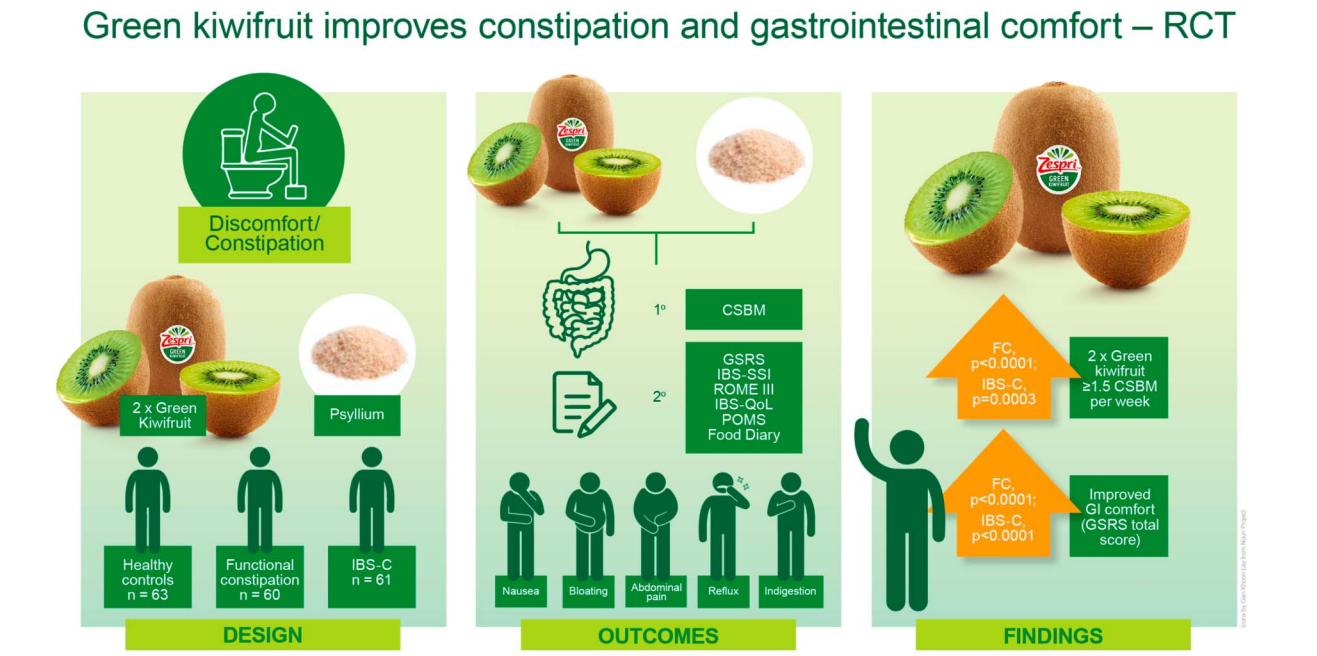
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Consumption of 2 Green Kiwifruits Daily Improves Constipation and Abdominal Comfort—Results of an International Multicenter Randomized Controlled Trial

Richard Gearry, MD, PhD*[1], Shin Fukudo, MD, PhD*[2,3], Giovanni Barbara, MD*[4], Barbara Kuhn-Sherlock, PhD[5], Juliet Ansell, PhD[6], Paul Blatchford, PhD[6], Sarah Eady, MSc[7], Alison Wallace, PhD[7], Christine Butts, PhD[7], Cesare Cremon, MD[4], Maria Raffaella Barbaro, PhD[4], Isabella Pagano, MD[4], Yohei Okawa, PhD[2], Tomohiko Muratubaki, PhD[2], Tomoko Okamoto, PhD[8], Mikiko Fuda, MS[9], Yuka Endo, MD[3], Michiko Kano, MD, PhD[2], Motoyori Kanazawa, MD, PhD[2,3], Naoki Nakaya, PhD[10], Kumi Nakaya, PhD[10] and Lynley Drummond, BTech (Hons)[11]



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INTRODUCTION: **Consumption of green kiwifruit is known to relieve constipation. Previous studies have also reported improvements in gastrointestinal (GI) comfort. We investigated the effect of consuming green kiwifruit on GI function and comfort.**

[1]Department of Medicine, University of Otago, Christchurch, New Zealand; [2]Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; [3]Department of Psychosomatic Medicine, Tohoku University Hospital, Sendai, Japan; [4]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [5]BKS Consulting Limited, Hamilton, Waikato, New Zealand; [6]Zespri International Limited, Tauranga, New Zealand; [7]The New Zealand Institute for Plant and Food Research Limited, Palmerston North and Christchurch, New Zealand; [8]Department of Nutrition, Sapporo University of Health Sciences, Sapporo, Japan; [9]Department of Clinical Nutrition, Tohoku University Hospital, Sendai, Japan; [10]Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan; [11]Drummond Food Science Advisory Limited, Killinchy, Canterbury, New Zealand.
Correspondence: Richard Gearry, MD, PhD. E-mail: richard.gearry@otago.ac.nz.
*Richard Gearry, Shin Fukudo, and Giovanni Barbara contributed equally to this work.
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METHODS: **Participants included healthy controls (n = 63), patients with functional constipation (FC, n = 60), and patients with constipation-predominant irritable bowel syndrome (IBS-C, n = 61) randomly assigned to consume 2 green kiwifruits or psyllium (7.5 g) per day for 4 weeks, followed by a 4-week washout, and then the other treatment for 4 weeks. The primary outcome was the number of complete spontaneous bowel movements (CSBM) per week. Secondary outcomes included GI comfort which was measured using the GI symptom rating scale, a validated instrument. Data (intent-to-treat) were analyzed as difference from baseline using repeated measures analysis of variance suitable for AB/BA crossover design.**

RESULTS: **Consumption of green kiwifruit was associated with a clinically relevant increase of ≥ 1.5 CSBM per week (FC; 1.53, $P < 0.0001$, IBS-C; 1.73, $P = 0.0003$) and significantly improved measures of GI comfort (GI symptom rating scale total score) in constipated participants (FC, $P < 0.0001$; IBS-C, $P < 0.0001$). No significant adverse events were observed.**

DISCUSSION: **This study provides original evidence that the consumption of a fresh whole fruit has demonstrated clinically relevant increases in CSBM and improved measures of GI comfort in constipated populations. Green kiwifruits are a suitable dietary treatment for relief of constipation and associated GI comfort.**

