treatment effects were heterogeneous given the differences in probiotic strain, study design characteristics, and subject characteristics among studies. The standardized mean difference (SMD) and 95% confidence interval (CI) were the statistics of interest to describe treatment effects since different measures of ITT (*e.g.*, whole gut, colonic, oro-cecal, *etc*.) were utilized in the included studies. The SMD is calculated as the mean difference in ITT between probiotic and control groups divided by the pooled standard deviation in ITT. SMD values of 0.2, 0.5, and 0.8 are defined as small, medium, and large, respectively[11]. Positive SMDs imply that probiotics were more effective in reducing ITT *vs* control while negative SMDs imply a greater treatment effect with control *vs* probiotics. A forest plot was used to illustrate the individual study findings and the random effects meta-analysis results. Heterogeneity of effects across studies was estimated with the I^2 statistic where values of $\leqslant$ 25%, 50%, and $\geqslant$ 75% represent low, moderate, and high inconsistency, respectively[12]. In addition, a one study removed meta-analysis was performed to assess the influence of individual studies on the meta-analysis findings. Publication bias was visually assessed with a funnel plot and quantitatively assessed using Egger's test[13]. Meta-regression and subgroup analyses were performed to explore sources of heterogeneity. All analyses were performed using Comprehensive Meta-analysis (version 2.2, Biostat, Englewood NJ). The statistical methods of this study were reviewed by Clinton Hagen, MS (Mayo Clinic, Rochester, MN).

RESULTS

Study selection

Our initial database search retrieved 618 titles and abstracts; hand searching relevant bibliographies identified 3 additional records. After screening records for inclusion criteria, 101 full text articles were reviewed for eligibility. Ultimately, 15 RCTs with 17 treatment effects representing 675 unique subjects were included in the final analysis[14-28]. A flow chart of study identification and selection is shown in Figure 1.

Study characteristics

Sample sizes ranged from 10 to 36 per treatment arm for parallel groups designs (9 studies) and from 12 to 83 for cross-over designs (6 studies). Thirteen RCTs contributed one treatment effect each and two RCTs contributed two effects each; the study of Rosenfeldt

