Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Predictors of response to a multidisciplinary internet-delivered intervention for irritable bowel syndrome: An explorative secondary analysis of a randomized controlled trial

**Camilla Thuen**

camilla.thuen@uib.no

University of Bergen

**Blake Dear**

Macquarie University

**Robin Maria Francisca Kenter**

Haukeland University Hospital

**Elisabeth Kjelsvik Steinsvik**

Haukeland University Hospital

**Linn Anja Slåke Vikøren**

Haukeland University Hospital

**Gülen Arslan Lied**

University of Bergen

**Birgitte Berentsen**

Haukeland University Hospital

---

**Research Article**

**Keywords:** Irritable bowel syndrome, functional gastrointestinal disorders (FGID), disorders of gut-brain interaction (DGBI), internet-delivered intervention, digital treatment program, eHealth, predictors

**Posted Date:** May 11th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-9503908/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** Competing interest reported. BB has developed and is the managing director of the internet-delivered intervention but derives no financial benefits from it. The other authors have no

competing interests to declare.

## Abstract

# Background

Internet-delivered interventions for irritable bowel syndrome (IBS) have proven effective, but predictors of treatment response remain unclear.

# Aim

To explore baseline patient characteristics and treatment-related variables associated with clinically meaningful improvement in IBS symptoms and quality of life following a multidisciplinary internet-delivered intervention.

# Methods

This exploratory secondary analysis used data from a RCT (n = 350) comparing internet-delivered cognitive behavioral therapy (CBT), FODMAP diet or their combination to patient education. Predictors were selected pragmatically based on clinical relevance and included demographic, clinical, psychological, dietary, and treatment-related variables related to outcomes. The primary outcome was defined as ≥ 50-point reduction on the IBS Severity Scoring System (IBS-SSS). For sensitivity analysis, two secondary outcomes were defined: 1) ≥ 30% reduction on the IBS-SSS and 2) ≥ 14-point improvement on the Irritable Bowel Syndrome Quality of Life (IBS-QoL). Univariable and multivariable logistic regression models were used to explore the associations.

# Results

More severe baseline IBS symptoms and higher baseline IBS-QoL were associated with increased odds of achieving ≥ 50-point reduction in IBS-SSS, whereas longer symptom duration and previous poor treatment effect of the FODMAP diet were associated with reduced odds of reduction. When treatment-related factors were added, adherence to patient education was associated with increased odds of reduction. For the secondary outcomes, the multivariable models including treatment-related factors indicated that previous poor treatment effect of the FODMAP diet was associated with reduced odds of achieving a ≥ 30% reduction in IBS-SSS, whereas higher baseline IBS-QoL was associated with reduced odds of improved IBS-QoL. Across all outcomes, the explained variance of the models was low to modest.

# Conclusions

No robust or consistent predictors of clinically meaningful improvement in IBS symptoms or quality of life were identified. Prior poor response to the FODMAP diet was the only variable consistently associated with reduced odds of improvement, suggesting that previous treatment experiences may influence symptomatic outcomes and highlighting the potential benefit of early intervention. Overall, these results highlight the limited utility of the assessed variables for forecasting individual treatment response and underscore the need for future research to identify more robust predictors and explore mechanisms of change in internet-delivered interventions for patients with IBS.

# Trial registration

ClinicalTrials.gov ID NCT06117865. Registered 31.10.2023.

## 1. Introduction

Irritable bowel syndrome (IBS) is a common disorder of gut-brain interaction characterized by recurrent abdominal pain and altered bowel habits (1, 2). IBS affects 4–9% globally and is associated with reduced quality of life, increased psychological distress, and work absenteeism (3–5). Beyond the individual burden, IBS places considerable strain on healthcare systems due to frequent consultations, repeated diagnostic testing, and the associated societal costs are substantial (6, 7). Despite this high resource use, many patients describe limited satisfaction with the care they receive (8). Together, this highlights a need for accessible, effective, and resource-efficient treatment options.

Because IBS symptoms often extend beyond the gut and impact psychological and somatic domains, integrated care combining dietary, psychological, and medical strategies is recommended (9–12). Despite these recommendations, access to integrated care remains limited. High healthcare costs and limited access to trained professionals create barriers for access to treatment, highlighting the need for scalable solutions (6, 7, 12). Internet-delivered interventions offer scalability, reduced waiting times, and comparable effectiveness to traditional delivery settings (13, 14). Previous trials have demonstrated that internet-based interventions targeting diet and psychological mechanisms can improve gastrointestinal symptoms, psychological indices, and quality of life (15–19). However, treatment response varies, and little is known about which patients benefit most in internet-delivered settings.

Previous research on predictors for response to IBS treatment in general, suggests that higher symptom severity at baseline is the most consistent predictor of treatment response, while less psychological distress, better quality of life, female sex and higher treatment expectations have also been associated with treatment response in some studies (20–24). Looking beyond IBS symptoms, greater diarrhea severity at baseline, unemployment, psychosocial factors, history of sexual abuse, higher treatment expectations and lower quality of life at baseline have been associated with quality of life outcomes (24–27).

