Fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs), but not gluten, elicit modest symptoms of irritable bowel syndrome: a double-blind,

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Fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs), but not gluten, elicit modest symptoms of irritable bowel syndrome: a double-blind, placebo-controlled, randomized three-way crossover trial

Elise Nordin,[1] *Carl Brunius,*[1] *Rikard Landberg,*[1] *and Per M Hellström*[2]

[1]Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden; and [2]Department of Medical Sciences, Uppsala University, Uppsala, Sweden

ABSTRACT

Background: Irritable bowel syndrome (IBS) has been associated with diets rich in fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs), and gluten. Most previous studies have been single-blind and have focused on the elimination of FODMAPs or provocation with single FODMAPs. The effect of gluten is unclear, large trials isolating the effect of gluten from that of FODMAPs are needed.

Objectives: The aims of this study were to ensure high intakes of a wide range of FODMAPs, gluten, or placebo, and to evaluate the effects on IBS symptoms using the IBS-severity scoring system (IBS-SSS).

Methods: The study was carried out with a double-blind, placebo-controlled, randomized 3-way crossover design in a clinical facility in Uppsala from September 2018 to June 2019. In all, 110 participants fulfilling the IBS Rome IV criteria, with moderate to severe IBS, were randomly assigned; 103 (90 female, 13 male) completed the trial. Throughout, IBS participants maintained a diet with minimal FODMAP content and no gluten. Participants were block-randomly assigned to 1-wk interventions with FODMAPs (50 g/d), gluten (17.3 g/d), or placebo, separated by 1-wk washout. All participants who completed ≥1 intervention were included in the intention-to-treat analysis.

Results: In participants with IBS (n = 103), FODMAPs caused higher IBS-SSS scores (mean 240 [95% CI: 222, 257]) than placebo (198 [180, 215]; $P = 0.00056$) or gluten (208 [190, 226]; $P = 0.013$); no differences were found between the placebo and gluten groups ($P = 1.0$). There were large interindividual differences in IBS-SSS scores associated with treatment. No adverse events were reported.

Conclusion: In participants with IBS, FODMAPs had a modest effect on typical IBS symptoms, whereas gluten had no effect. The large interindividual differences in responses to the interventions warrant further detailed studies to identify possible underlying causes and enable individual prediction of responses. This trial was registered at www.clinicaltrials.gov as NCT03653689. *Am J Clin Nutr* 2022;115:344–352.

Keywords: diet, fermentation, functional gastrointestinal disorder, polyols, saccharides, irritable bowel syndrome, FODMAPs, gluten, double-blind, crossover trial

Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder affecting 3–5% of the population (1). It is characterized by recurring abdominal pain over ≥3 mo within a 6-mo

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Supplemental Tables 1–5 and Supplemental Methods 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to EN (e-mail: elise.nordin@chalmers.se).

Abbreviations used: A, FODMAPs; B, gluten; C, placebo in blocks of 12; FODMAPs, fermentable oligo-, di-, monosaccharides, and polyols; IBS-C/D/M/U, irritable bowel syndrome-constipation/diarrhea/mixed/unsubtyped; IBS-SSS, irritable bowel syndrome-severity scoring system; ITT, intention-to-treat; PP, per-protocol; SF-36v2, Short Form 36 version 2; QoL, quality of life.

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period, in association with altered bowel habits. IBS is subtyped based on the predominant stool pattern: constipation (IBS-C), diarrhea (IBS-D), a mix of constipation and diarrhea (IBS-M), or unsubtyped (IBS-U) (2). The diagnosis is symptom based, using the Rome IV criteria, currently with no biochemical diagnostic markers (2). People with IBS experience lower quality of life (QoL) than the general population (3).

Symptomatic treatment of IBS includes dietary adaptation, with a focus on prebiotics (4), probiotics (5), gluten (6), and fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) (6, 7). FODMAPs are poorly absorbable carbohydrates that exert an osmotic load on the gut, and are rapidly fermented by colonic bacteria, resulting in gas production causing abdominal distention, bloating, and pain (7). A low FODMAP diet has been shown to improve IBS symptoms (8–16) and is currently the dietary factor with most evidence as a regimen for IBS (6). However, many FODMAP restriction studies suffer from suboptimal design, being no or single-blind (8–15). In fact, only 1 double-blind study with a low FODMAP diet has been conducted and was carried out in children (16). Furthermore, most studies have focused on the elimination of FODMAPs from the diet, rather than provocation (8–16). A few studies, all single-blind, have employed provocations using all FODMAP components (12, 17), though similar double-blind studies have used provocations with only a few FODMAPs (18–21). No previous studies have employed the combination of double-blinding with multiple FODMAPs, which better represents FODMAP exposure in real life. A gluten-containing diet in people with IBS, but no defined celiac disease, has been shown to cause IBS symptoms in randomized control trials (22, 23), but other studies have found no such effect (18, 24). Alleviation of IBS symptoms through a gluten-free diet may be due to so-called nonceliac gluten or wheat sensitivity, but the mechanisms are unclear (25). FODMAPs and gluten often coexist in foods and it is difficult to disentangle the separate effects of these 2 components (24), but isolated effects of these 2 constituents have been estimated (18).