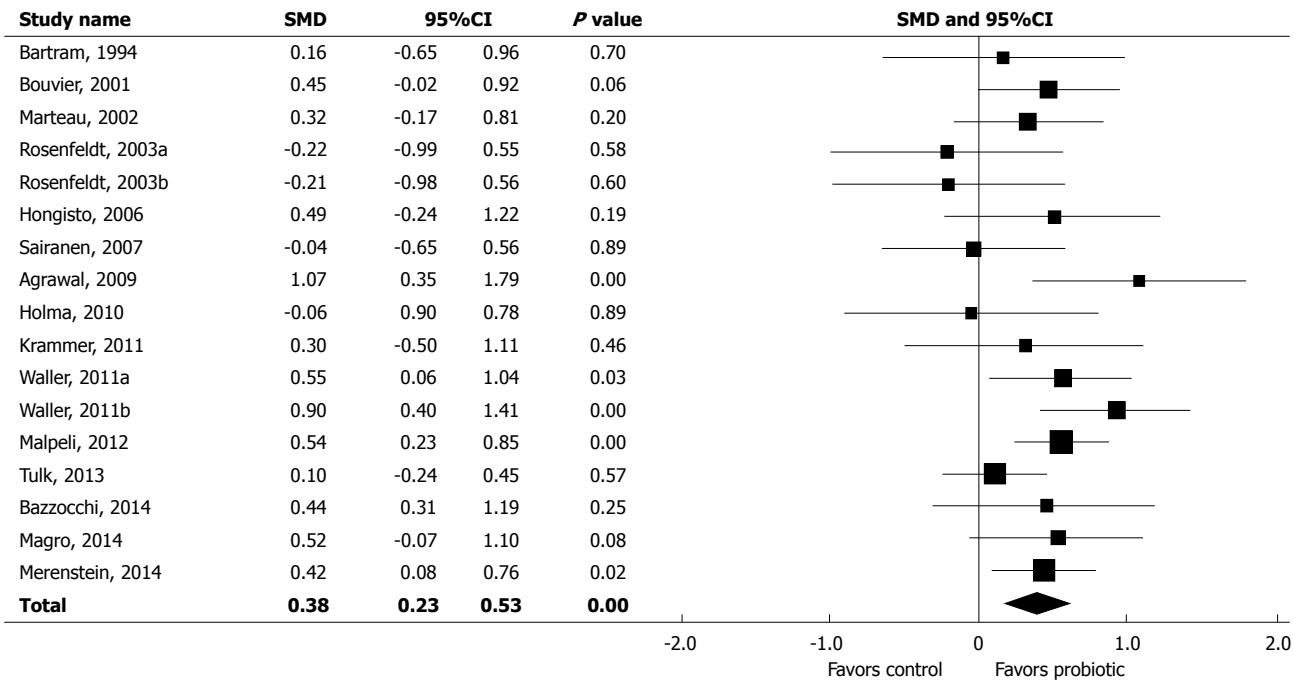

Figure 2 Forest plot of standardized mean difference in intestinal transit time across studies. Random effects model. I^2 = 20%, P = 0.22. SMD: Standardized mean difference.

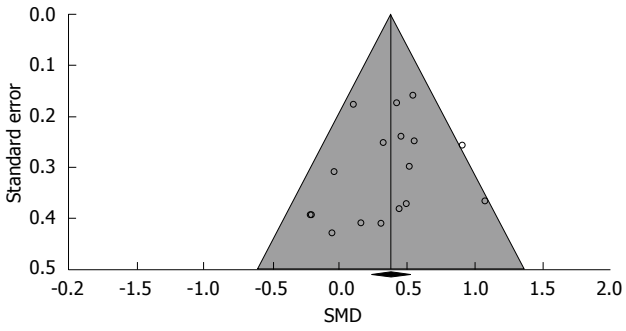

Figure 3 Funnel plot of standardized mean difference in intestinal transit time across studies. Egger's P value = 0.44 for publication bias. SMD: Standardized mean difference.

and colleagues[21] assessed two different probiotic formulations and the study of Waller and colleagues[23] assessed two different dosages of the same probiotic strain. Daily probiotic dosages varied considerably among studies, ranging from 5×10^8 to 9.8×10^{10} colony forming units (CFU) per day (median 1.6×10^{10} CFU per day). Probiotic treatment periods ranged from 10 to 28 d (median 18 d). Intestinal transit time was measured using radiopaque markers in 13 studies and with carmine red dye in 2 studies. The most commonly tested product format was yogurt or other forms of fermented milk. Six (40%) studies included other components in the active product known to influence ITT such as lactulose, psyllium, inulin, polydextrose, maltodextrose, and oligofructose (Table 2).

Subject characteristics

Nine treatment effects were calculated for subjects with constipation or IBS-C while 8 effects were based on healthy subjects. Subjects were predominantly female, mean age ranged from 23 to 50 years, and mean body mass index ranged from 19 to 32 kg/m^2 (Table 3).

Study quality assessment

Overall, the quality of RCT reporting was medium with a median Jadad score of 3 (range: 1-5). Twelve of 17 treatment effects were based on high quality (Jadad score 3-5) trials. The method of randomization was inadequately described in most studies. Descriptions of blinding were adequate overall. Subject accountability in RCTs was sufficiently detailed in 11 of 17 cases (Table 4).

Main results

In relation to controls, probiotic supplementation statistically decreased ITT, with an SMD of 0.38 (95%CI: 0.23-0.53, $P < 0.001$) (Figure 2). Only 5 of 17 treatment effects statistically favored probiotic supplementation. There was low heterogeneity among studies (I^2 = 20%, P = 0.22) with no evidence of publication bias (Egger's regression test: P = 0.44) (Figure 3). A one study removed sensitivity analysis was performed to determine the influence of individual studies on main outcomes. Overall, no single study significantly influenced the observed SMD of ITT with probiotics *vs* control. SMDs ranged from 0.35 to 0.42 (all $P < 0.001$) following removal of each study one at a time from the meta-analysis (Figure 4).