KEYWORDS: Kiwifruit, constipation, irritable bowel syndrome, GI comfort

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C809

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INTRODUCTION

Functional gastrointestinal disorders (FGID), now termed disorders of gut-brain interaction, are common and troublesome, leading to significant morbidity, cost to society, and reduced quality of life (1). In the United States in 2014 alone, FGID resulted in close to 223,000 hospital admissions at an estimated cost of more than $6B USD (2). FGID include, among others, functional constipation (FC) and irritable bowel syndrome with predominant constipation (IBS-C). Recent global epidemiological survey with Rome IV criteria revealed the global prevalence of FC at 11.7% (95% confidence interval [CI] 11.4%–12.0%) and IBS-C 1.3% (95% CI 1.2%–1.4%) (3). While both FC and IBS-C are defined by constipation, patients with IBS-C also experience abdominal pain (4). Patients with FGID may have multiple symptoms including abdominal bloating and pain. Many factors contribute to the development of functional GI symptoms, including age, diet, lifestyle, medications, dysbiosis, increased intestinal permeability, low-grade intestinal inflammation, and psychological comorbidities such as anxiety and depression (5). Of individuals with constipation, only approximately 22% seek medical care and those who do are often dissatisfied with the medical therapies offered (6). Laxatives such as stool softeners, colonic stimulants, and bulking agents are commonly prescribed and are effective in increasing stool frequency and a softer stool consistency but are not universally tolerated by patients (7).

Several studies support the consumption of individual foods to improve laxation and GI comfort. A growing body of evidence suggests regular consumption of fresh green kiwifruit (*Actinidia chinensis* var. *deliciosa* "Hayward") may be of benefit (8–12). However, these studies have typically been single-centered, with relatively small cohorts, and have used nonstandardized end points. In an exploration of the potential of kiwifruit to improve upper GI symptoms, Bayer et al (13) considered a range of kiwifruit varieties and kiwifruit products. Based on GSRS outcomes, they found evidence that green kiwifruit may reduce abdominal pain and improve GI comfort, together with some evidence for the attenuation of indigestion symptoms.

In this large, multicenter, crossover, randomized controlled trial in 3 diverse populations, the effect of consuming 2 green kiwifruits daily on normalization of bowel habit and improving measures of GI comfort was investigated. The study was conducted to establish further substantive evidence that could contribute to a positive opinion on the effects of green kiwifruit from the European Food Safety Authority (EFSA) and subsequent approval of a health claim through the European Commission.

METHODS

Study design and participants

This prospective randomized, single-blinded, crossover, controlled 16-week trial was undertaken in 3 countries (New Zealand, Italy, and Japan). The effects of the daily consumption of 2 Zespri green kiwifruits (*A. chinensis* var. *deliciosa* "Hayward") compared with those of 7.5 g of psyllium for 4 weeks on parameters of bowel habit and GI comfort were determined. Two green kiwifruits, as consumed, of the grade used in this trial provided approximately 6 g of dietary fiber. The psyllium dosage (7.5 g) also provided approximately 6 g of dietary fiber. The consumption of at least 6 g of fiber provided from psyllium is known to provide a beneficial physiological effect for the normalization of bowel habit in constipated individuals (14–16). Psyllium is considered as a first-line treatment for constipation both in individuals with IBS-C and FC (17).

On enrollment, participants were randomized to consume either of the interventions. Participants were instructed to consume the kiwifruit without the skin. No other changes to their habitual diet were mandated over the study period. Psyllium was used as a positive control because it has a proven laxative effect and its use is included in international guidelines for the treatment of constipation (18,19). Furthermore, the fiber content of psyllium could be matched with that of 2 green kiwifruits. The daily time or occasion for the consumption of either intervention

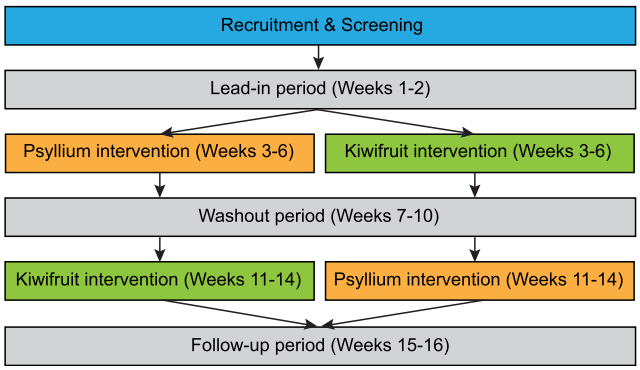


Figure 1. Crossover study design.

was not specified. After a 2-week lead-in period, participants completed a 4-week intervention period with the allocated intervention. This was followed by a 4-week washout period, after which participants crossed over to the other intervention, also consumed for 4 weeks. There was a 2-week follow-up period after the completion of the final intervention (Figure 1).

Eligible participants were adults aged between 18 and 65 years, with a body mass index (BMI) of 18–35 kg/m^2. Participants either had FC, IBS-C as defined by the Rome III diagnostic criteria (20), or were healthy controls (HC). Participants with an IBS-symptom severity index (IBS-SSI) (21) ≥300 were excluded together with those with GI alarm symptoms (20). Other exclusions were previous diagnoses of significant GI disorders or surgery and significant renal, cardiovascular, oncological, neurological, or psychiatric disease. Women who were pregnant, breastfeeding, or planning pregnancy during the study period were excluded, as were those with known kiwifruit or latex allergy. Participants with diagnosed and stable conditions requiring the use of selective serotonin reuptake inhibitors, tricyclic antidepressants, opiates, or anti-inflammatories were permitted into the trial on the condition these medications were used continually and the condition was stable for more than 3 months before study enrollment. Similarly, those with stable and controlled diabetes were permitted to participate; however, participants with fasting blood glucose concentration of ≥7.2 mmol/L were excluded. Significant deviations in full blood count, renal function, liver biochemistry, and C-reactive protein were also exclusions.

Ethics approval was granted for each participating institution, and the study was registered in each country: New Zealand (Australian New Zealand Clinical Trials Registry ACTRN12614000460606); Italy (ClinicalTrials.gov NCT02888392); and Japan (University Hospital Medical Information Network, UMIN000020090). All participants provided written informed consent. The trial was undertaken in accordance with the Declaration of Helsinki and applicable local regulations. All protocol amendments were reviewed and approved before implementation by the applicable individual institutional or national ethics committees.

