J. Dairy Sci. 101:4830–4841
https://doi.org/10.3168/jds.2017-13803

Bifidobacterium bifidum YIT 10347 fermented milk exerts beneficial effects on gastrointestinal discomfort and symptoms in healthy adults: A double-blind, randomized, placebo-controlled study

A. Gomi,*[1] K. Yamaji,* O. Watanabe,† M. Yoshioka,† K. Miyazaki,* Y. Iwama,‡ and Y. Urita§
*Yakult Central Institute, 5-11 Izumi, Kunitachi-shi, Tokyo 186-8650, Japan
†Faculty of Research and Development, Yakult Honsha, 1-19 Higashi Shimbashi, Minato-ku, Tokyo 105-8660, Japan
‡Nihonbashi Cardiology Clinic, Kyodo Bldg. #201, 13-4 Nihonbashi Kodenmacho, Chuo-ku, Tokyo 103-0001, Japan
§Department of General Medicine and Emergency Care, Toho University School of Medicine, 6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-8541, Japan

ABSTRACT

In a preliminary open-label trial by our group, *Bifidobacterium bifidum* YIT 10347 (YIT10347) relieved gastric symptoms in patients with functional gastrointestinal disorders. Hence, in this study, we investigated the effects of YIT10347 on gastrointestinal symptoms in healthy adults. In this prospective double-blind, randomized, placebo-controlled trial (UMIN000024654), 100 healthy Japanese adults were randomly assigned to a YIT10347 group or placebo group and consumed 100 mL of YIT10347-fermented milk or placebo fermented milk, respectively, every day for 4 wk. Gastrointestinal symptoms were evaluated by using the modified Frequency Scale for Symptoms of Gastroesophageal Reflux Disease (m-FSSG) and Gastrointestinal Symptom Rating Scale (GSRS) as primary endpoints. Mental symptoms, quality of life, salivary stress markers, and gastric emptying were evaluated as secondary endpoints. Effectiveness and safety were analyzed in a per-protocol set (YIT10347 group, n = 39; placebo group, n = 40) and full analysis set (YIT10347 group, n = 50; placebo group, n = 50), respectively. In the m-FSSG evaluation, the YIT10347 group had a significantly higher relief rate of postprandial discomfort and greater changes in postprandial epigastric pain score from baseline than the placebo group. In the GSRS evaluation, the YIT10347 group had significantly higher relief rates of overall gastrointestinal symptoms, upper gastrointestinal symptoms, flatus, and diarrhea than the placebo group. We detected no significant differences in scores or relief rates of mental symptoms and quality of life, a salivary stress marker, or gastric emptying between the 2 groups. No severe adverse events associated with test beverage consumption were observed in either group. These findings suggest that daily consumption of YIT10347-fermented milk exerts beneficial effects on gastrointestinal discomfort and symptoms such as postprandial discomfort and epigastric pain in healthy adults.

Key words: probiotics, functional dyspepsia, gastrointestinal symptom, healthy adult

INTRODUCTION

Increasing numbers of healthy Japanese adults occasionally have abdominal symptoms, with epidemiological studies revealing that about one-quarter of the Japanese population experiences digestive symptoms such as abdominal pain, stomach heaviness, and acidic regurgitation (Stanghellini, 1999). Gastrointestinal (**GI**) symptoms can occur in the presence or absence of organic abnormalities such as gastritis caused by *Helicobacter pylori* infection (Manabe et al., 2011). However, those who temporarily experience GI symptoms often prefer to receive functional foods rather than medical treatment because their symptoms are mild and temporary.

Probiotics, which are living microorganisms that confer health benefits in the host (FAO/WHO, 2002), might have beneficial effects on not only the gut but also the upper GI tract. *Bifidobacterium bifidum* YIT 10347 (**YIT10347**) is a typical probiotic with benefits on upper GI symptoms such as *H. pylori*-associated gastritis (Miki et al., 2007) and gastric symptoms of serious functional gastrointestinal disorders (**FGID**; Urita et al., 2015) in patients with FGID, gastric symptoms in healthy adults (Gomi et al., 2015), and acute gastric mucosal injury in an animal model (Gomi et al., 2013), via its strong adherence to the gastric mucosa (Shibahara-Sone et al., 2016). However, there is little evidence regarding its effects on temporary gastric symptoms in healthy adults.

Therefore, in this study we aimed to clarify the beneficial effects of YIT10347 on temporary gastric symptoms in healthy Japanese adults in a prospective

Received September 8, 2017.
Accepted February 2, 2018.
[1]Corresponding author: atsushi-gomi@yakult.co.jp

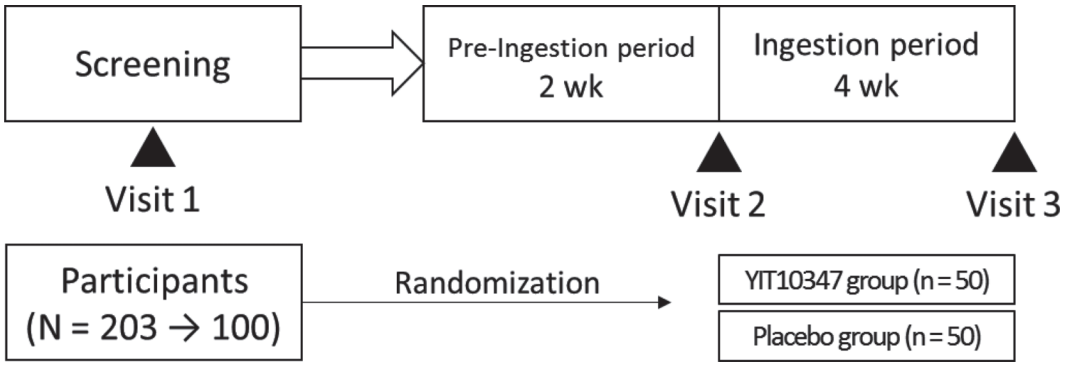

Figure 1. Study design. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk.

randomized, double-blind, placebo-controlled, parallel-group trial.

MATERIALS AND METHODS

Test Beverage

Milk fermented with YIT10347 was prepared by anaerobic culture of YIT10347 and *Streptococcus thermophilus* YIT 2021, obtained from the Culture Collection Laboratory at Yakult Central Institute (Tokyo, Japan). The placebo milk was prepared by anaerobic culture of *Streptococcus thermophilus* YIT 2021 and was followed by the addition of lactic acid and acetic acid to match the appearance, taste, flavor, pH, and nutritional content of the active fermented milk as much as possible. The beverages (100 mL/package), which had identical appearance, packaging, and labeling to maintain blinding of investigators and participants, were delivered to subjects at 1-wk intervals and stored in a refrigerator ($\leq$10°C) before and during delivery and before consumption. During the trial, the active beverage, YIT10347-fermented milk, contained more than 3×10^7 cfu/mL of YIT10347 and more than 1×10^7 cfu/mL of *S. thermophilus* YIT 2021, whereas the placebo milk contained more than 1×10^7 cfu/mL of *S. thermophilus* YIT 2021 only.

Trial Design

This prospective, randomized, double-blind, placebo-controlled, parallel-group trial (UMIN Clinical Trials Registry number: UMIN000024654; http://www.umin.ac.jp/ctr/), designed by the authors (Figure 1), was conducted from October 2016 to March 2017. The study protocol was approved by the Ethics Committee of Nihonbashi Cardiology Clinic (Tokyo, Japan; No. YLT-008-01; October 7, 2016), and written informed consent was obtained before subject enrollment. The study was performed in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan (http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf).