While most studies have focused on single modalities and a traditional delivery setting, evidence from digital interventions remains limited and mixed. For internet-delivered cognitive behavioral therapy (CBT), baseline IBS symptoms was the only identified predictor, while female sex predicted response to an app providing dietary advice for the Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP) diet (16, 28). Beyond IBS, research on guided, psychological internet-based interventions highlights treatment-related variables such as adherence, treatment credibility and therapeutic relationship, as consistent predictors of better outcomes (29).

The aim of this study was to explore both baseline characteristics and treatment-related variables associated with clinically meaningful improvements in IBS symptoms and quality of life following a multidisciplinary internet-delivered intervention. Understanding variables associated with improvements may contribute to hypothesis generation and future development of predictive models that can inform patient and clinician decision-making, enhance precision in IBS care, and support program optimization of internet-delivered interventions for IBS patients.

# 2. Methods

## 2.1 Design

The present study is a secondary analysis of data from an RCT comparing internet-delivered CBT (n = 145), FODMAP diet (n = 139), or their combination (n = 142), against internet-delivered general patient education (n = 131) as an active control (30). Because the original RCT demonstrated no statistically significant between-group differences in the outcomes of interest, and adherence patterns were comparable across groups, data from all groups were pooled. Treatment arm was included as a covariate in all models to account for the original randomization structure. The study was reviewed and approved by the Regional Committees for Medical and Health Research Ethics Western Norway, Bergen, Norway (ID # 630038), was registered on ClinicalTrials.gov ID (#NCT06117865), and all participants provided written informed consent.

## 2.2 Participants

Participants were self-recruited between December 2023 and March 2025 through social media, national newspapers and magazines, local radio interviews, professional journals, and the national IBS patient organization. Screening was conducted through an online form followed by telephone confirmation. Eligible participants were adults (18–70 years) living in Norway who reported a clinician-confirmed diagnosis of IBS established in primary or secondary healthcare services. Additional inclusion criteria are detailed in Table 1. Participants were included in this secondary analysis if they completed baseline and 3-month follow-up measures for the primary outcome.

Table 1
Eligibility criteria. Reproduced from Thuen et al (30), licensed under CC BY 4.0.

| Category | Criterion |
|---|---|
| Diagnosis | Diagnosed with IBS in primary or secondary healthcare. |
| Age | 18–70 years. |
| Diagnostic criteria | Meets Rome IV criteria for IBS. |
| Medical history | No known history or current presence of:<br>– Symptomatic endometriosis<br>– Type 1 or 2 diabetes mellitus<br>– Malignant disease (excluding basal cell carcinoma)<br>– Severe psychiatric disorder (e.g., treatment-requiring schizophrenia or bipolar disorder with functional impairment)<br>– Alcohol or drug abuse<br>– Inflammatory bowel disease (including microscopic colitis)<br>– Celiac disease<br>– Diverticulitis or ileus<br>– Major abdominal surgery (except appendectomy, cholecystectomy, cesarean section, and hysterectomy)<br>Negative colonoscopy within the last 5 years (if > 55 years)<br>Not pregnant and not planning pregnancy within the next 6 months<br>No unexplained symptoms such as:<br>– Night sweats (repeated episodes soaking nightclothes or bedding)<br>– Unintentional weight loss ≥ 4.5 kg or ≥ 5% of normal body weight within < 6 months<br>– Blood in stool |
| Technological access | Access to a national electronic ID system (BankID) and a tablet, smartphone, or personal computer with internet. |
| Protocol compliance | Able to comply with study protocol requirement and able to read and understand Norwegian. |

# 2.3 Intervention

Full details on the intervention can be found in the original research study (30). Briefly, the internet-delivered intervention provides educational modules designed to support self-management of IBS symptoms. All participants received three core patient education modules providing basic information

about IBS symptoms, pain physiology, and general diet and lifestyle advice. Depending on randomization, participants in three of the four original treatment groups also received a CBT module targeting symptom-related avoidance and exposure, a structured FODMAP diet module, or both. Figure 1 illustrates the shared and group-specific components of the interventions (30).

**Note**

Module 1: Basic information about IBS (23 pages); Module 2: Information about pain physiology (13 pages); Module 3: General diet and lifestyle advice (14 pages); Module 4: Cognitive behavioral therapy (14 pages of psychoeducational content, 15 pages of exercises, and 3 audio files); Module 5: the FODMAP diet (45 pages, recipe booklet, suggested daily menus, and a structured reintroduction worksheet). CBT = Cognitive behavioral therapy; FODMAP = Fermentable Oligo-, Di-, Monosaccharides And Polyols.