The primary aim was to investigate the effects of week-long interventions with high intakes of a wide range of FODMAPs, gluten, or a nonfermentable placebo in subjects with moderate to severe IBS, using the IBS-severity scoring system (IBS-SSS). The secondary aim was to identify effects on reported IBS outcomes such as QoL, stool habits, and anthropometric measures in relation to the dietary interventions. It was hypothesized that IBS symptoms, as well as stool habits and QoL, would be worsened by a 1-wk FODMAP challenge, but not with gluten or placebo.

Methods

Study design

The double-blind, placebo-controlled, randomized 3-way study with triple crossover design was conducted from September 2018 to June 2019 in Uppsala, Sweden. The study was approved by the Ethics Review Board, Uppsala (2018/159). Before enrollment, participants had a primary consultation with a dietician specialized in IBS and were instructed to maintain a low-impact diet with minimal FODMAP content and exclusion of gluten throughout the study. Food intake advice was adapted to each individual's dietary habits, and participants were provided with food lists based on the Monach University presentation of FODMAP contents in various foods (26, 27), recipes, and an app (Belly Balance Sverige AB, Stockholm, Sweden) for verifying the FODMAP and gluten contents by scanning product labels.

After a first run-in week with a low-impact diet, participants were exposed to a single combined FODMAP/gluten challenge, with blood samples drawn over the course of 4 h after the challenge. The purpose of this FODMAP/gluten challenge test was to provide samples to be analyzed at a later time. On the following morning, a spot urine sample was collected, after which participants continued the low-impact diet for another week. Participants were then prompted to consume blinded food in the form of rice porridge with added FODMAPs, gluten, or placebo during weeks 3, 5, and 7, but no porridge during weeks 4 and 6 (**Figure 1**). Blood and feces samples were collected at visits at the end of each study week (to be analyzed at a later time). Before each visit, participants were fasted overnight and arrived in the early morning for investigations.

Participants

Inclusion criteria of the study were: female and male with moderate to severe IBS (IBS-SSS score >175) (28), BMI 18.5–38 kg/m^2, age 18–70 y, hemoglobin 120–160 g/L, thyroid-stimulating hormone <4 mU/L, C-reactive protein <5 mg/L, transglutaminase immunoglobulin A <7 U/mL, and systolic/diastolic blood pressure ≤160/≤105 mmHg. Participants were diagnosed by a gastroenterologist based on the Rome IV criteria, and subtyped to IBS-C, IBS-D, or IBS-M (2). Exclusion criteria were: celiac disease, functional dyspepsia, *Helicobacter pylori* infection during the preceding 6 mo, or other functional or inflammatory gastrointestinal disease, previous or ongoing cancer treatment, previous bariatric or abdominal surgery other than appendectomy, treatment of weight reduction, >10 kg body weight change in the preceding year, refusal to give informed consent, unstable medication from 14 d prior to inclusion or during the study, concurrent probiotic or antibiotic medication, reluctance to consume rice porridge daily during 3 separate weeks, pregnancy or lactation, blood donation or participation in other intervention trials within 30 d prior to screening or any time during the study, history of drug or alcohol abuse, smoking, and inability to understand the Swedish language. Pharmaceuticals to mitigate symptoms of IBS (proton pump inhibitors, prokinetics, tricyclic antidepressants, serotonin reuptake inhibitors, opioids or opioid analogues, as well as nonsteroid anti-inflammatory drugs and laxatives) were not allowed. Both FODMAP-naïve and participants with previous experience of FODMAP restrictions were included.

Recruitment of participants was conducted through a Swedish IBS online community (Belly Balance Sverige AB), at the gastroenterology outpatient clinic of Uppsala University Hospital, at the campuses of Uppsala University and the Swedish University of Agricultural Sciences, Uppsala, and in local newspapers. The study is reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) (http://www.consort-statement.org/consort-2010).