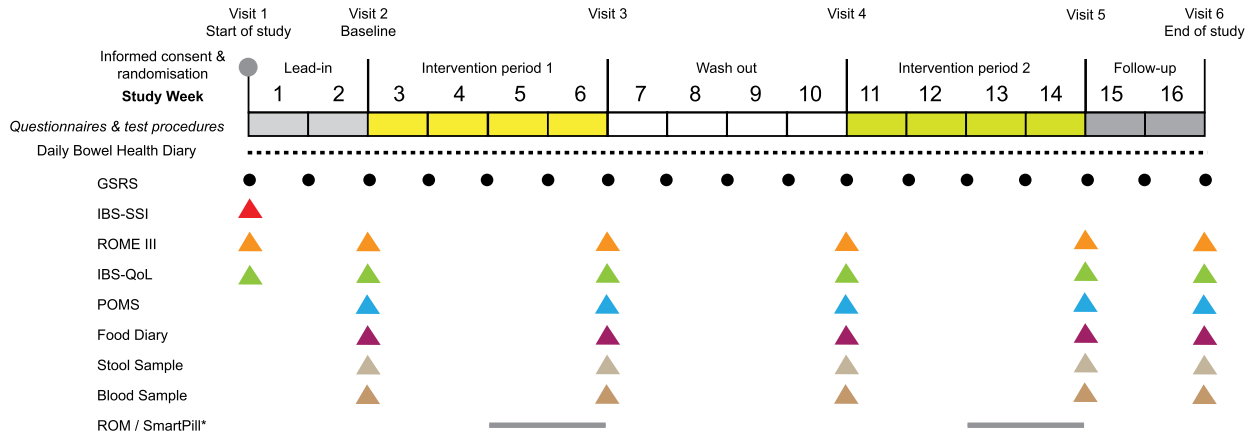
Randomization and masking

Computer-generated randomization using a stratified (country and study group) block (4 blocks of 10 per stratum) was applied to participants in Italy and Japan. New Zealand participants were randomized using a computer-generated 10-participant block design. Statisticians who generated the randomization sequences had no further role in the trial. Allocation concealment was by sealed envelope in Italy and New Zealand. Participants in New Zealand received their allocated intervention at study visits, while participants in Italy received the kiwifruit from a distribution center and the psyllium from the dispensary at S. Orsola Malpighi Hospital, Bologna. In Japan, concealed allocation was sent by an independent home delivery company who delivered the intervention foods directly to participants.

Study personnel performing participant assessments, data management and analysis, and clinical trial management were blinded to the treatments. All participants were informed that the study involved a comparison between kiwifruit and psyllium. The whole food nature of the interventions meant neither could be blinded to participants.

Procedures

This study was performed in 3 countries: Italy (Bologna), Japan (Sendai), and New Zealand (Christchurch and Palmerston North). The nature and timing of all study procedures are outlined in Figure 2. After recruitment and screening, there was a 2-week lead-in period for participants to habituate to recording



GSRS – Gastrointestinal Symptom Rating Scale; IBS-SSI – Irritable Bowel Syndrome – Symptom Severity Index; IBS-QoL – Irritable Bowel Syndrome – Quality of Life; POMS – Profile of Mood States; ROM – Radio-opaque markers. *ROM performed in Japan, SmartPill in NZ and Italy.

Figure 2. Overview of study plan and test procedures.

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daily assessments in the Daily Bowel Health Diaries (DBHD) and to provide baseline data. The DBHD asked participants to describe their bowel movements for frequency, completeness, and spontaneity of evacuation. Stool form, laxative use, and degree of straining were also recorded daily. A range of other self-reported validated questionnaires and food diaries were completed at time points throughout the study, as indicated in Figure 2. Regular compliance evaluation was possible with the collection and review of the DBHD at each visit. DBHD were issued at study visits for the 14-day period after visits. All participant information, questionnaires, and other study information were provided in English, Italian, or Japanese, as appropriate.

Blood samples were drawn at baseline and the completion of subsequent study phases for analysis at certified laboratories for biochemistry and vitamin C. Stool specimens were collected and stored at −80 °C before microbiome analysis (results to be published elsewhere).

To encourage adherence to the study intervention, excess kiwifruit was supplied for other household members to consume. Excess psyllium was returned at each study visit to assess adherence to the protocol, in addition to direct questioning of the participants. The protocol allowed for a period of ±2 days around the exact date of study period cutoff, to allow for weekends and personal schedules of participants. Visit dates were recorded in the electronic case report form. A subgroup of participants in NZ and Italy had GI transit measured using SmartPill (n = 48) or, in Japan, radio-opaque markers (n = 55) in the final 2 weeks of each intervention period.

Adverse events were captured at each study visit and between study visits, as reported by the participants in a standardized format. Two bisacodyl suppositories (5 g) were available to each participant to take as a pharmacological rescue therapy. All local study data were entered blindly into an independent, centralized study database that was monitored, verified, and managed by an independent and blinded clinical research organization (OPIS, Italy). Study monitors were appointed for each study center.

Outcome measures

The primary outcome, the number of complete spontaneous bowel movements (CSBM) per week, was recorded in the DBHD throughout the entire study period. The change in CSBM recorded in the fourth week of each intervention period was compared with that in the baseline period. For each intervention, the baseline value was defined as the average number of CSBM in the 2-week lead-in period before intervention 1, and in week 4 of the washout period before intervention 2. For constipated individuals, an increase of >1 CSBM per week is clinically relevant for improving constipation (22,23). This trial set a primary outcome of an increase of ≥ 1.5 CSBM per week, based on previously published data for kiwifruit and to ensure outcomes were beyond the regulatory threshold requirement of effective treatments for constipation (9).

Key secondary outcomes were GI comfort (GI symptom rating scale [GSRS] (24)), stool consistency (Bristol stool form scale (25)), and degree of straining (scale of 1–3 recorded in the DBHD). IBS-associated quality of life (QoL) was assessed by the IBS-QoL questionnaire (26), at the end of each study period, together with appropriate modules from the Rome III Diagnostic Questionnaire for the Adult FGID's to monitor constipation status and the Profile of Mood State Standard questionnaire (27) to determine changes in mood. The severity of GI symptoms was measured by the IBS-SSI at study entry (21).

Plasma vitamin C is an established marker of kiwifruit consumption and was used as an indicator of compliance (28). Three-day food diaries were evaluated to identify significant changes in diet during the study. In a subgroup from each center, GI transit time was reported for total and segmental gut using SmartPill (New Zealand and Italy) (29,30), or radio-opaque marker (Japan) (31). Adverse events were evaluated by the principal investigator at each center for severity and whether they were likely to be attributable to the intervention. All adverse events were reviewed by an independent, blinded clinical monitor.