Additional analyses

Subgroup analyses (SA) (Table 5) and meta-regression

Table 2 Study characteristics

Study	Country	Study design	*n* (active: control)	Transit time outcome, method	Probiotic strain	Daily dosage (10^9 CFU)	Delivery method	Treatment duration (d)
Agrawal *et al*[14], 2009	United Kingdom	Parallel groups	17:17	CTT, radiopaque markers	*B. lactis* DN-173 010	25	Active: Yogurt + probiotic Control: Nonfermented milk-based product	28
Bartram *et al*[15], 1994	Germany	Cross-over	12	OATT, radiopaque markers	*B. longum*	> 0.5	Active: Yogurt with 2.5 g lactulose + probiotic Control: Yogurt	21
Bazzocchi *et al*[25], 2014	Italy	Parallel groups	19:12	TITT, radiopaque markers	*L. plantarum*, *L. acidophilus*, *L. rhamnosus*, *B. longum*, *B. breve*	-	Active: Sachet with psyllium+probiotic Control: Sachet with 2.8 g maltodextrin	56
Bouvier *et al*[16], 2001	France	Parallel groups	36:36	CTT, radiopaque markers	*B. lactis* DN-173 010	97.5	Active: Probiotic fermented milk Control: Heat-treated probiotic fermented milk	11
Holma *et al*[17], 2010	Finland	Parallel groups	12:10	TITT, radiopaque markers	*L. rhamnosus* GG	20	Active: Buttermilk + probiotic and white wheat bread Control: White wheat bread	21
Hongisto *et al*[18], 2006	Finland	Parallel groups	16:14	TITT, radiopaque markers	*L. rhamnosus* GG	15	Active: Yogurt + probiotic and low fiber toast Control: Low fiber toast	21
Krammer *et al*[24], 2011	Germany	Parallel groups	12:12	CTT, radiopaque markers	*L. casei* Shirota	6.5	Active: Probiotic fermented milk drink Control: Nonfermented milk drink	28
Magro *et al*[26], 2014	Brazil	Parallel groups	26:21	CTT, radiopaque markers	*L. acidophilus* NCFM, *B. lactis* HN019	2	Active: Yogurt + polydextrose + probiotic Control: Yogurt	14
Malpeli *et al*[19], 2012	Argentina	Cross-over	83	OCTT, carmine red dye	*B. lactis* BB12	2-20	Active: Yogurt with 0.625 g inulin and oligofructose + probiotic	15
					L. casei CRL 431	2-12	Control: Yogurt	
Marteau *et al*[20], 2002	France	Cross-over	32	CTT, radiopaque markers	*B. lactis* DN-173 010	18.75	Active: Yogurt + probiotic Control: Yogurt	10
Merenstein *et al*[27], 2014	United States	Crossover	68	CTT, radiopaque markers	*B. animalis ssp. lactis Bf-6*	20-56	Active: Yogurt + probiotic Control: Yogurt	14
Rosenfeldt *et al*[21], 2003a	Denmark	Cross-over	13	GTT, radiopaque markers	*L. rhamnosus* 19070-2	20	Active: Freeze-dried powder + probiotic	18
					L. reuteri DSM 12246	20	Control: Skimmed milk powder w/dextrose	
Rosenfeldt *et al*[21], 2003b	Denmark	Cross-over	13	GTT, radiopaque markers	*L. casei* subsp. alactus CHCC 3137	20	Active: Freeze-dried powder + probiotic	18
					L. delbrueckii subsp. lactis CHCC 2329	20	Control: Skimmed milk powder w/dextrose	
					L. rhamnosus GG	20		
Sairanen *et al*[22], 2007	Finland	Parallel groups	22:20	CTT, radiopaque markers	*B. longum* BB536, *B. lactis* 420	2.4-18[1]	Active: Probiotic fermented milk	21
					L. acidophilus 145	0.48	Control: Fermented milk	
Tulk *et al*[28], 2013	Canada	Crossover	65	GTT, carmine red/carbon black capsules	*B. lactis* Bb12, *L. acidophilus* La5, *L. casei* CRL431	2	Active: Yogurt + probiotic + inulin Control: Yogurt	15
Waller *et al*[23], 2011a	United States	Parallel groups	33:34	WGTT; radiopaque markers	*B. lactis* HN019	1.8	Active: Capsule, maltodextrin, probiotic Control: Capsule, maltodextrin	14
Waller *et al*[23], 2011b	United States	Parallel groups	33:34	WGTT; radiopaque markers	*B. lactis* HN019	17.2	Active: Capsule, maltodextrin, probiotic Control: Capsule, maltodextrin	14

[1]Represents the reported range of total Bifidobacterium. CFU: Colony-forming units; CTT: Colonic transit time; GTT: Gastrointestinal transit time; OATT: Oro-anal transit time; OCTT: Oro-cecal TT; TITT: Total intestinal transit time; WGTT: Whole gut transit time.