Randomization and masking

Computer randomization (Sequences CBA, ACB, BAC, where A = FODMAPs, B = gluten, C = placebo in blocks of 12. Randomization was restricted to three treatment orders,

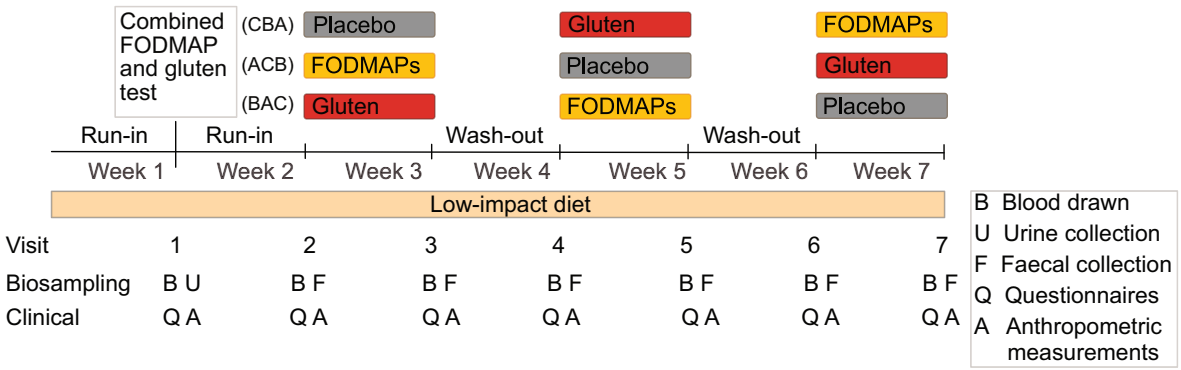

FIGURE 1 Study design with the 3 intervention sequences used. A, FODMAPs; B, gluten; C, placebo in blocks of 12; FODMAPs, fermentable oligo-, di-, monosaccharides, and polyols.

to ensure sufficient statistical power to allow differentiation of a potential effect of sequencing.) was done by personnel with no involvement in the study. Randomization was carried out before the combined FODMAPs/gluten challenge. The randomization outcomes were delivered to the study site 1–3 d before participants were allocated to treatments. Two individuals were mistakenly assigned the sequence ABC. It did not affect the results. For clarity, the individuals are therefore presented as receiving their planned sequence (ACB/BAC). Unblinding of data was done after database locking and completion of the study, before the statistical analyses. For the participants, there were no assessments of consumption order of the diets. During product development by our research group, a panel of 20 people evaluated the rice porridge produced, which could not be distinguished based on appearance, taste, or consistency.

Intervention diets

The initial combined FODMAPs/gluten challenge consisted of a cake containing FODMAPs (fructose 19.5 g, lactose 15.7 g, fructo-oligosaccharides 7 g, galacto-oligosaccharides 1.5 g, sorbitol 4.5 g, and mannitol 1.8 g) or gluten (17.3 g), each with cocoa for taste and 150 mL water (**Supplementary Tables 1** and **2**). During the following intervention weeks, participants consumed 3 portions daily of rice porridge with high amounts of FODMAPs or gluten, using placebo as a reference point. The amount of FODMAPs and gluten in the combined challenge test corresponded to the daily dose of FODMAPs or gluten provided during test weeks. Rice porridge was selected as the vehicle for FODMAP, gluten, and placebo because of its neutral taste and palatability. The intervention foods were similar in sweetness (added sucrose; Supplementary Tables 1 and 2) and consistency, to ensure accurate blinding. The porridge was delivered in portion packs with an instruction to add 125 mL water and heat before intake. The FODMAP intake during the interventions was 50% higher than that reported for an Australian population (15). Lactose and gluten intakes were 50% higher than estimates of the average Swedish population intake (29).

Anthropometric measurements and questionnaires

At screening, participant height was measured using a wall-mounted stadiometer. At each visit, compliance with the following aspects was noted: avoidance of vigorous physical activity and alcohol consumption during the preceding 24 h and adherence to fasting routines overnight. Bodyweight, waist circumference at the umbilicus level, and systolic and diastolic blood pressure were measured after the participant had rested in supine position for $\geq$10 min. At each visit, the following questionnaires were filled out for the preceding study week: IBS-SSS (28), Short Form 36 version 2 (SF-36v2) (30), stool diary, study compliance form for the amount of porridge eaten during the week, and notes on any deviations from the protocol due to dietary changes, illness, or changes of medication.

The IBS-SSS is a validated questionnaire used to estimate the severity of IBS during a 10-d period by addressing severity of abdominal pain, abdominal distension, dissatisfaction with bowel habits, and interference with QoL, on a 0–100 mm visual analogue scale. The item frequency of abdominal pain is addressed as ordinal data on a scale $\leq$100 points (10 levels). The total IBS-SSS score ranges between 0 and 500, with $<$175 considered mild, 175–300 considered moderate, and $>$300 considered to represent severe IBS. The SF-36v2 measures health and QoL over the last 7 d. The study period of the questionnaires was modified to reflect the preceding 5 d (the IBS-SSS item frequency of abdominal pain was modified to multiply the value by 20 instead of 10, in order to keep the scale to 100), and fit the study interventions with minimal carry-over effect. Questions concerning headache, fatigue, joint pain, dizziness, skin rash, numbness, and vomiting were added to the SF-36v2 questionnaire (scoring low 1 to high 5). The questions were added to monitor extraintestinal symptoms, commonly present in participants with nonceliac gluten or wheat sensitivity (25). All questionnaires used in the trial are presented in **Supplementary Methods 1**. The stool diary retrieved information on bowel movements as spontaneous, complete and spontaneous, or requiring a rescue laxative (31), stool consistency (32), and pain during bowel movements (visual analogue scale 0–100). Procedures for the collection of blood, urine, and feces samples are described in detail in **Supplementary Methods 2**. Adverse events were monitored during the study and within 1 mo after the last food intervention week.