Participants

The study enrolled healthy adults aged from 20 to 64 yr who had temporary gastric symptoms with a modified Frequency Scale for Symptoms of Gastroesophageal reflux disease (**m-FSSG**) score $\geq$8 (Kusano et al., 2012) but were not defined as having "functional dyspepsia" by the Rome IV classification (Stanghellini, 2016). The participants had one or more symptoms but no evidence of organic diseases such as peptic ulcer disease, *H. pylori*-associated gastritis diagnosed by the presence of anti-*H. pylori* antibodies in the blood, gastric cancer, or gastritis, based on their answers to a physician's questions.

The enrolled participants met the following inclusion criteria: (1) healthy men and women aged from 20 to 64 yr old, (2) with an m-FSSG score of $\geq$8, and (3) who understood the details of the study and provided written informed consent. Exclusion criteria were (1) *H. pylori* infection; (2) regular use of gastrointestinal drugs; (3) functional dyspepsia (Rome IV classification); (4) refusal to stop ingestion of probiotics, prebiotics, foods containing lactic acid bacteria or bifidobacteria, and other healthy foods that might affect gastrointestinal symptoms; (5) food allergy; (6) severe complications or diseases requiring urgent treatment; (7) a medical history of diseases or operations affecting digestion, absorption, or defecation; (8) those deemed unsuitable for the study based on blood results of the screening test; (9) those who were pregnant or lactating or planning to

become pregnant during the study; (10) those receiving treatment for or with a history of drug addiction or alcoholism; (11) those planning to participate or already participating in other clinical studies; and (12) those deemed unsuitable for the study by the investigator for other reasons.

Sample Size and Study Conduct

According to a previous trial (Gomi et al., 2015), the relief rates of dyspepsia symptoms in healthy volunteers were presumed to be 32 and 60% in the placebo and YIT10347 groups, respectively. We determined that a similar percentage of volunteers should be treated with YIT10347 in this study. Assuming an effective YIT10347 ratio of 60%, placebo effective ratio of 32%, α-error of 0.05, β-error of 0.20, and power of 0.80, approximately 100 participants would be required, 50 in the placebo group and 50 in the YIT10347 group. Therefore, 100 healthy adults were recruited in this study.

Randomization

During the pre-ingestion period, 100 participants were sequentially randomized 1:1 to the 2 groups by the data analysis department of KSO Corp. (Tokyo, Japan). Participant allocation was concealed by the controller for clinical trials (Tsurumi Univ., Kanagawa, Japan). After all data had been collected by the data analysis department of KSO Corp., the data code key was requested from the controller, enabling data analysis.

Study Design

During the pre-ingestion and consumption periods, upper GI symptoms were evaluated using the m-FSSG questionnaire, which comprises 14 questions as follows: 1, heartburn; 2, bloated stomach; 3, heavy stomach after meals; 4, subconscious chest rubbing; 5, postprandial discomfort; 6, heartburn after meals; 7, unusual sensation in throat; 8, full feeling while eating meals; 9, food stuck when swallowing; 10, acid coming up into throat; 11, burping; 12, heartburn while bending over; 13, postprandial epigastric pain; and 14, epigastric pain before meals. The scores for the 14 questions were assigned as follows: never = 0; occasionally = 1; sometimes = 2; often = 3; and always = 4, with lower and higher scores indicating milder and more severe symptoms, respectively. Based on the questions, the reflux syndrome score (**RS**; questions 1, 4, 6, 7, 9, 10, and 12), acid-related dyspepsia score (**ARD**; questions 2, 3, 5, 8, 11, 13, and 14), and total score (questions 1–14; given by the sum of both scores) were calculated (Kusano et al., 2004, 2012; Kusano, 2007). In addition, the relief rate was evaluated via a modification of the protocol in the previous report (Kusunoki et al., 2009). Relief rate was defined as the number of participants whose symptom ratings were "alleviated," "no change," or "deteriorated" by comparing the "before ingestion" and "after ingestion" scores.

Overall GI symptoms were also assessed using the Japanese version of the Gastrointestinal Symptom Rating Scale (**GSRS**) questionnaire, which includes 15 scoring criteria: abdominal pain, heartburn, acid regurgitation, sucking sensations in the epigastrium, nausea and vomiting, borborygmus, abdominal distension, eructation, increased flatus, decreased passage of stools, increased passage of stools, loose stools, hard stools, urgent need for defecation, and feeling of incomplete evacuation, scored on a 7-point Likert scale. This gives a total value range between 15 and 105, where the highest score (7) for any item represents the most pronounced symptom and the lowest score (1) represents no symptoms. The criteria were grouped into the following 5 domains: RS (questions 2 and 3), abdominal pain (**AP**; questions 1, 4, and 5), indigestion syndrome (**IS**; questions 6, 7, 8, and 9), constipation syndrome (**CS**; questions 10, 13, and 15), and diarrhea syndrome (**DS**; questions 11, 12, and 14). Furthermore, these 5 domains were subdivided into upper GI symptoms (RS, AP, and IS) and lower GI symptoms (CS and DS) (Svedlund et al., 1988; Hongo et al., 1999). These 5 domains, upper and lower GI symptoms, and total score were calculated as (sum of each question score)/(number of questions).

Subjective psychological symptoms were evaluated using the Japanese translation of the Profile of Mood States 2nd Edition-Adult Short (POMS 2; Kaneko Shobo Inc., Tokyo, Japan; McNair et al., 1971; Yokoyama et al., 1990; Heuchert and McNair, 2012). The questionnaire includes 35 items and uses a 5-point Likert scale to evaluate 7 domains; namely, anger–hostility, confusion–bewilderment, depression–dejection, fatigue–inertia, tension–anxiety, vigor–activity, and friendliness. Higher scores indicate more severe symptoms of anger–hostility, confusion–bewilderment, depression–dejection, fatigue–inertia, tension–anxiety, but better conditions of vigor–activity, and friendliness; each item was scored from 0 to 100 and compared with values from normal individuals.

Subjective quality of life was evaluated using the 36-Item Short Form Health Survey version 2 (SF-36v2; Fukuhara and Suzukamo, 2004). The questionnaire includes 36 items and uses a 5-point Likert scale to evaluate 3 domains; namely, physical component summary, mental component score, and role–social component score, and 8 subdomains; namely, physical function-

ing, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health; each item was scored from 0 to 100 and compared with values from normal individuals.

Subjects were asked to report their symptoms about the past 1 wk from "before ingestion" (visit 2) and "after ingestion" (visit 3).

Salivary Cortisol and Gastric Emptying

Saliva samples were taken while participants were fasting in the morning at a predetermined time. Cortisol levels were determined using a commercial salivary cortisol enzyme assay kit (Salimetrics, State College, PA).

Subjective gastric emptying was evaluated using the ^{13}C-acetate breath test according to a previously reported method (Sanaka et al., 2013). Participants consumed a liquid test meal (protein 8.76 g, fat 4.46 g, carbohydrate 31.24 g, 200 kcal/200 mL; Racol, Otsuka Pharmaceuticals Co. Ltd., Tokyo, Japan). Breath samples were collected at baseline and every 10 min after consumption of the liquid test meal until 120 min. Samples were analyzed for $^{13}CO_2$ using an infrared spectrophotometer (UBiT-IR200; Otsuka Electronics Co. Ltd., Osaka, Japan). Gastric emptying time was expressed as the time of maximal $^{13}CO_2$ excretion ($\mathbf{T_{max}}$).