Table 3 Subject characteristics

Study	Mean age (yr)	Female gender (%)	Mean BMI (kg/m^2)	Condition
Agrawal *et al*[14], 2009	40	100	25	IBS-C
Bartram *et al*[15], 1994	23	58	-[2]	None
Bazzocchi *et al*[25], 2014	40	86	19	Constipation
Bouvier *et al*[16], 2001	33	50	22	None
Holma *et al*[17], 2010	44	92[1]	24	Constipation
Hongisto *et al*[18], 2006	43	100	24	Constipation
Krammer *et al*[24], 2011	50	100	-[2]	Constipation
Magro *et al*[26], 2014	32	91	28	Constipation
Malpeli *et al*[19], 2012	41	100	-[2]	Constipation
Marteau *et al*[20], 2002	27	100	21	None
Merenstein *et al*[27], 2014	29	100	23	None
Rosenfeldt *et al*[21], 2003a	25	0	-[2]	None
Rosenfeldt *et al*[21], 2003b	25	0	-[2]	None
Sairanen *et al*[22], 2007	39	64	25	None
Tulk *et al*[28], 2013	29	60	24	None
Waller *et al*[23], 2011a	44	65	31	Constipation
Waller *et al*[23], 2011b	44	65	32	Constipation

[1]Percentage estimated from larger study cohort; [2]Represents missing data. BMI: Body mass index; IBS-C: Irritable bowel syndrome, constipation predominant.

Table 4 Assessment of study quality

Study	Jadad scale			
	Randomization range: 0-2	Double blinding range: 0-2	Subject account range: 0-1	Total score[1] range: 0-5
Agrawal *et al*[14], 2009	1	2	1	4
Bartram *et al*[15], 1994	1	2	0	3
Bazzocchi *et al*[25], 2014	1	2	1	4
Bouvier *et al*[16], 2001	1	2	0	3
Holma *et al*[17], 2010	1	0	1	2
Hongisto *et al*[18], 2006	1	0	0	1
Krammer *et al*[24], 2011	1	1	1	3
Magro *et al*[26], 2014	2	2	1	5
Malpeli *et al*[19], 2012	0	2	1	3
Marteau *et al*[20], 2002	1	2	1	4
Merenstein *et al*[27], 2014	2	2	1	5
Rosenfeldt *et al*[21], 2003a	1	1	0	2
Rosenfeldt *et al*[21], 2003b	1	1	0	2
Sairanen *et al*[22], 2007	1	1	0	2
Tulk *et al*[28], 2013	1	1	1	3
Waller *et al*[23], 2011a	2	2	1	5
Waller *et al*[23], 2011b	2	2	1	5

[1]Higher scores represent better study quality.

Table 5 Subgroup analysis of study- and subject-related factors on intestinal transit time

Study	SMD	95%CI	*P* value (pre-post)	*P* value (between groups)
Subject condition				
Constipation/IBS-C (n = 9)	0.57	0.39-0.75	< 0.001	< 0.01
Healthy (n = 8)	0.22	0.05-0.39	0.01	
Study quality				
Jadad score ⩾ 3 (n = 12)	0.45	0.31-0.59	< 0.001	0.01
Jadad score < 3 (n = 5)	0.00	-0.33-0.33	> 0.99	
Age[1]				
⩾ 39 yr (n = 9)	0.51	0.29-0.73	< 0.001	0.08
< 39 yr (n = 8)	0.27	0.09-0.44	< 0.01	
Publication year				
After 2008 (n = 10)	0.47	0.29-0.65	< 0.001	0.08
Before 2008 (n = 7)	0.20	-0.03-0.44	0.09	
Number of probiotic strains				
Single strain (n = 10)	0.49	0.32-0.66	< 0.001	0.09
Multiple strains (n = 7)	0.23	-0.01-0.47	0.06	
Study design				
Parallel groups (n = 11)	0.48	0.31-0.65	< 0.001	0.09
Cross-over (n = 6)	0.26	-0.02-0.46	0.07	
Body mass index[1,2]				
⩾ 25 kg/m^2 (n = 5)	0.59	0.24-0.94	< 0.001	0.16
< 25 kg/m^2 (n = 7)	0.31	0.13-0.49	< 0.001	
Treatment duration[1]				
< 18 d (n = 8)	0.45	0.29-0.60	< 0.001	0.17
⩾ 18 d (n = 9)	0.22	-0.06-0.50	0.12	
Geographic location				
Americas (n = 6)	0.47	0.26-0.67	< 0.001	0.20
Europe (n = 11)	0.28	0.07-0.49	< 0.01	
Female gender proportion[1]				
⩾ 86% (n = 9)	0.47	0.30-0.64	< 0.01	0.22
< 86% (n = 8)	0.27	0.00-0.54	< 0.05	
Confounding treatments[3]				
Yes (n = 7)	0.46	0.24-0.67	< 0.001	0.32
No (n = 10)	0.30	0.10-0.51	< 0.01	
Daily probiotic dosage[1]				
⩾ 1.6^{10} CFU (n = 8)	0.40	0.12-0.67	< 0.01	0.74
< 1.6^{10} CFU (n = 7)	0.34	0.16-0.52	< 0.001	