Statistical analyses

A sample size calculation, assuming a relevant difference in total IBS-SSS (50 points) (28) with a power of 0.8, and 20% dropout rate, was performed posthoc using individual SD for the

interventions (SD = 111.6) in the study. Under these conditions, the required number of participants was 64, with the level of significance in a 2-sided test set to 0.05/3 (Bonferroni correction). The primary analysis was performed as intention-to-treat (ITT), including all participants who completed assessment of ≥1 intervention. As a secondary analysis, a per-protocol (PP) test was performed, using ≥80% self-reported intake of the intervention foods as cutoff. The effect of diet was analyzed through linear mixed modeling in R, using the lme4 v 1.1–25 package, with intervention and period as fixed factors and study participant as the random factor. Overall effects were investigated using type III tests, and when significant, subsequent pairwise comparisons were based on differences in least square means, both adjusted with Bonferroni correction. Intervention × IBS subtype was initially included as a fixed factor but later removed, as it was not significant in any of the models. Residual distributions were investigated for normality by visual inspection of Q-Q and residual compared with fitted plots. Comparisons between subtypes at screening were conducted through 1-factor ANOVA. From the stool diary, the variable concerning whether medication was needed for bowel emptying was removed due to severe zero inflation (91% zeros). Proportion tests were performed using McNemar's test. Descriptive results are presented as mean and SD and number of occurrences for demographic data. Outcome data from the trial are presented as means, SEM, and 95% CIs. All analyses were performed in the programming language R version 4.0.0. A P value <0.05 was considered significant. The trial was registered at www.clinicaltrials.gov as NCT03653689.

Results

In all, 195 participants were screened, 110 of whom were eligible and randomly assigned for the study (**Figure 2**). Reasons for exclusion were: not fulfilling IBS criteria (n = 27), abnormal blood chemistry (n = 11), high blood pressure (n = 4), antibiotic treatment (n = 1), and high BMI (n = 1). There were 7 dropouts: 6 before completion of any intervention; another completed 1 intervention, but did not return any questionnaires. In all, 103 participants completed the study and were included in the ITT analysis, 74 in the PP analysis (n = 24, 28, and 22 in treatment sequence CBA, ACB, and BAC, respectively). Loss of participants in the PP analysis was due to noncompliance (n = 7), intake of antibiotics (n = 2), or intake of probiotics (n = 1) during the study. Some participants who deviated from the inclusion criteria at screening were later rescreened and considered eligible. They deviated as regards BMI (n = 2, BMI 16.9 and 18.0 kg/m^2), age (n = 2, > 70 but ≤72 y), lactose intolerance (n = 5), intake of symptom-mitigating pharmaceuticals (n = 2), or had unsubtyped IBS (n = 14).

Participant baseline characteristics are shown in **Table 1**. No differences were observed between the IBS subtypes in age, blood pressure, BMI, or waist circumference (not shown). Study "week" length varied between 5 and 9 d for practical reasons, but the majority of participants (>80%) had 7 d between visits at the study site. For 6 participants, 1 washout week was extended to 10–21 d.

The IBS-SSS score was highest with the FODMAP intervention (mean [SEM] = 240 [9]) compared with placebo (198 [9]; P = 0.00056) or gluten (208 [9]; P = 0.013) (**Table 2**). No difference was observed between gluten and placebo (P = 1.0). The IBS-SSS score was 40 [10] points higher during the FODMAP intervention compared with during the preceding washout week (P = 0.0012), whereas the corresponding values for the gluten and placebo interventions were 27 [10] (P = 0.11) and 10 [10] (P = 1.0). The IBS-SSS score ratings were similar between placebo treatment and the washout weeks of the interventions (P >0.98; **Supplementary Table 3**). When comparing the separate interventions, no differences were identified in the proportion of participants with an increase of >50 points (FODMAPs 46%, gluten 37%, placebo 35%) or >100 points (FODMAPs 26%, gluten 20%, placebo 22%) in IBS-SSS scores (**Figure 3**). When IBS-SSS scores were itemized, abdominal distension scores were found to be higher with FODMAPs than with placebo (P <0.0001) or gluten (P = 0.023), again with no difference between gluten and placebo (P = 0.25). Frequency of abdominal pain showed higher scores for FODMAPs than for placebo (P = 0.0020) and borderline significantly higher than for gluten (P = 0.072), with no difference between gluten and placebo (P = 0.74), Table 2. No differences were observed between the interventions as regards the severity of abdominal pain, dissatisfaction with bowel habits, or interference with QoL (Table 2). There was no period effect between the interventions for any of the items in the IBS-SSS (0.23 ≤ P ≤0.89). The IBS-SSS score during baseline week 2 was significantly higher compared with week 4 (P = 0.00074) or week 6 (P = 0.0032), with no differences between week 4 and 6 (P = 1.0) (Table 1). IBS-SSS scores at screening were significantly higher compared with those of any other intervention (0.0001 < P <0.021) for all items except frequency of abdominal pain (P = 1.0) (Tables 1 and 2).