Blood Examination and Vital Signs

Blood was collected at clinical visit 1 for the general biochemical examination and evaluation of *H. pylori* infection via anti-*H. pylori* antibodies. Vital signs were evaluated at all clinical visits.

Outcomes

Most analyses were conducted in the per-protocol set (**PPS**), which excluded several ineligible participants according to the protocol from the full intake set (**FIS**) population. Some analyses were conducted in the FIS, which excluded the participants who dropped out from the full analysis set (**FAS**) population. Adverse events were evaluated in the FAS.

Primary Endpoint

The primary endpoint was defined as relief of GI symptoms evaluated by m-FSSG and GSRS questionnaires at wk 4 of the consumption period between the YIT10347 and placebo groups in the PPS population.

Secondary Endpoints

The secondary endpoints were (1) changes in the scores of psychological symptoms and quality of life at wk 4 during the consumption period from the baseline in the YIT10347 and placebo groups; and (2) gastric emptying time measured by the ^{13}C breath test in the 2 groups.

Adverse Events

Adverse events were defined as any undesirable medical symptoms or conditions that emerged in participants during the consumption period, regardless of an apparent causal relationship. If serious adverse events occurred in association with test beverage consumption, the attending physician was to immediately stop participants' consumption of the test beverage.

Compliance

Compliance with test beverage consumption was self-recorded daily by participants in a diary. An acceptable compliance was defined as a consumption rate exceeding 80%.

Statistical Analysis

All data were analyzed by a statistician in the contract research organization (KSO Co., Tokyo, Japan) using IBM Statistics 24 (IBM Japan Ltd., Tokyo, Japan). Baseline characteristics of participants were compared between the YIT10347 and placebo groups by an unpaired *t*-test for continuous variables. Gastrointestinal symptoms were compared between the 2 groups by the Wilcoxon signed-rank and chi-squared tests. Data are expressed as means ± standard deviations. Two-sided P-values < 0.05 were considered statistically significant.

RESULTS

Participants

The flowchart in Figure 2 shows the enrollment, allocation, dropout, and inclusion of participants in the analysis. Based on the inclusion criteria, 100 participants were enrolled from 203 initial participants and randomized to either the YIT10347 group (n = 50) or the placebo group (n = 50). They consumed YIT10347-fermented milk or placebo milk once a day for 4 wk. In the YIT10347 group, one subject dropped out and was excluded from the FIS population due to an injury caused by a fall while walking. The fall was considered by the attending physician to have no as-

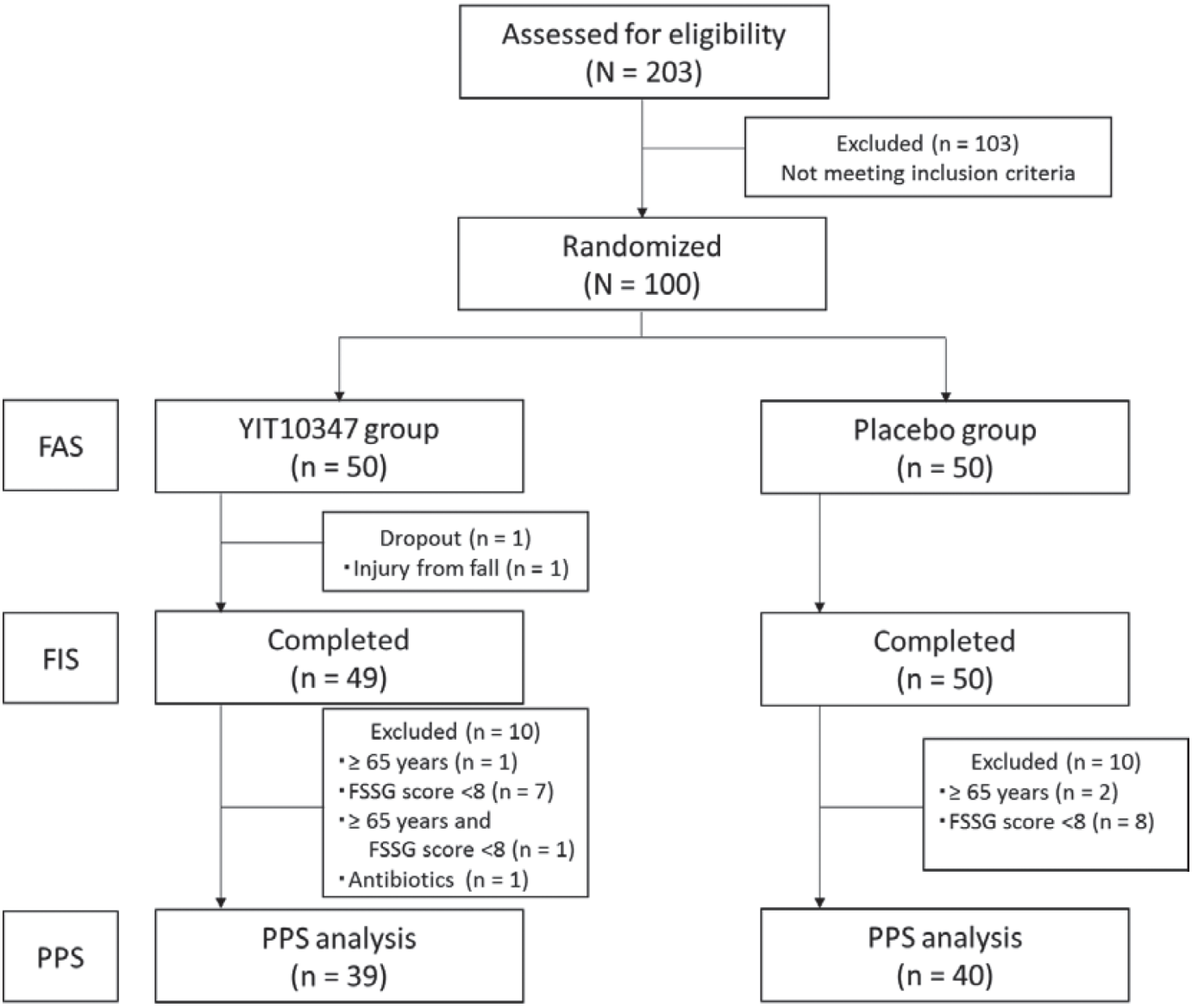

Figure 2. Flow of participants throughout the study. FAS = full analysis set; FIS = full intake set; PPS = per-protocol set. Safety was evaluated using the FAS; efficiency was evaluated using PPS and FIS. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. FSSG score = Frequency Scale for Symptoms of Gastroesophageal Reflux Disease.

sociation with daily consumption of the test beverage. Therefore, the FIS analysis included 99 participants, and the YIT10347 and placebo groups had 49 and 50 participants, respectively.

In addition, because 20 of the participants who completed the trial did not meet the primary inclusion criteria—that is, their m-FSSG scores were <8 at wk 0, despite ≥8 to satisfy the inclusion criteria at prescreening—they were excluded from the PPS population. Therefore, the PPS analysis included 79 participants, and the YIT10347 group and placebo groups had 39 and 40 participants, respectively.

Table 1 (PPS) and Supplemental Table S1 (https://doi.org/10.3168/jds.2017-13803; FIS and FAS) show the baseline demographics and clinical characteristics of both groups in the PPS, FIS, and FAS populations. We detected no significant differences in the characteristics of the 2 treatment groups among the populations, showing that participant randomization was well balanced.