Statistical analysis

The trial sample size was determined using primary outcome data (CSBM) from the earlier trial of Chan et al (9) to provide the inputs for power calculation. The study was powered, for each study center, to detect an increase of at least 1.5 CSBM per week in each of the constipated groups (FC and IBS-C), compared with the baseline period after the kiwifruit intervention. The final sample size calculation was based on using a 2-sided, paired *t* test for the comparison of kiwifruit vs baseline. Chan et al (9) reported an SD of 2.6 for weekly bowel movements in constipated patients. Assuming a strong within-subject correlation for CSBM of $r = 0.75$, the SD of the change in CSBM was calculated as 1.84. To detect a change in CSBM of 1.5 per week, with 1.84 SD of the change, 90% power, and 5% significance, 16 patients per group were required to complete the trial. Allowing for a 25% dropout rate, 20 participants were recruited for each of 3 subpopulations (HC, FC, and IBS-C), or a total of 60 participants per study center, with 180 across all 3 study centers. While the study was powered to detect an increase of ≥ 1.5 CSBM per week from baseline in each of the constipated cohorts (FC and IBS-C), it was acknowledged that based on clinical relevance, these 2 groups could potentially be grouped as a single cohort, further increasing the power of the study. Sample size calculations were completed using the University of California San Francisco sample size calculator (http://www.sample-size.net/sample-size-study-paired-t-test/).

All data for analyses were transferred to the blinded study statistician directly through secure linkages from the electronic case report form database (OPIS, Italy) as SAS files. Statistical analysis was completed using SAS software, version 9.3 (SAS 9.3 2002–2010 SAS Institute, Cary, NC, on X64_7PRO platform under Windows 7 Enterprise 2009 Microsoft) and SAS software, version 9.4 (SAS 9.4 2016 SAS Institute, Cary, NC, on the X64_10PRO platform under Windows 10 Enterprise 2015 Microsoft). All data were analyzed based on intention-to-treat basis.

Data were analyzed separately for each participant group HC, FC, and IBS-C and for the combined constipated group (FC + IBS-C). Participant demographics and baseline characteristics are presented as mean, SD, and range for continuous variables and counts and percentages for categorical variables (Table 1). Continuous end points were analyzed as difference from baseline (lead-in for intervention 1 and week 4 of washout for intervention 2) using a mixed models approach to repeated measures analysis of variance (Proc Mixed, SAS/STAT 14.1) and allowing for treatment heterogeneous variance. Categorical end points were analyzed using cross-tabulation and the χ^2 test of independence. Significance was declared if $P < 0.05$. The model included center, intervention sequence, trial phase, and treatment as fixed effects and subject as random effect. Treatment was repeated within subjects, and the covariance pattern model was UNR (unstructured correlations).

Table 1. Participant demographics and baseline characteristics of study population

Demographic/characteristic	Total study (n = 184)	Full study cohort			
		HC (n = 63)	FC (n = 60)	IBS-C (n = 61)	Combined constipation group (IBS-C and FC) (n = 121)
Gender, n (%)					
Female	136 (73.9)	37 (58.7)	43 (71.7)	56 (91.8)	99 (81.8)
Male	48 (26.1)	26 (41.3)	17 (28.3)	5 (8.2)	22 (18.2)
Age, yr					
Mean (SD)	35.5 (14.58)	34.3 (13.54)	38.1 (15.56)	40.2 (14.22)	39.2 (14.88)
Range	18–65	19–64	18–65	19–64	18–65
Ethnicity, n (%)					
European	109 (59.2)	37 (58.7)	36 (60.0)	36 (59.0)	72 (59.5)
Māori	3 (1.6)	2 (3.2)	1 (1.7)	0 (0.0)	1 (0.8)
Indian	1 (0.5)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese	64 (34.9)	20 (31.7)	22 (36.7)	22 (36.1)	44 (36.4)
Hispanic/Latino	2 (1.1)	1 (1.6)	1 (1.7)	0 (0.0)	1 (0.8)
Other	5 (2.7)	2 (3.2)	0 (0.0)	3 (4.9)	3 (2.5)
Weight, kg					
Mean (SD)	64.4 (14.73)	66.5 (15.29)	65.5 (16.53)	61.0 (11.55)	63.2 (14.36)
Range	54.0–128.0	42.0–101.7	42.0–128.0	42.0–100.0	42–128
Height, m					
Mean (SD)	1.67 (0.093)	1.70 (0.105)	1.67 (0.089)	1.63 (0.071)	1.65 (0.082)
Range	1.46–1.95	1.51–1.95	1.46–1.90	1.51–1.82	1.46–1.90
Body mass index, kg/m^2					
Mean (SD)	23.0 (4.00)	22.9 (3.95)	23.4 (4.36)	22.9 (3.70)	23.1 (4.03)
Range	16.6–35.5	16.9–35.3	16.6–35.5	17.5–35.1	16.6–35.5
IBS-SSI score					
Mean (SD)	113 (82.9)	52 (43.5)	115 (69.4)	173 (81.5)	145 (80.8)
Range	0–345	0–143	5–345	0–345	0–345

FC, functional constipation; HC, healthy controls; IBS-C, irritable bowel syndrome with predominant constipation; IBS-SSI, Irritable bowel syndrome–symptom severity index.

To deal with multiple secondary end points, a hierarchical procedure was used, where no numerical adjustment of each single hypothesis test was necessary. However, significant effects could not be declared for end points that have a rank lower than or equal to that variable whose null hypothesis was the first that could not be rejected (32).

RESULTS

Between June 12, 2014, and June 17, 2017, 184 of 667 screened participants (63 HC, 60 FC, and 61 IBS-C) were enrolled into the trial across the 3 study centers (Figure 3).