In the ITT analysis, the QoL questionnaire (SF-36v2) showed no differences between the interventions, including the added questions (headache, fatigue, joint pain, dizziness, skin rash, numbness, and vomiting) (**Supplementary Table 4**). In the PP analysis, however, FODMAPs scored lower than gluten in Role-Physical (P = 0.0022) and lower than either gluten (P = 0.0033) or placebo (P = 0.023) in the Physical Component Score.

The stool diary did not reveal any differences between the interventions concerning frequency (P = 1.0), consistency (P >0.45), or pain during bowel movements (P = 1.0) (**Supplementary Table 5**). There were no differences in the number of complete spontaneous bowel movements (P = 1.0) or spontaneous bowel movements (P = 0.11). There were no differences in body weight, systolic or diastolic blood pressures, or waist circumference between the interventions (not shown). No participants reported severe or serious adverse events as a result of the dietary interventions.

Discussion

This double-blind, placebo-controlled, randomized 3-way crossover study examined the possible exacerbating effects of FODMAPs and gluten on gastrointestinal symptoms in people with IBS, compared with placebo. The study indicated an effect of FODMAP, but not gluten, in participants with IBS compared with placebo.

The higher total IBS-SSS scores with FODMAPs than with placebo or gluten were mainly driven by the features abdominal