Table 1. Background characteristics of participants (per-protocol set)[1]

Characteristic	YIT10347 (n = 39)	Placebo (n = 40)
Age, yr	41.1 ± 10.1	41.6 ± 9.9
Sex, no. male/female	19/20	19/21
Body mass index	21.7 ± 2.0	22.6 ± 2.4
m-FSSG total score[2]	15.4 ± 4.7	15.0 ± 4.6

[1]Data are expressed as the mean ± SD or the number of subjects. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk.

[2]Modified Frequency Scale for Symptoms of Gastroesophageal Reflux Disease.

Compliance with test beverage consumption exceeded 95% for all participants.

Primary Endpoint

Table 2 shows the changes in the m-FSSG score and relief rate of m-FSSG scores in the PPS population. We detected no significant differences in RS, ARD, and total score change of the m-FSSG between the YIT10347 and placebo groups. However, compared with the placebo group, the YIT10347 group had a significantly higher relief rate of postprandial discomfort and a greater change in the postprandial epigastric pain score from baseline (both $P < 0.05$). In addition, the YIT10347 group tended to have higher scores for subconscious chest rubbing and burping and higher relief rate of burping than the placebo group ($P = 0.077$, 0.084, and 0.052, respectively). We found similar results in the FIS population (Supplemental Table S2; https://doi.org/10.3168/jds.2017-13803), with the YIT10347 group showing significantly higher relief rates of postprandial discomfort and burping than the placebo group (both $P < 0.05$).

Table 3 shows the changes in the GSRS scores and relief rates of GSRS scores in the PPS population. The relief rates of overall GI symptoms, upper GI symptoms, flatus, and diarrhea were significantly higher in the YIT10347 group than in the placebo group (all $P < 0.05$). In addition, compared with the placebo group, the YIT10347 group had tendencies for greater changes in upper GI symptoms, abdominal pain, and heartburn scores from baseline ($P = 0.089$, 0.097, and 0.063, respectively), showing tendencies for relief in these parameters; the YIT10347 groups also had higher relief rates of heartburn and borborygmus ($P = 0.085$ and 0.074, respectively). We found similar results in the FIS population (Supplemental Table S3; https://doi.org/10.3168/jds.2017-13803), showing that the YIT10347 group had significantly higher relief rates in overall GI symptoms and improved flatus than the placebo group (both $P < 0.05$).

Secondary Endpoints

Tables 4 and 5 show changes in mental symptoms and quality of life, evaluated by the POMS-2 and SF-36v2 tools, respectively. Table 6 shows changes in salivary cortisol levels and gastric emptying in the PPS population. We found no significant differences in either the levels or their relief rates between the YIT10347 and placebo groups, and no significant differences were observed for the same parameters in the FIS population (Supplemental Tables S4, S5, and S6; https://doi.org/10.3168/jds.2017-13803).

Adverse Events

During the trial, 7 and 12 adverse events occurred in the YIT10347 and placebo groups, respectively, with no significant difference in the number of events between the 2 groups. In the YIT10347 group, the 7 adverse events comprised mild symptoms such as headache (1 case), cold (3 cases), injury in a fall (1 case), stomatitis (1 case), and hard stool (1 case). In the placebo group, the 12 adverse events comprised the following mild symptoms: fatigue (1 case), abdominal pain (3 cases), cold (4 cases), stomatitis (1 case), suppuration of gums (1 case), gastric distention (1 case), and cystitis (1 case). These adverse events were not considered serious or associated with daily consumption of the test beverages.

No abnormal changes were detected in the general blood biochemical parameters in either group after daily consumption for 4 wk. These findings suggested that both beverages were safe.

DISCUSSION

This prospective randomized, double-blind, placebo-controlled, parallel comparative trial investigated the beneficial effects of YIT10347 on the temporary gastric symptoms of healthy Japanese adults. The results showed that the YIT10347 group achieved significantly better relief from some upper GI symptoms, such as postprandial discomfort and postprandial epigastric pain, compared with the placebo group.

Although there was a higher relief rate of postprandial discomfort, the average score change did not differ between YIT10347 and placebo in the m-FSSG evaluation. Additionally, there was a higher score change for postprandial epigastric pain but no difference in the relief rate between YIT10347 and placebo in the m-FSSG evaluation. Relief rate was greatly influenced by the number of participants with GI symptoms in the "before ingestion" period. For example, 17 and 13 participants had postprandial epigastric pain symptoms in

Table 2. Total, reflux syndrome, and acid-related dyspepsia score changes and relief rates on the modified Frequency Scale for Symptoms of Gastroesophageal Reflux Disease (m-FSSG) (per-protocol set)[1]

		Score change[2]				Relief rate[3]			
Symptom (items)	Group	Wk 0	Wk 4	Δ (Wk 4 – 0)	*P*-value Wilcoxon	Alleviate	No change	Deteriorate	*P*-value χ^2
Total	YIT10347	15.36 ± 4.74	9.64 ± 5.36	−5.72 ± 5.36	0.222	33	1	5	0.529
	Placebo	15.00 ± 4.64	10.58 ± 5.32	−4.43 ± 5.80		30	1	9	
Reflux syndrome	YIT10347	6.51 ± 2.71	4.08 ± 3.26	−2.44 ± 3.08	0.438	31	2	6	0.472
(1, 4, 6, 7, 9, 10, 12)	Placebo	6.28 ± 3.05	4.33 ± 2.78	−1.95 ± 2.94		28	5	7	
1. Heartburn	YIT10347	1.31 ± 0.73	0.82 ± 0.60	−0.49 ± 0.64	0.360	18	20	1	0.508
	Placebo	1.23 ± 0.66	0.88 ± 0.61	−0.35 ± 0.70		15	22	3	
4. Subconsciously rub	YIT10347	0.79 ± 0.52	0.41 ± 0.59	−0.38 ± 0.63	0.077†	16	21	2	0.222
	Placebo	0.70 ± 0.69	0.60 ± 0.78	−0.10 ± 0.67		10	25	5	
6. Heartburn after meals	YIT10347	1.31 ± 0.69	0.77 ± 0.74	−0.54 ± 0.79	0.312	20	16	3	0.654
	Placebo	1.25 ± 0.67	0.90 ± 0.67	−0.35 ± 0.77		17	18	5	
7. Unusual sensation in	YIT10347	0.69 ± 0.77	0.56 ± 0.75	−0.13 ± 0.86	0.460	12	19	8	0.419
throat	Placebo	0.70 ± 0.97	0.43 ± 0.75	−0.28 ± 0.72		13	23	4	
9. Food stuck when	YIT10347	0.85 ± 0.96	0.49 ± 0.68	−0.36 ± 0.90	0.857	14	20	5	0.929
swallowing	Placebo	1.05 ± 0.96	0.70 ± 0.85	−0.35 ± 0.80		16	19	5	
10. Acid coming up into	YIT10347	1.03 ± 0.81	0.77 ± 0.78	−0.26 ± 0.75	0.872	16	18	5	0.835
throat	Placebo	0.95 ± 0.88	0.60 ± 0.59	−0.35 ± 0.77		15	21	4	
12. Heartburn while	YIT10347	0.54 ± 0.72	0.26 ± 0.59	−0.28 ± 0.72	0.665	11	25	3	0.946
bending over	Placebo	0.40 ± 0.59	0.23 ± 0.53	−0.18 ± 0.55		10	27	3	
Acid-related dyspepsia (2, 3,	YIT10347	8.85 ± 2.90	5.56 ± 2.65	−3.28 ± 3.02	0.193	31	5	3	0.114
5, 8, 11, 13, 14)	Placebo	8.73 ± 2.65	6.25 ± 3.11	−2.48 ± 3.37		29	2	9	
2. Bloated stomach	YIT10347	1.95 ± 0.79	1.49 ± 0.76	−0.46 ± 0.79	0.498	18	19	2	0.848
	Placebo	1.85 ± 0.86	1.23 ± 0.89	−0.63 ± 0.84		21	17	2	
3. Heavy stomach after	YIT10347	1.77 ± 0.71	1.28 ± 0.83	−0.49 ± 0.64	0.881	18	20	1	0.357
meals	Placebo	1.78 ± 0.73	1.25 ± 0.78	−0.53 ± 0.88		19	17	4	
5. Postprandial discomfort	YIT10347	1.18 ± 0.72	0.62 ± 0.67	−0.56 ± 0.85	0.103	23	11	5	0.017*
	Placebo	1.10 ± 0.71	0.78 ± 0.77	−0.33 ± 0.73		13	24	3	
8. Full feeling while eating	YIT10347	1.13 ± 0.92	0.69 ± 0.66	−0.44 ± 0.97	0.460	17	18	4	0.312
meals	Placebo	1.03 ± 0.86	0.75 ± 0.74	−0.28 ± 0.68		13	25	2	
11. Burping	YIT10347	1.67 ± 1.24	1.05 ± 1.02	−0.62 ± 0.71	0.084†	19	20	0	0.052†
	Placebo	1.73 ± 1.26	1.35 ± 1.17	−0.38 ± 0.87		11	26	3	
13. Postprandial epigastric	YIT10347	0.51 ± 0.68	0.13 ± 0.34	−0.38 ± 0.67	0.047*	15	22	2	0.113
pain	Placebo	0.43 ± 0.71	0.35 ± 0.62	−0.08 ± 0.69		9	24	7	
14. Epigastric pain before	YIT10347	0.64 ± 0.78	0.31 ± 0.57	−0.33 ± 0.66	0.777	13	24	2	0.911
meals	Placebo	0.83 ± 0.93	0.55 ± 0.90	−0.28 ± 0.64		13	24	3	