Participant demographics and characteristics are summarized in Table 1. More detailed demographics by study center are listed in Supplementary Digital Content (see Supplementary Table S1, http://links.lww.com/AJG/C809). In the full cohort, there were significantly more women than men (136 vs 48, $P < 0.01$). This pattern was consistent across the 3 study centers and in line with the known higher prevalence of FC and IBS-C in women. Statistically significant differences ($P < 0.01$) between study centers were observed for participant age (years, mean [SD]: New Zealand 44.8 [14.3]; Italy 36.9 [12.8]; and Japan 30.5 [13.0]) and BMI (kg/m^2, mean [SD]: New Zealand 25.4 [4.3]; Italy 23.0 [3.7]; and Japan 20.6 [2.0]). Differences in the BMI of study populations of each country reflect national mean BMI (kg/m^2, mean [± standard error]) data, as reported by the World Health Organisation (New Zealand 28.2 [27.9–28.5], Italy 26.3 [25.7–26.8], and Japan 22.8 [22.5–23.2]), for adults older than 18 years, 2016, crude data) (33). Age and BMI were not predictors of any outcome measures. While the baseline demographic and anthropometric data suggested some heterogeneity between the study center populations, which is not unexpected, less difference was observed within each of the bowel health groupings (HC, FC, and IBS-C) when the total study cohort was combined; hence, differences at the study center level did not affect the study results. Furthermore, as detailed in the Statistical Analysis section, the model used to analyze the study data included center, intervention sequence, trial phase, and treatment as fixed effects and subject as random effect. The

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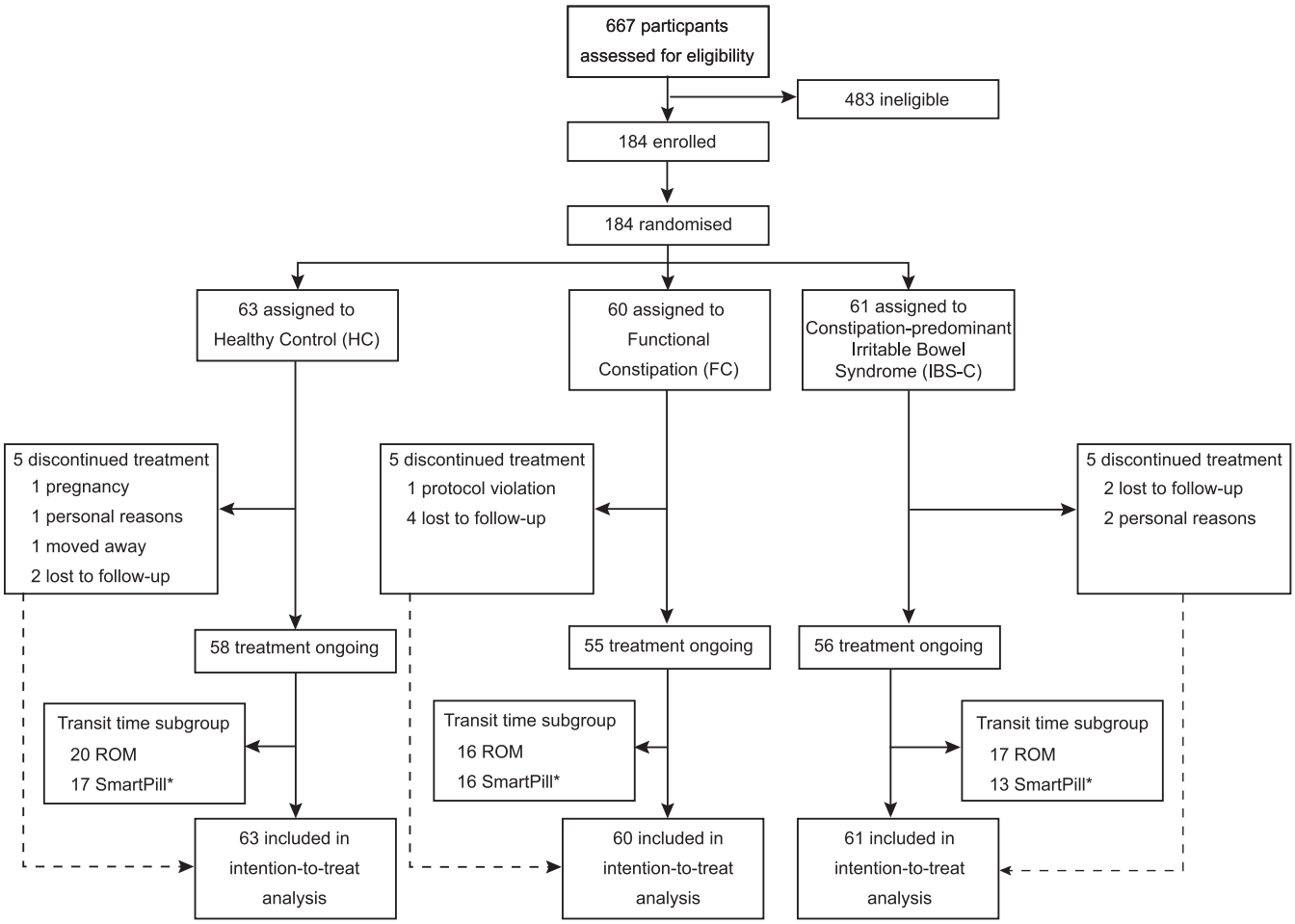


Figure 3. Consolidated Standards of Reporting Trials.

analyzed data showed there were no significant differences in the outcomes between study sites.

Overall study compliance was high. Of the 184 participants entering the study, 169 (92%) completed the study, and compliance based on diary completion was more than 80%. Compliance with the intervention (kiwifruit or psyllium) was reported at the completion of each intervention phase. Aside from 1 participant recorded as having not complied with the psyllium intervention, based on a strong sensory (taste and texture) dislike of the psyllium, all other participants complied with the interventions. The markedly different organoleptic properties of psyllium and kiwifruit did not affect study compliance, and formal preference data were not collected as a part of the study design.

The primary outcome of an increase of $\geq$ 1.5 CSBM per week was achieved in the FC (mean 1.53, $P < 0.0001$), IBS-C (mean 1.73, $P = 0.0003$), and combined FC + IBS-C (mean 1.69, $P < 0.0001$) groups after the kiwifruit intervention. After the psyllium intervention, the primary outcome was observed only in the IBS-C (mean 1.87, $P = 0.0051$) group (Table 2). In the combined FC and IBS-C group, the effect of 2 green kiwifruits per day was significantly greater than the effect of psyllium ($P = 0.038$) (Figure 4).

Repeated measures analysis showed both interventions resulted in significant and sustained increases in the weekly frequency of CSBM in all study groups, with that for the combined constipated group shown in Figure 5. There were no significant differences in the frequencies between the kiwifruit and psyllium treatments in any week. Order effects were included in the model, and the results showed that there was no significant crossover effect. Although not specified in the trial analysis plan, responder rates (22) of the FC and IBS-C cohorts were determined *post hoc* (see Supplementary Table S3, http://links.lww.com/AJG/C809).