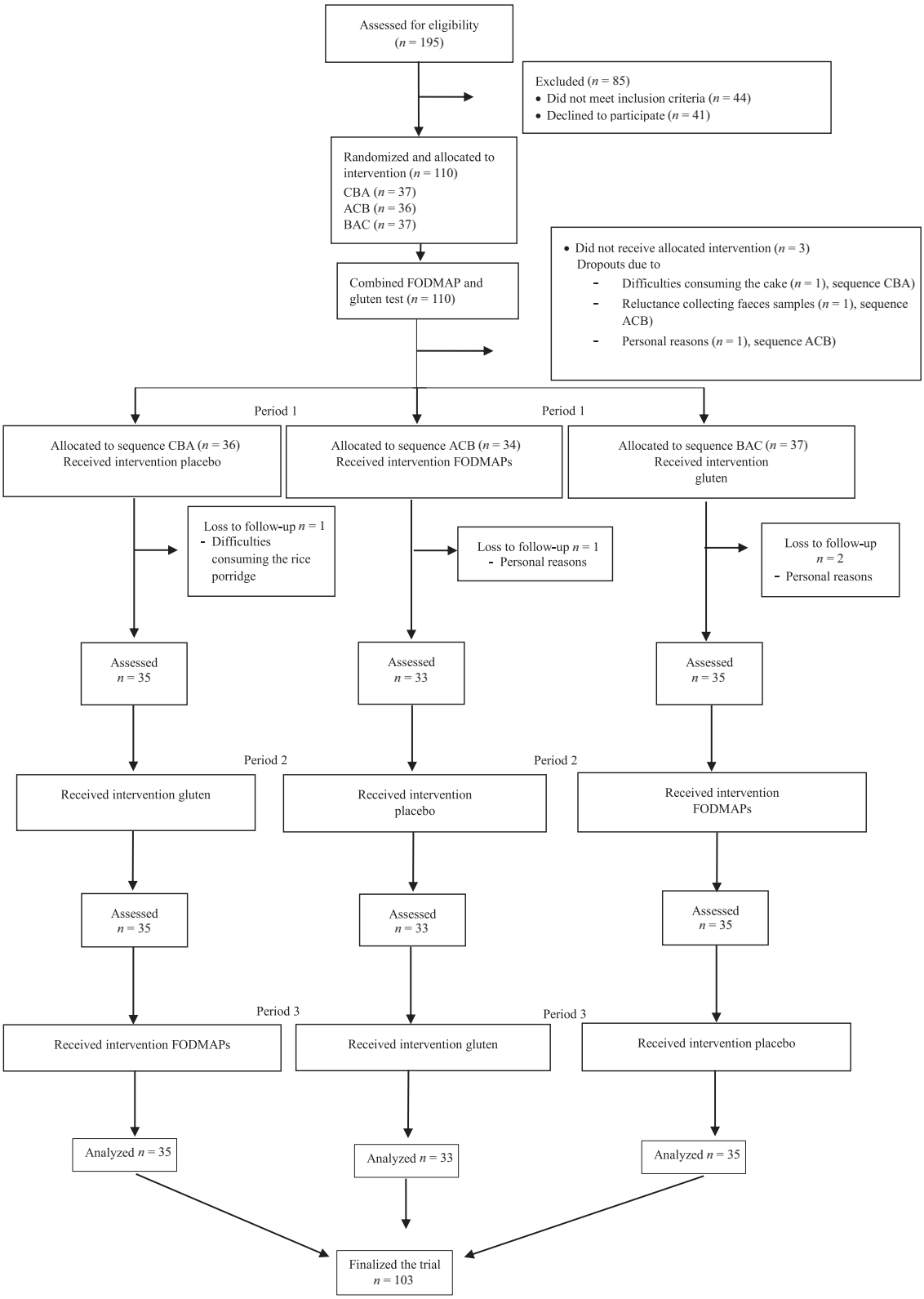

FIGURE 2 Flow chart of participants by sequence and food intervention period. A, FODMAPs; B, gluten; C, placebo in blocks of 12; FODMAPs, fermentable oligo-, di-, monosaccharides, and polyols.

pain and abdominal distension. This is in line with previous studies of IBS and FODMAPs (8, 10, 12–14, 17). The increase in total IBS-SSS score was modest, as all interventions raised the IBS-SSS score <50 points. According to Francis et al., a clinically significant difference can be assumed for a score >50 (28), which has been the customary interpretation of results. Several studies eliminating FODMAPs from the diet of subjects with IBS have found large effects of a low FODMAP diet

TABLE 1 Baseline characteristics by intervention sequence (CBA, ACB, BAC; A = FODMAPs, B = gluten, C = placebo)[1] and in total. Data are presented for the full analysis set

Baseline characteristics	CBA ($n = 35$)	ACB ($n = 33$)	BAC ($n = 35$)	Total ($n = 103$)
Female/male, *n*	26/9	32/1	32/3	90/13
Mean age, y ± SD	43 ± 17	44 ± 15	50 ± 13	46 ± 15
Mean BMI, kg/m^2 ± SD	24 ± 3	23 ± 4	25 ± 4	24 ± 4
Dietary preference, %				
Omnivorous diet	83	76	91	83
Vegetarian	17	18	9	15
Vegan	0	3	0	1
Dietary restrictions, %				
Exclusion of gluten	37	42	49	43
Exclusion of lactose	43	58	46	49
Other exclusions	34	55	57	49
No dietary exclusions	23	12	20	18
Mean blood pressure ± SD				
Systolic, mmHg	123 ± 14	120 ± 12	128 ± 16	124 ± 14
Diastolic, mmHg	76 ± 8	74 ± 12	79 ± 9	76 ± 10
Mean waist circumference, cm ± SD	88 ± 11	88 ± 10	93 ± 11	90 ± 11
IBS severity at baseline				
Total IBS-SSS >175–300, *n*	14	20	21	41
Total IBS-SSS >300, *n*	21	13	14	62
IBS subtype, *n*				
Constipation	9	11	9	29
Diarrhea	17	7	11	35
Mixed	9	15	15	39
Mean total IBS-SSS ± SD				
Week 2	222 ± 88	232 ± 69	178 ± 78	210 ± 82
Week 3	226 ± 88	241 ± 80	191 ± 96	218 ± 90
Week 4	183 ± 84	192 ± 87	158 ± 96	177 ± 90
Week 5	205 ± 90	197 ± 91	229 ± 93	210 ± 91
Week 6	209 ± 105	186 ± 88	148 ± 90	181 ± 97
Week 7	248 ± 94	230 ± 92	172 ± 86	216 ± 96
Mean total IBS-SSS at baseline ± SD				
Total IBS-SSS score (0–500)	309 ± 48	309 ± 41	306 ± 61	308 ± 50
Severity of abdominal pain (0–100)	49 ± 17	54 ± 16	54 ± 18	52 ± 17
Frequency of abdominal pain (0–100)	64 ± 25	62 ± 22	59 ± 26	62 ± 24
Abdominal distension (0–100)	51 ± 24	56 ± 17	51 ± 23	52 ± 22
Dissatisfaction with bowel habits (0–100)	71 ± 19	65 ± 17	73 ± 20	70 ± 19
Interference with quality of life (0–100)	74 ± 12	72 ± 11	69 ± 11	72 ± 11