[1]Categorized by median value; [2]Body mass index not reported for 5 treatment effects; [3]Includes studies where treatment included probiotics plus fiber or non-digestible sugar. Variables sorted from lowest to highest between-groups *P* value; n represents the number of treatment effects. IBS-C: Irritable bowel syndrome, constipation predominant; SMD: Standardized mean difference.

(MR) (Table 6) were performed to determine the influence of study- and subject-related characteristics on ITT. Probiotic supplementation reduced ITT in comparison to controls in several of the analyzed subgroups. Greater reductions in ITT were observed with probiotics in subjects with *vs* without constipation (SA and MR, $P < 0.01$) and in high-quality (Jadad score ⩾ 3) *vs* low-quality (Jadad score < 3) studies (SA and MR, $P = 0.01$). There were trends for greater probiotic efficacy with older age (SA, $P = 0.08$, MR, $P = 0.02$), in recently published studies (SA, $P = 0.08$), with parallel groups study designs (SA, $P = 0.08$), higher percentage of female subjects (SA, $P = 0.08$,

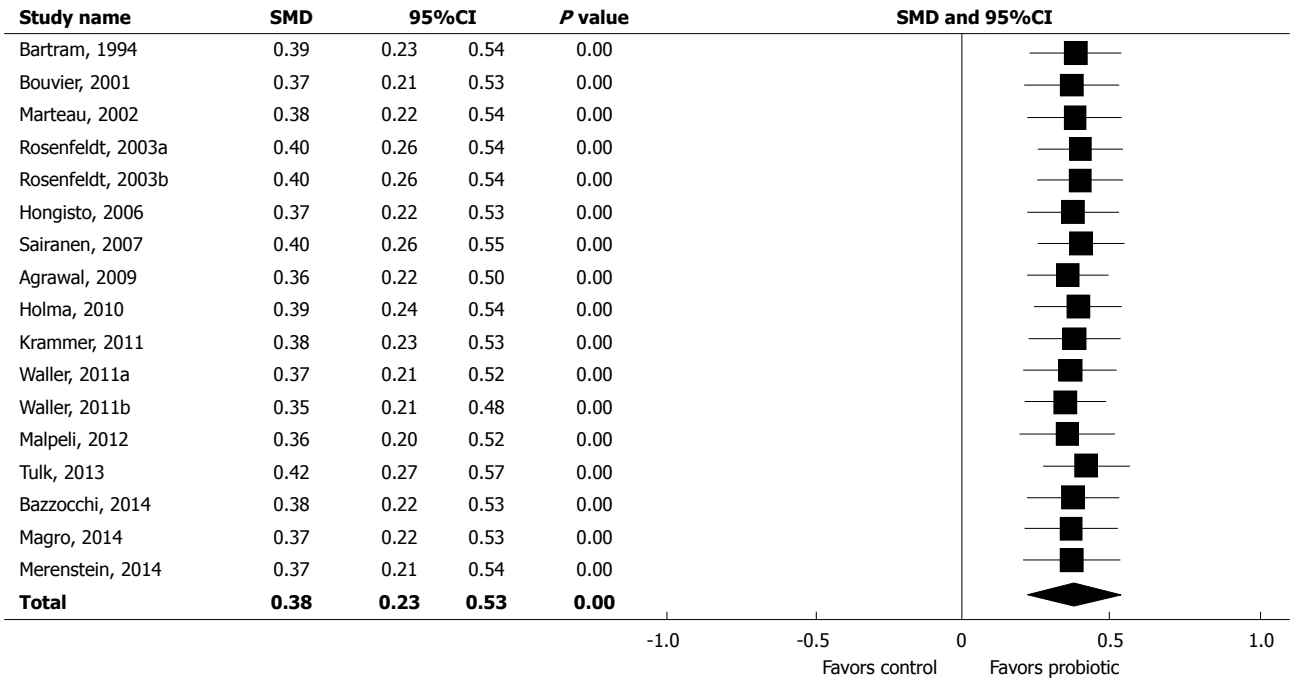

Figure 4 One study removed forest plot of standardized mean difference in intestinal transit time across studies. SMD: Standardized mean difference.

Table 6 Meta-regression of study- and subject-related factors on intestinal transit time

Variable	Unit of measure	Intercept	Point estimate	Explained variance (%)	*P* value
Constipation/ IBS-C	1 = Yes; 0 = No	0.218	0.352	38	< 0.01
Jadad score	Per 1 unit	-0.117	0.141	31	0.01
Age	Per 1 yr	-0.352	0.021	27	0.02
Female gender proportion	Per 10%	-0.045	0.055	26	0.02
Number of probiotic strains	Per 1 strain	0.618	-0.133	20	< 0.05
Body mass index[1]	Per 1 kg/m^2	-0.526	0.037	22	0.08
Treatment duration	Per 1 d	0.392	-0.004	0	0.96
Daily probiotic dosage	Per 10 × 10^9 CFU	0.385	-0.001	0	0.98

[1]Body mass index not reported for 5 treatment effects. Variables sorted from greatest to least explained variance.

Table 7 Subgroup analysis of probiotic strains on intestinal transit time

Probiotic strain	No. of treatment effects	SMD	95%CI	*P* value
B. lactis HN019	3	0.67	0.37-0.97	< 0.001
B. lactis DN-173 010	3	0.54	0.16-0.92	< 0.01