Daily consumption of 2 green kiwifruits was associated with a significant reduction, compared with that at baseline, in overall GI symptoms, as determined by the GSRS total score for FC, IBS-C, and the combined FC + IBS-C group (Figure 6). Consumption of psyllium was associated with a significant reduction in GI symptoms in the IBS-C group only. Consumption of 2 green kiwifruits was associated with a significant reduction in GI symptoms for the FC and combined FC-IBS-C groups compared with psyllium.

Individual GSRS domain scores and other secondary outcomes are summarized in Table 2. Kiwifruit consumption was associated with significant changes from baseline constipation scores in the FC ($P < 0.0001$), IBS-C ($P < 0.0001$), and combined constipation ($P < 0.0001$) groups, compared with psyllium, where the changes from baseline were significant in the IBS-C ($P < 0.0001$) and combined constipation ($P < 0.0001$) groups.

Table 2. Effect of green kiwifruit (KF) and psyllium (PS) on primary and secondary outcomes

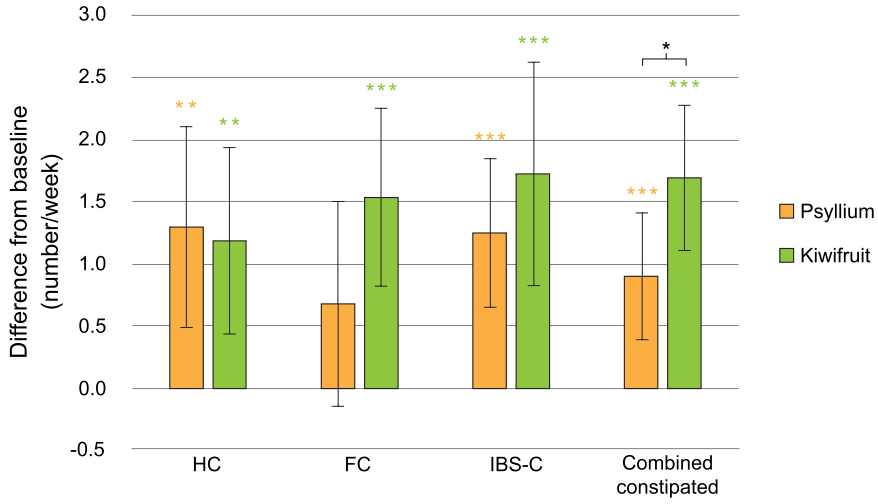
Outcome	Measure	Study group	Kiwifruit		Psyllium		KF vs PS
			Mean difference	p value	Mean difference	p value	*p* value
CSBM	Per wk	HC	1.19	0.0022	1.30	0.0022	0.8396
		FC	1.53	<0.0001	0.67	0.1125	0.0624
		IBS-C	1.73	0.0003	1.25	0.0001	0.3940
		Combined constipation	1.69	<0.0001	0.90	0.0007	0.0380
GSRS total	Overall score	HC	−0.08	0.2186	−0.02	0.9851	0.4949
		FC	−0.22	<0.0001	−0.04	0.6549	0.0436
		IBS-C	−0.36	<0.0001	−0.17	0.0420	0.0504
		Combined constipation	−0.30	<0.0001	−0.10	0.0796	0.0027
GSRS	Constipation score	HC	−0.10	0.2039	0.06	0.5146	0.2061
		FC	−0.66	<0.0001	−0.26	0.0544	0.0259
		IBS-C	−0.8	<0.0001	−0.69	<0.0001	0.4588
		Combined constipation	−0.77	<0.0001	−0.48	<0.0001	0.0237
	Abdominal pain score	HC	−0.02	0.7738	−0.03	0.6432	0.9382
		FC	−0.07	0.5406	0.05	0.6403	0.4445
		IBS-C	−0.30	0.0237	−0.06	0.6189	0.1398
		Combined constipation	−0.19	0.0267	0.00	0.9820	0.0833
	Indigestion score	HC	−0.16	0.0277	−0.05	0.4960	0.2502
		FC	−0.22	0.0173	0.07	0.5751	0.0425
		IBS-C	−0.40	0.0016	−0.12	0.3061	0.0832
		Combined constipation	−0.31	<0.0001	−0.01	0.8620	0.0047
BSFS	Score	HC	0.40	0.0036	−0.04	0.7392	0.0152
		FC	0.49	0.0008	0.18	0.2432	0.1399
		IBS-C	0.71	<0.0001	0.37	0.0011	0.0462
		Combined constipation	0.60	<0.0001	0.27	0.0042	0.0119
Straining	Score	HC	−0.01	0.4319	0.00	0.8947	0.5916
		FC	−0.14	0.0003	−0.04	0.4154	0.0507
		IBS-C	−0.14	0.0004	−0.09	0.0232	0.2902
		Combined constipation	−0.14	<0.0001	−0.06	0.0308	0.0201
IBS-QoL	Overall score	HC	0.89	0.1232	−0.18	0.5077	0.1181
		FC	1.79	0.0736	1.45	0.0834	0.7794
		IBS-C	5.05	0.0002	4.66	<0.0001	0.7818
		Combined constipation	3.53	<0.0001	3.07	<0.0001	0.6237

BSFS, Bristol stool form scale; CSBM, complete spontaneous bowel movement; FC, functional constipation; GSRS, gastrointestinal symptom rating scale; HC, healthy controls; IBS-C, constipation-predominant irritable bowel syndrome; IBS-QoL, irritable bowel syndrome quality-of-life questionnaire.

Compared with psyllium, kiwifruit consumption was associated with a greater improvement in constipation symptoms in the FC ($P = 0.026$) and FC + IBS-C ($P = 0.024$) groups indigestion in the FC ($P = 0.04$) and the combined constipation groups ($P < 0.01$). The clinical relevance of shifts in GSRS domain scores has been determined as minimally important differences (MID) defined by the level of shift from baseline scores (constipation domain 0.7; abdominal pain domain 0.6; indigestion domain 0.7) (34). The kiwifruit intervention met the MID for the constipation domain for both constipated groups (FC and IBS-C) compared with the psyllium intervention, which met the MID for the IBS-C group only. A significant difference for the abdominal pain domain score was observed between treatments, but neither met the MID requirement. Subgroup analysis of participants that entered the study with moderate to severe abdominal pain (IBS-SSI score ≥ 175) (35) showed that kiwifruit approached the MID for abdominal pain in IBS-C participants with a shift from baseline of 0.5.