[1]Two individuals were by mistake assigned the sequence ABC. It did not affect the results, for clarity, the individuals are therefore presented as receiving their original sequence (ACB/BAC). A, FODMAPs; B, gluten; C, placebo in blocks of 12; FODMAPs, fermentable oligo-, di-, monosaccharides, and polyols; IBS-SSS, irritable bowel syndrome-severity scoring system.

compared with either a sham or habitual diet (11, 12, 14, 19). However, the intervention effect in those studies was likely confounded with general treatment or placebo effects and the non- or single-blind design. Like us, Hustoft et al. (19) found that provocation with fructo-oligosaccharides increased IBS-SSS scores only slightly. Skodje et al. (18) found symptoms only moderately increased by FODMAPs but not by gluten, whereas Shepherd et al. (20), who included only subjects with IBS with fructose malabsorption in their study, found profound effects of provocation with fructose and/or fructan. The modest effects of the dietary challenges in our study do not rule out that some people experience strong responses to FODMAPs and gluten, since there were pronounced interindividual differences in response to the interventions. Future investigations should evaluate the magnitude and causes of differential responses among individuals and how such responses can be predicted (33–35).

Previous studies suggest that people without a diagnosis of celiac disease may be sensitive to gluten (25). However, methodological issues such as differences in study design, inclusion criteria, gluten exposure level, and the presence of other food components (e.g. FODMAPs [36], amylase trypsin inhibitors [36], and wheat lectin agglutinin [37]) make it difficult to draw firm conclusions (36). To minimize such methodological issues, we exposed the participants to a high dose of a gluten fraction while actively excluding FODMAPs, but were unable to obtain gluten free from amylase trypsin inhibitors and wheat lectin agglutinin. Still, the levels of these components in our study are unknown.

Several IBS studies employing a low FODMAP diet over time have reported increased QoL (8, 10–12, 14). One study provoking with fructo-oligosaccharides found no effect on QoL (19), whereas another study found negative effects on vitality (18). In our study, there were no differences between

TABLE 2 Total IBS-SSS score after intervention with FODMAPs, gluten, or placebo. Higher scores indicate more severe symptoms[1]

	FODMAPs	Gluten	Placebo	*P* value	FODMAPs-placebo	FODMAPs-gluten	Gluten-placebo
Total IBS-SSS score	240 [9] (222, 257)	208 [9] (190, 226)	198 [9] (180, 215)	0.0023	42 [11] (20, 64) *P* = 0.00056	32 [11] (10, 54) *P* = 0.013	10 [11] (–11, 31) *P* = 1.0
Severity of abdominal pain	35 [2] (31, 40)	34 [2] (29, 38)	32 [2] (27, 36)	1.0			
Frequency of abdominal pain	58 [4] (51, 65)	49 [4] (42, 55)	44 [3] (37, 51)	0.012	14 [4] (6, 22) *P* = 0.0020	9 [4] (1, 17) *P* = 0.072	5 [4] (3, 13) *P* = 0.74
Abdominal distension	45 [2] (40, 49)	37 [2] (33, 42)	32 [2] (28, 37)	0.00025	13 [3] (7, 19) *P* <0.0001	8 [3] (2, 14) *P* = 0.023	5 [3] (–1, 11) *P* = 0.25
Dissatisfaction with bowel habits	56 [2] (52, 60)	52 [2] (48, 56)	50 [2] (46, 54)	0.51			
Interference with quality of life	55 [2] (51, 59)	50 [2] (46, 54)	52 [2] (47, 56)	0.29			

[1]Mixed linear models were used with intervention and period as fixed factors and participant as the random factor (total $n = 103$). Data are presented as mean [SEM] (95% CI). FODMAPs, fermentable oligo-, di-, monosacharides, and polyols; IBS-SSS, irritable bowel syndrome-severity scoring system.

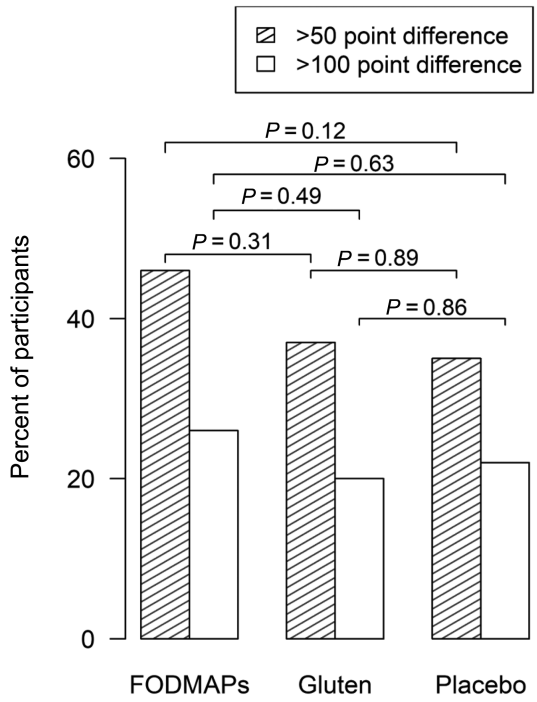

FIGURE 3 Percentage of participants with an increase in total IBS-SSS score of >50 points, or >100 points, for FODMAPs, gluten, and placebo interventions compared with the respective washout periods. Data were analyzed with McNemar's test. FODMAPs, fermentable oligo-, di-, monosaccharides, and polyols; IBS-SSS, irritable bowel syndrome-severity scoring system.