[1]Data are expressed as the mean ± SD or number of subjects. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. Subjects were asked to report their symptoms about the past week from "before ingestion" (wk 0) and "after ingestion" (wk 4).

[2]Total score = sum of the scores for the 14 individual questions, each of which was scored as follows: never = 0; occasionally = 1; sometimes = 2; often = 3; and always = 4.

[3]Relief rate = numbers of participants whose symptoms were alleviated, did not change, or deteriorated according to the "before ingestion" and "after ingestion" scores.

†$P < 0.1$, *$P < 0.05$.

the YIT10347 and placebo groups, respectively. Many of the participants scored zero for this symptom in the "before ingestion" period, making it difficult to detect a difference in relief rate. However, the average score of the 17 participants with postprandial epigastric pain symptoms in the YIT10347 group changed drastically from 1.18 to 0.18. On the other hand, 32 and 33 participants had postprandial discomfort symptoms in the YIT10347 and placebo groups, respectively. Because over 80% of all participants had felt this symptom in the "before ingestion" period, the difference in the relief rate was clear.

This study enrolled healthy adults who had temporary upper GI symptoms. A score of 8 on the m-FSSG is often used as a cutoff for screening participants with upper GI symptoms (Kusano et al., 2012; Tominaga et al., 2014). However, to exclude participants with chronic symptoms, the Rome IV classification was used, which comprises bothersome postprandial fullness, bothersome early satiety, bothersome epigastric pain, and bothersome epigastric burning during the preceding 6-mo period (or more), with such symptoms occurring regularly during the last 3-mo period.

A previous double-blinded, placebo-controlled, parallel trial found that daily consumption of YIT10347 helps to improve upper GI symptoms in patients with *H. pylori*-associated gastritis (Miki et al., 2007). Additionally, an open-label trial found beneficial effects on

Table 3. Overall, upper, and lower gastrointestinal (GI) score change and relief rate of Gastrointestinal Symptom Rating Scale (per-protocol set)[1]

		Score change[2]				Relief rate[3]			
Symptom (items)	Group	Wk 0	Wk 4	Δ (Wk 4 – 0)	*P*-value Wilcoxon	Alleviate	No change	Deteriorate	*P*-value Chi-squared
Overall	YIT10347	2.44 ± 0.76	1.77 ± 0.50	−0.67 ± 0.65	0.361	35	3	1	0.016*
	Placebo	2.39 ± 0.67	1.93 ± 0.53	−0.46 ± 0.79		28	2	10	
Upper GI (1–9)	YIT10347	2.57 ± 0.64	1.84 ± 0.49	−0.72 ± 0.53	0.089†	36	0	3	0.026*
	Placebo	2.47 ± 0.69	2.02 ± 0.66	−0.45 ± 0.80		28	4	8	
RS (2, 3)	YIT10347	2.45 ± 0.90	1.62 ± 0.54	−0.83 ± 0.82	0.112	27	8	4	0.427
	Placebo	2.18 ± 0.92	1.73 ± 0.82	−0.45 ± 1.16		23	9	8	
AP (1, 4, 5)	YIT10347	2.25 ± 0.70	1.56 ± 0.48	−0.68 ± 0.67	0.104	33	3	3	0.129
	Placebo	2.13 ± 0.76	1.82 ± 0.98	−0.31 ± 0.98		26	6	8	
IS (6, 7, 8, 9)	YIT10347	2.87 ± 0.79	2.17 ± 0.82	−0.70 ± 0.73	0.203	31	4	4	0.332
	Placebo	2.88 ± 1.00	2.32 ± 0.80	−0.56 ± 0.87		28	3	9	
1. Abdominal pain	YIT10347	2.62 ± 0.96	1.79 ± 0.73	−0.82 ± 1.07	0.097†	24	12	3	0.440
	Placebo	2.25 ± 0.98	1.88 ± 1.04	−0.38 ± 1.23		19	16	5	
2. Heartburn	YIT10347	2.59 ± 1.02	1.69 ± 0.61	−0.90 ± 1.02	0.063†	24	13	2	0.085†
	Placebo	2.30 ± 1.04	1.93 ± 0.94	−0.38 ± 1.27		17	15	8	
3. Acid regurgitation	YIT10347	2.31 ± 1.13	1.54 ± 0.64	−0.77 ± 1.01	0.443	22	14	3	0.582
	Placebo	2.05 ± 1.08	1.53 ± 0.93	−0.53 ± 1.24		20	14	6	
4. Sucking sensations in epigastrium	YIT10347	2.44 ± 1.10	1.64 ± 0.74	−0.79 ± 1.08	0.280	24	11	4	0.592
	Placebo	2.43 ± 1.13	1.98 ± 1.17	−0.45 ± 1.08		21	12	7	
5. Nausea and vomiting	YIT10347	1.69 ± 1.10	1.26 ± 0.59	−0.44 ± 1.10	0.461	12	24	3	0.591
	Placebo	1.70 ± 1.07	1.60 ± 1.37	−0.10 ± 1.35		11	23	6	
6. Borborygmus	YIT10347	2.92 ± 1.04	2.05 ± 0.79	−0.87 ± 0.95	0.567	23	16	0	0.074†
	Placebo	2.93 ± 1.23	2.30 ± 1.02	−0.63 ± 1.21		21	14	5	
7. Abdominal distension	YIT10347	2.74 ± 1.14	2.13 ± 1.20	−0.62 ± 1.27	0.984	22	12	5	0.812
	Placebo	2.85 ± 1.29	2.15 ± 0.95	−0.70 ± 1.11		20	15	5	
8. Eructation	YIT10347	2.38 ± 1.09	1.85 ± 1.18	−0.54 ± 1.02	0.225	21	14	4	0.507
	Placebo	2.48 ± 1.28	2.13 ± 1.04	−0.35 ± 1.03		17	16	7	
9. Increased flatus	YIT10347	3.41 ± 1.45	2.64 ± 1.14	−0.77 ± 1.18	0.141	25	7	7	0.020*
	Placebo	3.28 ± 1.43	2.70 ± 1.09	−0.58 ± 1.41		16	19	5	
Lower GI (10–15)	YIT10347	2.26 ± 1.19	1.67 ± 0.67	−0.59 ± 1.07	1.000	27	4	8	0.320
	Placebo	2.26 ± 0.94	1.79 ± 0.58	−0.47 ± 0.99		28	1	11	
DS (11, 12, 14)	YIT10347	2.23 ± 1.54	1.63 ± 0.80	−0.60 ± 1.20	0.656	19	11	9	0.349
	Placebo	2.30 ± 1.27	1.89 ± 0.95	−0.41 ± 1.26		22	6	12	
CS (10, 13, 15)	YIT10347	2.28 ± 1.16	1.71 ± 0.92	−0.57 ± 1.22	0.688	25	8	6	0.411
	Placebo	2.22 ± 0.94	1.69 ± 0.57	−0.53 ± 1.02		28	4	8	
10. Decreased passage of stools	YIT10347	1.90 ± 1.19	1.54 ± 0.97	−0.36 ± 1.14	0.987	13	23	3	0.470
	Placebo	1.93 ± 1.14	1.63 ± 0.77	−0.30 ± 1.11		15	19	6	
11. Increased passage of stools	YIT10347	1.97 ± 1.65	1.44 ± 0.85	−0.54 ± 1.33	0.104	13	23	3	0.040*
	Placebo	1.95 ± 1.40	1.83 ± 1.34	−0.13 ± 1.49		11	17	12	
12. Loose stools	YIT10347	2.23 ± 1.58	1.74 ± 0.97	−0.49 ± 1.52	0.588	14	19	6	0.708
	Placebo	2.38 ± 1.50	1.80 ± 0.97	−0.58 ± 1.34		18	17	5	
13. Hard stools	YIT10347	1.97 ± 1.20	1.51 ± 0.97	−0.46 ± 1.35	0.633	14	19	6	0.713
	Placebo	2.05 ± 1.08	1.58 ± 0.81	−0.48 ± 1.26		17	19	4	
14. Urgent need for defecation	YIT10347	2.49 ± 1.80	1.72 ± 1.00	−0.77 ± 1.35	0.438	18	17	4	0.126
	Placebo	2.58 ± 1.66	2.05 ± 1.18	−0.53 ± 1.87		17	12	11	
15. Feeling of incomplete evacuation	YIT10347	2.97 ± 1.61	2.08 ± 1.36	−0.90 ± 1.59	0.927	22	13	4	0.649
	Placebo	2.68 ± 1.25	1.88 ± 0.85	−0.80 ± 1.38		24	10	6	