L. casei CRL 431	2	0.33	-0.10-0.75	0.14
B. lactis BB12	2	0.33	-0.10-0.75	0.14
L. rhamnosus GG	3	0.10	-0.35-0.55	0.67

Probiotic strains sorted from highest to lowest standard mean difference. SMD: Standardized mean difference.

MR, $P = 0.02$), single-strain probiotics (SA, $P = 0.09$, MR, $P < 0.05$) and higher body mass index (SA, $P = 0.16$, MR, $P = 0.08$). Treatment duration, geographic location of study, inclusion of potentially confounding treatments, and daily probiotic dosage were not found to have a significant influence on probiotic efficacy in subgroup analysis and meta-regression. Analysis of outcomes by probiotic strain identified medium to large treatment effects with *B. lactis* HN019 (SMD: 0.67, $P < 0.001$) and *B. lactis* DN-173 010 (SMD: 0.54, $P < 0.01$) while treatment effects with other strains were small (SMD: 0.10-0.33) and not statistically significant (Table 7).

DISCUSSION

An ever-increasing body of evidence implicates the gastrointestinal microbiome in defining states of health and disease[29]. Probiotics may restore the composition of the gut microbiome and support beneficial functions to gut microbial communities, resulting in amelioration of gut inflammation and other disease phenotypes[30]. Consequently, probiotic supplementation is increasingly touted as an effective and accessible means of improving gut health, even in the general population of healthy adults. The current systematic review and meta-analysis demonstrates that short-term probiotic supplementation yielded moderate ITT reductions in adults. Additionally, the treatment effect of probiotics was greater in subjects with constipation, in high-quality studies, and with certain probiotic strains. In contrast to the moderate treatment effect observed in constipated subjects, probiotics only minimally influenced ITT in non-constipated adults. Given this finding, it appears that probiotic consumption will

not lead to undesired short ITT or diarrhea. However, probiotic consumption for the sole purpose of reducing ITT is unjustified in healthy adults. Nevertheless, this finding does not diminish other beneficial effects that have been observed with probiotics in healthy adults[31,32].