the interventions regarding interference with the QoL item in IBS-SSS or the secondary analysis of QoL. Concerning stool consistency, previous studies found an effect connected to lower FODMAP intake (9, 11, 14, 15), whereas others did not (10, 13). Similar discrepancies are reported for stool frequency (9–11, 13, 14). As regards gluten, there are corresponding discrepancies in perceived stool habits (18, 22, 24, 38). In this study, no effect on the consistency or frequency of stool was found for any intervention and similar results were observed for bowel habit dissatisfaction in IBS-SSS. Halmos et al. (39) found a large discrepancy in subjective reporting and objective measures of stool consistency and pointed out that patient-reported bowel habits warrant further investigation.

We found that the baseline IBS-SSS scores were higher than those for washout weeks. This may be explained by a drastically reduced FODMAP and gluten intake compared with participants' habitual diets, increased participant awareness of dietary choices, and more regular meal patterns. Another possibility is that the lower IBS-SSS scores during the study may relate to the psychological attention effect due to frequent visits to a health care environment, which has previously been shown to improve health and feelings of well-being (40). Also, behavioral and diet therapies have both been found to be important for the treatment of IBS (41).

A limitation of our interventions was the 7-d exposures, shorter than the 10 d usually applied when using IBS-SSS. However, previous studies have successfully conducted food challenges from 2 to 7 d (17, 18). Furthermore, the low-impact diet was not provided as ready-made meals, but as dietary advice to the

participants to consume foods with a low likelihood to provoke IBS symptoms. However, the low IBS-SSS scores during all washout periods suggest high compliance with the low-impact diet throughout the study. Moreover, compliance with the low-impact diet was based on self-reporting, which is one of the main hurdles in nutrition research. There are no validated compliance biomarkers reflecting FODMAP or gluten intake. There was unfortunately no monitoring of the advised low-impact diet during the trial, but participants were provided extensive support to ensure compliance with a low-impact background diet. Also, sweetening of the diet with sucrose can be questioned, due to reported mutations in the sucrase-isomaltase gene in IBS (42). These genetic variants are rare, so major bias is excluded, as confirmed by the similarity between placebo and washout weeks. Inclusion of lactose in the FODMAP intervention may be questioned, but 89% of participants were of Swedish descent, where the prevalence of hypolactasia is 7% (43). Since the prevalence of hypolactasia is low, it should not have any impact of the results. Moreover, not all possible permutations of sequences for the 3 interventions were used. Ultimately, sequence was not included in the model and all the permutations could have been used. Lastly, this study was designed for assessment of efficacy rather than effectiveness, which comes with limited generalizability.

There are several strengths of our study. First, the study was double-blinded, placebo-controlled, and randomized in a 3-way crossover design with a large number of participants. Second, symptom assessment was based on provocation from a low-impact diet with a wide range of FODMAPs and gluten compared with placebo, whereas previous studies have primarily focused on symptom reduction by limiting FODMAP intake or provoking only with a few FODMAPs. Third, this study combined and compared FODMAPs and gluten provocations, which to our knowledge has rarely been done (18). Fourth, we evaluated the impact of dietary FODMAPs and gluten on the general symptoms of IBS between different subtypes of the syndrome.

To conclude, a mixture of widely consumed FODMAPs caused only modest worsening of gastrointestinal symptoms compared with gluten and placebo in a double-blind, placebo-controlled randomized 3-way crossover trial. However, there was considerable interindividual variability in the intervention responses which should be taken into account. Future studies should investigate these differences to understand possible underlying disease mechanisms.

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The authors' responsibilities were as follows—RL, CB, and PH: designed the research and had primary responsibility for the final content; EN: conducted research, analyzed data, and wrote the manuscript; EN: developed the food products used in the study; EN and PH: recruited participants; PH: was the medical doctor responsible for the study; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytical code will be made available upon request. For data to be shared, a written request must be sent including a data analysis plan which needs to be approved by the authors. Before data are shared a data access agreement must be concluded. Only deidentified data can be shared. In order to access data, contact the corresponding author at elise.nordin@chalmers.se.

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