[1]Data are expressed as the mean ± SD or number of subjects. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. Subjects were asked to report their symptoms about the past week from "before ingestion" (wk 0) and "after ingestion" (wk 4).

[2]Overall score = (sum of each question score)/(number of questions, 15). Upper and lower GI symptom, reflux syndrome (RS), abdominal pain (AP), indigestion syndrome (IS), diarrhea syndrome (DS), and constipation syndrome (CS) scores = (sum of each question score)/(number of questions). Each score is on a 7-point Likert scale.

[3]Relief rate = numbers of participants whose symptoms were alleviated, did not change, or deteriorated according to the "before ingestion" and "after ingestion" scores.

†$P < 0.1$, *$P < 0.05$.

serious FGID (Urita et al., 2015) and a double-blind, placebo-controlled, crossover trial found positive effects in healthy adults (Gomi et al., 2015). However, these trials used YIT10347-fermented milk containing YIT10347 and *S. thermophilus* YIT 2021 and placebo milk without either strain as test beverages, meaning that the effects of *S. thermophilus* YIT 2021 in the active milk could not be completely excluded. In contrast, our

Table 4. Change in Profile of Mood States second edition (POMS-2) score (per-protocol set)[1]

State	Group	Score change			*P*-value Wilcoxon
		Wk 0	Wk 4	Δ (Wk 4 – 0)	
Total mood disturbance	YIT10347	47.59 ± 8.68	45.51 ± 7.41	−2.08 ± 6.93	0.683
	Placebo	47.58 ± 8.02	45.43 ± 8.47	−2.15 ± 5.48	
Anger–hostility	YIT10347	48.90 ± 9.21	46.36 ± 7.10	−2.54 ± 7.10	0.921
	Placebo	47.10 ± 7.65	45.48 ± 7.48	−1.63 ± 5.16	
Confusion–bewilderment	YIT10347	49.41 ± 10.00	47.46 ± 8.58	−1.95 ± 7.94	0.546
	Placebo	50.00 ± 9.41	47.83 ± 9.23	−2.18 ± 6.21	
Depression–dejection	YIT10347	48.13 ± 7.53	47.38 ± 6.94	−0.74 ± 6.89	0.479
	Placebo	48.45 ± 6.86	46.68 ± 6.69	−1.78 ± 5.85	
Fatigue–inertia	YIT10347	47.59 ± 7.89	45.74 ± 6.85	−1.85 ± 7.95	0.753
	Placebo	48.63 ± 8.21	47.10 ± 8.79	−1.53 ± 6.41	
Tension–anxiety	YIT10347	48.77 ± 8.24	45.72 ± 7.24	−3.05 ± 7.12	0.933
	Placebo	50.05 ± 7.64	47.20 ± 8.82	−2.85 ± 5.36	
Vigor–activity	YIT10347	54.85 ± 9.66	54.49 ± 10.15	−0.36 ± 7.28	0.844
	Placebo	55.48 ± 11.71	55.78 ± 11.22	0.30 ± 9.32	
Friendliness	YIT10347	54.79 ± 9.91	54.79 ± 10.70	0.00 ± 7.46	0.356
	Placebo	57.73 ± 10.16	56.58 ± 9.39	−1.15 ± 5.94	

[1]Data are expressed as the mean ± SD. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. Subjects were asked to report their symptoms about the past week from "before ingestion" (wk 0) and "after ingestion" (wk 4).

study used *S. thermophilus* YIT 2021-fermented milk as the milk to distinguish the effects of YIT10347 in the active milk. We used *S. thermophilus* YIT 2021-fermented milk as the placebo because we found that *S. thermophilus* YIT 2021 had no beneficial probiotic effects in a previous study (Miki et al., 2007; Gomi et al., 2013) but also did not aggravate GI symptoms. Hence, our findings clarify that daily consumption of YIT10347 has benefits in healthy Japanese adults with temporary gastric symptoms.