In the combined constipation group, daily consumption of 2 green kiwifruits was associated with softening of the stool

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Note: *p< 0.05; ** p< 0.01; *** p< 0.001 vs baseline. CSBM, complete spontaneous bowel movement; HC, Healthy Controls; FC, Functional Constipation; IBS-C, Irritable Bowel Syndrome with predominant constipation.

Figure 4. Change from baseline in CSBM frequency during interventions.

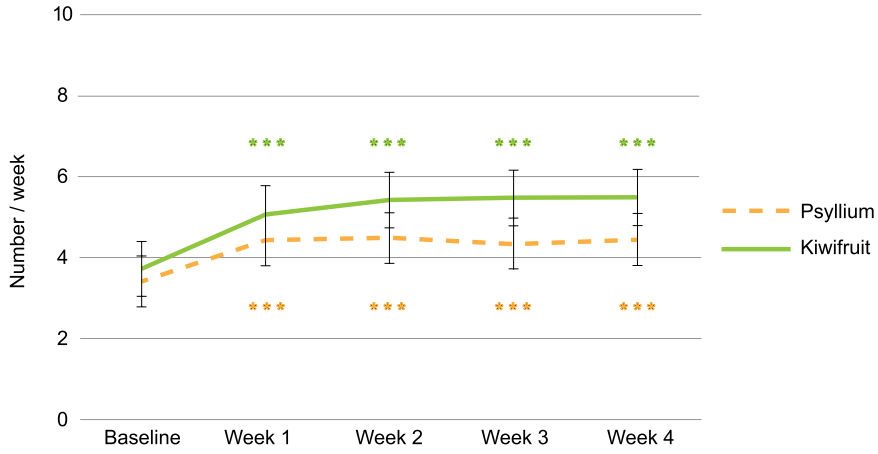
consistency, a reduction in straining, and improvement in QoL compared with those at baseline. Kiwifruit consumption was associated with significantly better outcomes than psyllium for stool consistency and straining.

Owing to the multiple secondary outcomes for which the study was not specifically powered, a hierarchical strategy was adopted. By eliminating those secondary outcomes that are equal or lower in the hierarchy than the first variable with $P \geq 0.05$, GSRS abdominal pain, GSRS indigestion, Bristol stool form scale, straining, and IBS-QoL were designated not significant for the FC group receiving 2 green kiwifruits daily. For the psyllium intervention, none of the secondary outcomes except total GSRS and GSRS constipation passed the multiplicity threshold (Table 3). Bold text for the p-values in Table 3 signal the change to nonsignficant outcomes.

There were no significant differences in profile of mood state scores, laxative use, or overall GI motility, as measured by SmartPill. Analysis of dietary records at the end of each study period showed that except for reductions in other fruit intake during the kiwifruit intervention, no other significant changes in diet were observed over the duration of the study. Only mild adverse events were reported, none of which required unblinding of the study intervention. Adverse events are reported in Supplementary Digital Content (see Supplementary Table S2, http://links.lww.com/AJG/C809).

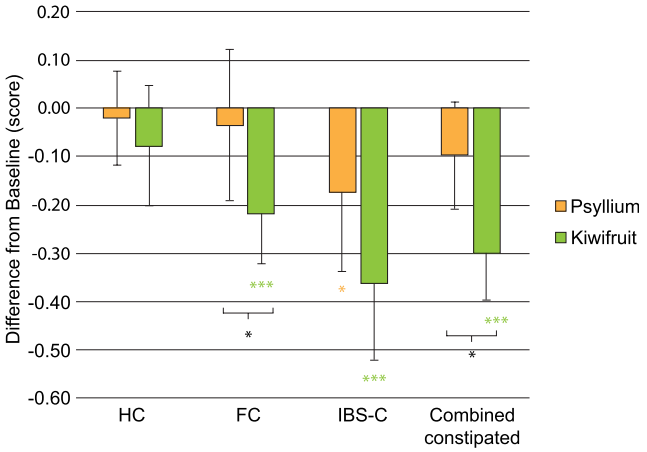
DISCUSSION

We have shown that consuming 2 green kiwifruits daily is associated with improved laxation and GI comfort in constipated individuals. Fresh fruit and vegetables are essential elements of a "healthy diet." In this study, a fresh fruit has been shown in a large multicenter randomized controlled trial to have clinically relevant and beneficial effects on a range of GI symptoms in free-living adults with constipation. Although nonpharmaceutical and natural products are of great interest to the public for the management of GI complaints, a naturally occurring fresh food that can be easily incorporated into the diet has never before undergone such a rigorous controlled trial. Building on



Note: *** *p< 0.001* vs baseline. CSBM, complete spontaneous bowel movement.

Figure 5. Weekly CSBM frequencies in the combined constipated group during each intervention.



Note: *p<0.05; ***p<0.001 vs baseline. GSRS, gastrointestinal symptom rating scale; HC, Healthy Controls; FC, Functional Constipation; IBS-C, Irritable Bowel Syndrome with predominant constipation.

Figure 6. Change from baseline in GSRS total scores.

previously published studies, these data have provided substantive evidence leading to a positive opinion from the EFSA Panel on Nutrition, Novel Foods, and Food Allergens for the role of green kiwifruit in the maintenance of normal defecation (36). This study was completed in 2017; the delay in submission for publication was a consequence of awaiting the outcome of the EFSA opinion.

Constipation is a common condition affecting >10% of the worldwide population and is a major contributing factor to GI discomfort (37). It accounts for a significant reduction in QoL and is a major burden on healthcare systems worldwide (through visits to primary and secondary care facilities). A survey of patient perspectives recorded that 43% of patients were not completely satisfied by current pharmacological treatments for constipation (7). In addition to a range of prescribed medications, there are many over-the-counter supplements and nutraceutical therapies marketed to improve constipation and improve GI comfort. However, most of these approaches lack robust scientific evidence supporting their efficacy. This study shows that robust randomized controlled trials of nonpharmaceutical treatments can be successfully conducted for the management of GI symptoms.

In addition to the daily consumption of green kiwifruit demonstrating a clinically significant improvement in laxation, similar benefits were also obtained for GI comfort. Although not the only factor, improvement in laxation is associated with improved GI comfort (38). Several studies have shown how consumption of green kiwifruit leads to improved laxation in constipated individuals and improves measures of GI comfort, including bloating (8,9,12). In a meta-analysis of 27 clinical trials of interventions in constipated individuals (38), a meta-regression demonstrated a significant correlation between treatment-induced increases in bowel frequency and decreased pain ratings. Therefore, the effects on abdominal pain may be mediated, partly, by improvements in constipation. The results of regular consumption of green kiwifruit on further secondary outcomes from this study demonstrate improvements in abdominal pain and indigestion, as measured by GSRS, straining during defecation, and stool consistency. All these outcomes are consistent with changes that are observed in people with improved laxation, adding clinical and biological plausibility to these findings.