In this meta-analysis, there was a trend for greater treatment effects with probiotics in parallel groups study designs compared to crossover studies (SMD: 0.48 *vs* 0.26, $P = 0.09$). Although there is no clear explanation for this finding, data from one included study deserves further discussion. The study of Merenstein *et al*[27] enrolled 68 healthy women using a crossover design, with a 6-wk washout between treatment periods. However, a significant carry-over effect was observed at the start of the second treatment period. For purposes of this meta-analysis, we treated this study as a parallel groups design using data from the first treatment period only[33]. Although the presence of a carry-over effect was not mentioned in the other crossover studies included in this analysis, the fact that washout periods ranged from 2 to 6 wk with significant carryover identified even after 6 wk in the Merenstein study raises the question of whether carry-over effects may have influenced outcomes of other crossover studies. Although crossover studies may initially appear attractive to researchers given the smaller sample size requirements compared to parallel groups designs, we propose that crossover designs are inappropriate in probiotic clinical trials unless the washout period for the probiotic has been previously established for the specific condition under study.

In comparison to our previous meta-analysis on this topic, the treatment effect of probiotics on ITT was largely unchanged (SMD: 0.40 *vs* 0.38). Importantly, with the addition of more studies, we were able to explore potential sources of heterogeneity among studies with greater precision. Novel subgroup findings included the observation of moderate probiotic treatment effects (SMD: 0.45) in high-quality studies, but no treatment effect (SMD: 0.0) in low-quality studies. Although the treatment effect sizes in parallel groups and crossover studies remained largely unchanged, study design is now a considerably stronger predictor of heterogeneity in ITT outcomes given the inclusion of additional studies. We also identified that single-strain probiotics were more efficacious than multiple strain probiotics. Although *B. lactis* HN019 and *B. lactis* DN-173 010 remained the most efficacious probiotic strains, we were able to analyze additional probiotic strains that yielded modest improvements in ITT relative to placebo.

The strengths of this systematic review and meta-analysis are inclusion of only RCTs and a comprehensive assessment of the influence of moderator variables on ITT with probiotic supplementation. Our study also revealed several limitations in the design of ITT studies with probiotics. First, the treatment duration of included studies ranged from 10 to 56 d. Although the long-term safety of probiotics is well established[34], probiotic efficacy on ITT beyond 8 wk cannot be interpreted with the current analysis. Second, although the therapeutic benefit of probiotics appears to be strain-specific, the small number of studies performed with each strain prevented robust strain-specific comparisons. Finally, subject characteristics were relatively homogenous among studies with regard to age and gender. Therefore, the generalizability of these findings to the general population, particularly males and the elderly, is unknown. These findings give specific suggestions for future research in this field.

In conclusion, probiotic supplementation is moderately efficacious for reducing ITT in adults. Probiotics were most efficacious in constipated subjects, when evaluated in high-quality studies, and with certain probiotic strains.

COMMENTS

Background

Functional gastrointestinal disorders are common in the general population, with slow intestinal transit a common symptom. No therapy is highly efficacious, safe, and cost effective for treatment of slow-transit bowel disorders. Probiotics have been extensively studied for treatment of gastrointestinal disorders and may confer improvements in bowel regularity.

Research frontiers

Clinical trials of probiotic supplementation on intestinal transit time (ITT) yield discrepant results. The authors performed a contemporary systematic review and meta-analysis on the efficacy of probiotic supplementation on ITT in adults, with a secondary focus on exploring sources of heterogeneity through meta-regression and subgroup analyses.

Innovations and breakthroughs

Probiotics are most efficacious in constipated subjects, when evaluated in high-quality studies, and with certain probiotic strains.

Applications

Probiotic supplementation appears to confer clinically meaningful improvements in intestinal transit in subjects with constipation. Probiotic efficacy also significantly differs according to strain.

Terminology

Probiotics are live micro-organisms that confer a health benefit on the host when administered in adequate dosages. Intestinal transit time is an indicator of the time taken for a food bolus to travel through the gastrointestinal system. The standardized mean difference is a statistical measure of effect size for continuous outcomes, defined as the mean difference between groups divided by the pooled standard deviation.

Peer-review

Very nice manuscript.

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