Our previous studies have shown that YIT10347 suppresses inflammation by regulating the nuclear factor-

Table 5. Change in Short Form Health Survey version 2 (SF-36v2) score (per-protocol set)[1]

Item	Group	Score change			*P*-value Wilcoxon
		Wk 0	Wk 4	Δ (Wk 4 – 0)	
Physical component summary	YIT10347	57.5 ± 7.6	57.5 ± 5.8	0.0 ± 5.8	0.757
	Placebo	54.2 ± 7.5	53.8 ± 6.0	−0.4 ± 6.8	
Mental component score	YIT10347	47.5 ± 10.2	50.5 ± 8.0	3.0 ± 7.6	0.600
	Placebo	50.2 ± 5.4	52.0 ± 7.3	1.7 ± 6.9	
Role–social component score	YIT10347	47.6 ± 9.7	49.3 ± 9.8	1.8 ± 9.5	0.118
	Placebo	52.1 ± 6.6	51.6 ± 6.2	−0.4 ± 6.7	
Physical functioning	YIT10347	55.3 ± 3.6	55.7 ± 3.0	0.4 ± 3.1	0.301
	Placebo	53.8 ± 4.8	53.7 ± 4.9	−0.1 ± 5.4	
Role physical	YIT10347	53.3 ± 4.3	53.1 ± 6.5	−0.3 ± 6.0	0.503
	Placebo	53.6 ± 4.5	53.2 ± 4.9	−0.3 ± 4.4	
Bodily pain	YIT10347	49.3 ± 10.6	54.7 ± 7.1	5.4 ± 11.0	0.073†
	Placebo	53.0 ± 8.5	54.0 ± 7.0	1.0 ± 9.0	
General health	YIT10347	55.2 ± 7.9	56.0 ± 8.3	0.8 ± 5.9	0.862
	Placebo	54.2 ± 6.6	54.4 ± 7.5	0.2 ± 5.3	
Vitality	YIT10347	47.0 ± 9.1	48.8 ± 8.2	1.8 ± 8.6	0.960
	Placebo	49.0 ± 7.2	50.8 ± 8.6	1.8 ± 8.3	
Social functioning	YIT10347	47.9 ± 10.7	51.1 ± 9.8	3.1 ± 11.1	0.208
	Placebo	53.6 ± 6.7	54.6 ± 4.3	1.0 ± 6.6	
Role emotional	YIT10347	49.6 ± 7.4	52.5 ± 7.0	3.0 ± 8.9	0.055†
	Placebo	52.4 ± 6.5	51.8 ± 7.0	−0.6 ± 7.3	
Mental health	YIT10347	48.4 ± 10.3	51.3 ± 8.0	3.0 ± 9.7	0.337
	Placebo	51.6 ± 6.8	52.6 ± 6.4	1.0 ± 6.1	

[1]Data are expressed as the mean ± SD. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. Subjects were asked to report their symptoms about the past week from "before ingestion" (wk 0) and "after ingestion" (wk 4).
†$P < 0.1$.

κB signaling pathway in human gastric epithelial cells in vitro (Shirasawa et al., 2010), alleviates drug-induced acute gastric injury via stimulated production of gastric mucin in an animal model (Gomi et al., 2013), and survives in a live state on the human gastric mucosa for 2 h after a single consumption via strong adherence to the gastric mucosa (Shibahara-Sone et al., 2016). Functional dyspepsia is characterized by chronic abdominal complaints without a structural or biochemical cause that could explain the symptoms. In addition, gastric pain in functional dyspepsia may be associated with hyperesthesia. It has been hypothesized that, in healthy adults, YIT10347 exerts beneficial effects on gastric symptoms such as postprandial discomfort and postprandial epigastric pain by stimulating the production of gastric mucin and other gastrointestinal or neuropeptide hormones to improve gastroduodenal function and relieve visceral hypersensitivity via signaling induced by its adherence to the gastric mucosa. In other words, YIT10347 is thought to maintain normal gastric function.

A previous open-label trial found that daily consumption of YIT10347 improves some subjective psychological symptoms and POMS scores (decreasing "anger–hostility" subscale scores and increasing "vigor" subscale scores) and reduces salivary cortisol levels (Urita et al., 2015). However, we detected no significant differences in the levels or relief rates of these parameters or gastric emptying in this trial. One reasonable explanation for the differences in results between the 2 trials is that the participants in this trial—all healthy adults—had normal levels of these parameters. Further study is necessary to clarify the effects of YIT10347 on mental parameters and gastric emptying in patients with FGID in a randomized, double-blind, placebo-controlled, parallel comparative trial.

To better understand the effects of YIT10347 on temporary gastric symptoms in healthy adults, subgroup analyses were conducted based on the baseline scores of the m-FSSG (Table 7) and GSRS (Table 8) in the PPS population. Interestingly, we detected no significant differences in changes in scores of all symptoms between the 2 groups in participants who had higher-than-median GSRS symptom scores at baseline. However, the YIT10347 group had significantly greater relief in overall, upper GI symptoms, abdominal pain, and indigestion scores of the GSRS compared with the placebo group in participants who had lower-than-median scores for the GSRS at baseline. In contrast, subgroup analysis based on the baseline score of the m-FSSG did not detect clear differences between the 2 groups, although the YIT10347 group had a tendency for relief in the total m-FSSG score compared with the placebo group ($P = 0.051$). Additionally, the YIT10347 group had significantly greater relief rates for overall and upper GI symptoms and for abdominal pain of the GSRS than the placebo group in participants who had a lower-than-median score for each symptom in the GSRS at baseline (data not shown).

Placebo effects are frequently observed in clinical trials of functional dyspepsia patients. These observations suggest that participants with mild gastric symptoms at baseline had a lesser placebo effect in this trial and were suitable responders to YIT10347, with both preventive and relief benefits. However, this does not mean that YIT10347 has no effect on subjects with severe symptoms. Indeed, the score change of the severe symptom group was higher than that of the mild symptom group. In the severe symptom group, the score change of the placebo group was similarly high, so there were no significant differences between the YIT10347 and placebo groups. This indicates that subjects with severe symptoms might more readily show psychological placebo effects. In a previous study (Urita et al., 2015), continuous consumption of fermented milk containing YIT10347 improved gastrointestinal symptoms in FGID patients, even though all participants with repeated medical care had seen no improvement. Thus, we consider that YIT10347 has potential for upper GI symptom improvement regardless of the presence or absence of a placebo effect.

One limitation of this study is that, even though we found that daily consumption of YIT10347-fermented milk helped to relieve lower GI symptoms such as flatus

Table 6. Change in salivary cortisol and gastric emptying time (per-protocol set)[1]

Item	Group	Change			*P*-value Wilcoxon
		Wk 0	Wk 4	Δ (Wk 4 – 0)	
Salivary cortisol, μg/dL	YIT10347	0.29 ± 0.22	0.32 ± 0.24	0.03 ± 0.13	0.404
	Placebo	0.22 ± 0.09	0.23 ± 0.11	0.01 ± 0.10	
Gastric emptying,[2] $^{13}CO_2$-T_{max}, min	YIT10347	48.72 ± 9.78	51.79 ± 10.73	3.08 ± 9.22	0.259
	Placebo	50.77 ± 12.65	51.03 ± 11.42	0.26 ± 12.46	

[1]Data are expressed as the mean ± SD. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk.

[2]T_{max} was the time at maximal $^{13}CO_2$ excretion.