Constipation is associated with significantly reduced QoL. In addition to symptom improvement, the consumption of both green kiwifruit and psyllium was associated with improved IBS-specific QoL. This novel finding supports the concept that dietary interventions can have an impact beyond simple nutrition.

Mechanisms by which green kiwifruit improve laxation and abdominal comfort have been reviewed (39). Fiber found in kiwifruit cell walls has a large swelling and water-holding capacity *in vitro*, which can lead to stool softening and increased stool frequency. Other components of kiwifruit, for example raphides, may alter mucin production, leading to improved laxation. The physiological effects of the ingestion of 2 kiwifruits have been explored using serial MRI scanning (40). Compared with the control, significant increases in water retention in the small bowel and ascending colon, in addition to increasing total colonic volume, were observed. These findings are consistent with the known swelling and water-retaining capacity of kiwifruit fiber.

Table 3. Hierarchy of end points accounting for multiplicity of outcomes

		Kiwifruit			Psyllium		
Rank	Endpoint	FC	IBS-C	Combined constipation	FC	IBS-C	Combined constipation
1	CSBM	<0.0001	0.0003	<0.0001	**0.1125**	0.0001	0.0038
2	GSRS total	<0.0001	<0.0001	<0.0001	**0.6549**	0.0420	**0.0796**
3	GSRS constipation	<0.0001	<0.0001	<0.0001	**0.0544**	<0.0001	**0.0420**
6	GSRS abdominal pain	**0.5406**	0.0237	0.0267	**0.6403**	**0.6189**	**0.9820**
7	GSRS indigestion	**0.0173**	0.0016	<0.0001	**0.5751**	**0.3061**	**0.8620**
4	BSFS	**0.0008**	<0.0001	<0.0001	**0.2432**	**0.0011**	**0.0042**
5	Straining	**0.0003**	<0.0001	<0.0001	**0.4154**	**0.0232**	**0.0308**
8	IBS-QoL	**0.0736**	0.0002	<0.0001	**0.0834**	**<0.0001**	**<0.0001**

Bold text for the p-values in Table 3 signal the change to nonsignficant outcomes.
BSFS, Bristol stool form scale; CSBM, complete spontaneous bowel movement; FC, functional constipation; GSRS, gastrointestinal symptom rating scale; HC, healthy controls; IBS-C, constipation-predominant irritable bowel syndrome; IBS-QoL, irritable bowel syndrome quality-of-life questionnaire.

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This study has a number of limitations. A key limitation was the inability to blind participants to the interventions. However, a single blind was maintained with all researchers who had contact with the participants. The potential effects of the unblinded kiwifruit intervention were managed by also using an unblinded positive control. It is possible that perceived effects for those consuming kiwifruit was differentially greater than those consuming psyllium or *vice versa*.

The treatment duration was relatively short (4 weeks). This is consistent with other studies and aligned with recommendations for clinical trials of FGID (41). The 4-week timeframe also minimized the effect of the menstrual cycle on GI symptoms because this can be a confounding factor, especially in functional GI studies where most participants are female (42).

This large multicenter study presented consistent results across the 3 geographically and culturally diverse populations. The study participants were well phenotyped, and the study was independently monitored. Although there is no validated measure for CSBM, compliance of daily diary completion was high. The rationale for use of a crossover design for this intervention trial was primarily due to the recognized variability in individuals with FGID (constipation related) and consequently the preference that each participant serves as his/her own control in the estimation of treatment effect and allowing for between-group comparisons (43). A further advantage of the crossover design, due to the within-individual measures, was the reduced sample size (compared with parallel design) required to achieve the desired statistical power (41). In addition, order effects were included in the model that we used to analyze our data, and the results show that there was no significant crossover effect.

In conclusion, we have shown that consumption of 2 Zespri green kiwifruits per day is associated with a clinically significant increase in CSBM, improvements in abdominal comfort, straining and stool form, and increases in QoL, translating into meaningful improvements for study participants. Taken in conjunction with previous clinical trials of green kiwifruit and the emerging physiological data from functional studies, consumption of 2 green kiwifruits can be safely recommended as an effective treatment for constipation in those with functional GI disorders that will also provide improvements in symptoms of GI comfort.

Study Highlights

WHAT IS KNOWN

- ✓ Green kiwifruit is known to promote normalization of bowel habit in constipated individuals.
- ✓ It is commonly accepted that there is a strong relationship between stool frequency and gastrointestinal (GI) comfort. For kiwifruit, little is known about the impact on GI comfort.

WHAT IS NEW HERE

- ✓ This study has built on those prior by definitively determining the association between green kiwifruit intake and improved bowel habit and GI comfort.
- ✓ In addition to improved measures of constipation status, there was a significant improvement in stool consistency, reduction in constipation, indigestion/reflux, and abdominal pain resulting in an improved overall level of GI comfort.
- ✓ With recent estimates of the global prevalence of functional constipation and constipation-predominant irritable bowel syndrome at 11.7% and 1.3%, respectively, kiwifruit can be considered an effective and well-tolerated dietary treatment for the relief of constipation and associated improvement in GI comfort.

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CONFLICTS OF INTEREST

Guarantor of the article: Richard Gearry, MD, PhD.

Specific author contributions: R.G., S.F., and G.B.: principal investigators who oversaw the trial in their respective countries and contributed to writing and review of the manuscript. B.K.S.: conducted the statistical analysis and reviewed the manuscript. J.A.: contributed to trial design and reviewed the manuscript. P.B.: conducted laboratory analysis and reviewed the manuscript. A.W.: and C.B.: involved in running the New Zealand clinical trial and reviewed the manuscript. C.C., M.R.B., and I.P.: involved in running the Italy clinical trial and reviewed the manuscript. Y.O., T.M., T.O., M.F., Y.E., Mi.K., Mo.K., N.K., and K.N.: involved in running the Japan clinical trial and reviewed the manuscript. L.D.: involved with trial design, contributed to writing, and review of the manuscript.

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Potential competing interests: J.A. and P.B. are employed by Zespri International who part-funded the study. R.G. and L.D. sit on the Science Advisory Board, have received travel and research grants from Zespri International. SF and GB have received research travel grants from Zespri International.

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