Table 7. Subgroup analysis: Score change of modified Frequency Scale for Symptoms of Gastroesophageal Reflux Disease (m-FSSG) (per-protocol set)[1]

		Participants with low m-FSSG score (<15) at wk 0 (YIT10347, n = 20; placebo, n = 19)				Participants with high m-FSSG score (≥15) at wk 0 (YIT10347, n = 20; placebo, n = 19)			
Item[2]	Group	Wk 0	Wk 4	Δ (Wk 4 – 0)	*P*-value Wilcoxon	Wk 0	Wk 4	Δ (Wk 4 – 0)	*P*-value Wilcoxon
Total	YIT10347	11.55 ± 1.79	7.80 ± 4.12	−3.75 ± 3.77	0.051†	19.37 ± 3.32	11.58 ± 5.91	−7.79 ± 6.07	0.713
	Placebo	11.00 ± 2.11	9.21 ± 3.26	−1.79 ± 3.31		18.62 ± 2.99	11.81 ± 6.50	−6.81 ± 6.56	
Reflux syndrome	YIT10347	4.80 ± 2.14	3.25 ± 2.92	−1.55 ± 2.42	0.253	8.32 ± 2.00	4.95 ± 3.46	−3.37 ± 3.48	0.786
	Placebo	4.21 ± 1.44	3.47 ± 1.58	−0.74 ± 2.10		8.14 ± 2.94	5.10 ± 3.39	−3.05 ± 3.20	
Acid-related dyspepsia	YIT10347	6.75 ± 1.89	4.55 ± 1.88	−2.20 ± 2.69	0.164	11.05 ± 1.99	6.63 ± 2.97	−4.42 ± 2.99	0.586
	Placebo	6.79 ± 1.55	5.74 ± 2.23	−1.05 ± 1.90		10.48 ± 2.18	6.71 ± 3.73	−3.76 ± 3.91	

[1]Data are expressed as the mean ± SD. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. Subjects were asked to report their symptoms about the past week from "before ingestion" (wk 0) and "after ingestion" (wk 4).

[2]Total, reflux syndrome, and acid-related dyspepsia score = sum of the score of each question (never = 0; occasionally = 1; sometimes = 2; often = 3; and always = 4).

†$P < 0.1$.

and diarrhea in a GSRS evaluation, subgroup analyses of the GSRS and m-FSSG showed that beneficial effects were obtained for upper GI symptoms and not lower GI symptoms. In fact, evidence for the beneficial effect of YIT10347 on lower GI symptoms in clinical trials remains poor. Therefore, further clinical trials with larger numbers of suitable participants are necessary to clarify the beneficial effects of YIT10347 on both upper and lower GI symptoms. Moreover, further studies are necessary to understand the detailed mechanism of action of YIT10347 in both upper and lower GI symptoms.

CONCLUSIONS

These findings suggest that daily consumption of milk fermented with *B. bifidum* YIT 10347 helps to relieve GI discomfort and symptoms such as postprandial discomfort and epigastric pain in healthy adults, with

Table 8. Subgroup analysis: Score change of Gastrointestinal Symptom Rating Scale (GSRS) (per-protocol set)[1]

		Participants with low GSRS score (<34) at wk 0 (YIT10347, n = 21; placebo, n = 17)				Participants with high GSRS score (≥34) at wk 0 (YIT10347, n = 18; placebo, n = 23)			
Item[2]	Group	Wk 0	Wk 4	Δ (Wk 4 – 0)	*P*-value Wilcoxon	Wk 0	Wk 4	Δ (Wk 4 – 0)	*P*-value Wilcoxon
Overall	YIT10347	1.90 ± 0.22	1.51 ± 0.21	−0.39 ± 0.30	0.003**	3.08 ± 0.66	2.08 ± 0.57	−1.00 ± 0.79	0.772
	Placebo	1.78 ± 0.25	1.84 ± 0.63	0.05 ± 0.61		2.83 ± 0.51	1.99 ± 0.45	−0.84 ± 0.69	
Upper GI symptoms	YIT10347	2.12 ± 0.31	1.62 ± 0.29	−0.50 ± 0.32	<0.001**	3.04 ± 0.58	2.08 ± 0.54	−0.96 ± 0.63	0.616
	Placebo	1.88 ± 0.33	1.94 ± 0.75	0.07 ± 0.61		2.87 ± 0.57	2.07 ± 0.59	−0.80 ± 0.74	
RS	YIT10347	1.95 ± 0.66	1.45 ± 0.51	−0.50 ± 0.77	0.119	2.97 ± 0.84	1.79 ± 0.51	−1.18 ± 0.77	0.141
	Placebo	1.63 ± 0.71	1.72 ± 0.81	0.09 ± 1.10		2.54 ± 0.90	1.73 ± 0.85	−0.81 ± 1.09	
AP	YIT10347	1.90 ± 0.58	1.32 ± 0.35	−0.58 ± 0.52	0.001**	2.61 ± 0.62	1.82 ± 0.49	−0.79 ± 0.81	0.946
	Placebo	1.65 ± 0.46	1.83 ± 1.25	0.19 ± 1.03		2.44 ± 0.78	1.81 ± 0.76	−0.64 ± 0.79	
IS	YIT10347	2.38 ± 0.48	1.94 ± 0.47	−0.44 ± 0.55	0.020*	3.38 ± 0.77	2.41 ± 1.05	−0.97 ± 0.84	0.596
	Placebo	2.17 ± 0.61	2.14 ± 0.79	−0.03 ± 0.46		3.35 ± 0.89	2.44 ± 0.80	−0.92 ± 0.91	
Lower GI symptoms	YIT10347	1.53 ± 0.40	1.37 ± 0.34	−0.16 ± 0.44	0.384	3.03 ± 1.24	1.99 ± 0.76	−1.04 ± 1.36	0.762
	Placebo	1.58 ± 0.36	1.73 ± 0.59	0.15 ± 0.79		2.71 ± 0.96	1.83 ± 0.58	−0.88 ± 0.94	
DS	YIT10347	1.47 ± 0.54	1.33 ± 0.43	−0.13 ± 0.57	0.464	3.04 ± 1.86	1.95 ± 0.97	−1.09 ± 1.52	0.626
	Placebo	1.46 ± 0.52	1.67 ± 0.77	0.21 ± 0.83		2.86 ± 1.33	2.04 ± 1.04	−0.82 ± 1.39	
CS	YIT10347	1.58 ± 0.63	1.40 ± 0.66	−0.18 ± 0.68	0.644	3.02 ± 1.10	2.04 ± 1.03	−0.98 ± 1.55	0.958
	Placebo	1.71 ± 0.52	1.79 ± 0.63	0.08 ± 0.88		2.56 ± 1.03	1.63 ± 0.53	−0.93 ± 0.92	

[1]Data are expressed as the mean ± SD. Subjects consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT 10347 (YIT10347 group) or placebo fermented milk daily for 4 wk. Subjects were asked to report their symptoms about the past week from "before ingestion" (wk 0) and "after ingestion" (wk 4).

[2]Overall, upper and lower gastrointestinal (GI) symptoms, reflux syndrome (RS), abdominal pain (AP), indigestion syndrome (IS), diarrhea syndrome (DS), and constipation syndrome (CS) scores = (sum of each question score)/(number of questions). Each score is on a 7-point Likert scale.

*$P < 0.05$, **$P < 0.01$.

no risk of side effects. The approach is less burdensome and less expensive than medical treatment.

ACKNOWLEDGMENTS

We thank all participants in this trial. We also thank Daisuke Nozaki and Yuki Kataoka of Yakult Honsha Co. Ltd. (Tokyo, Japan) for the production of the test beverages and the staff of KSO Corporation (Tokyo, Japan) for managing this trial and its participants and analyzing the data. The clinical trials, designed by authors, were performed under the management of KSO Corporation with the sponsorship and provision of test beverages from Yakult Honsha Co. Ltd. The sponsor provided salaries for A. Gomi, K. Yamaji, O. Watanabe, M. Yoshioka, and K. Miyazaki but did not have any additional role in data collection or interpretation. The remaining authors declare no potential conflicts of interest with respect to the authorship and publication of this article.

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