The intervention was developed to support self-management by addressing key physiological, cognitive, and behavioral processes known to influence IBS symptoms. The content aimed to strength participants' sense of control and confidence, normalize common IBS experiences, and promote insight into how daily routines, diet, and stress can shape symptom patterns. The modules were primarily text-based and supplemented with videos, exercises, and optional resources. To provide therapeutic support, all participants could initiate asynchronous messaging with a clinical dietitian. Both the intervention and the message function were accessed through a secure digital platform (EG CheckWare, Trondheim, Norway) and they were encouraged to complete the modules within three months.

# 2.4 Measures

All questionnaires were self-reported and completed at baseline, 3 months and 6 months through the same electronic platform used for the internet-delivered intervention. Because 3 months was our primary endpoint and the completion rate was low at 6 months, data from baseline and 3 months were used for this secondary analysis. Treatment adherence and use of the message function were based on platform-generated usage data.

# 2.4.1 Outcome measures

The primary outcome was a reduction in the total IBS Severity Scoring System (IBS-SSS) by at least 50 points, consistent with prior recommendations and with the broader literature on clinically meaningful symptom improvement in IBS (31). Using the same cut-off, the assumed placebo response rate in IBS patients is estimated to be 27% (32). In contrast, the original randomized controlled trial underpinning this predictor study showed response rates ranging from 43% to 45% (30). This supports the interpretation of this threshold as indicative of clinically relevant, treatment-related improvement.

To address the inherent score bounding of symptom scales, we conducted a sensitivity analysis using a cut-off for response of at least 30% reduction in IBS-SSS. Although the Food and Drug Administration (FDA) recommend using a cut-off of at least 30% improvement in abdominal pain score (33), we chose

to apply this cut-off to the global IBS-SSS to ensure comparability of the sensitivity analysis. The threshold of 30% improvement is also widely used as a responder cut-off in the chronic pain literature (34–37).

To explore effects beyond gut symptoms, IBS-QoL was chosen as a secondary outcome. An increase on the IBS-QoL score of at least 14 points was chosen as the responder cut-off, consistent with prior recommendations on clinically meaningful improvement (38).

## 2.3.2 Predictors

Given the exploratory aim of this study, and the limited literature on predictors of response in internet-delivered IBS interventions, predictors were pre-specified pragmatically based on clinical relevance, supported by prior IBS research where available. Predictor variables included demographic variables, IBS characteristics, and psychological and dietary characteristics. In addition to baseline variables, treatment-related variables were included to explore potential process effects on outcomes. All categorical predictors were examined for sparse categories. Where cell counts were insufficient for stable estimation, categories were collapsed based on conceptual similarity and distributional considerations.

### 2.3.2.1 Demographic variables

This included gender (categorical: female/male), education level (categorical: higher (university or college)/lower (primary or high school level)), age (continuous: years), work status (categorical: working (part-time, full-time or studying)/out of work (retired or disability pension) and marital status (categorical: married, cohabitant or single).

### 2.3.2.2 IBS characteristics

This included baseline IBS-SSS (continuous: 0-500, higher score indicates more severe IBS) (31), IBS diagnosis confirmed by the Rome IV criteria (categorical: no/yes), duration of gastrointestinal complaints (continuous: years) and IBS subtype defined the Rome IV criteria (categorical: IBS-M (including IBS-U)/IBS-C/IBS-D) (39).

### 2.3.2.3 Psychological and dietary characteristics

Psychological characteristics included baseline IBS-QoL overall score (continuous: 0-100, higher score indicates higher quality of life) (40), the Hospital Anxiety and Depression Scale (anxiety and depression subscale treated as separate variables) (continuous: 0–21, higher score indicates higher levels of anxiety or depression) (41) and the Credibility and Expectancy scale (credibility and expectancy subscales treated as separate variables) (continuous: 1–9, higher score indicates higher levels of credibility or expectancy) (42). Because numerous methods for scoring the CEQ scale are used, subscale scores were calculated as the mean of the three constituent items to ease interpretation and comparability with previous studies (43). Dietary characteristics included experience with the FODMAP

diet (categorical: no experience/having experienced poor effect (no or small effect)/having experienced good effect (medium, large or very large effect)).

#### 2.3.2.4 Treatment-related variables

This included adherence to the patient education (categorical: no/yes), adherence to the CBT module (categorical: no/yes), adherence to the FODMAP module (categorical: no/yes) and usage of the message function (categorical: no/yes). Adherence was defined as spending ≥ 10 minutes on the respective module. Adherence to patient education was defined as being adherent to two out of three core patient education modules. Usage of the message function was defined as having sent one or more messages.

## 2.4 Statistical analysis

Statistical analyses were conducted using R Version 4.5.0. Analyses followed a two-step process to identify significant predictors. Univariable logistic regression analyses were first performed to examine the unadjusted association between each independent variable and each binary outcome. Subsequently, multivariable logistic regression models were used to estimate the unique association of each variable with each outcome, adjusting for all other variables included in the model. For each outcome variable, two multivariable logistic regression models were fitted. The first model included only baseline predictors to examine their associations with treatment response. This model aimed to identify patient characteristics that predict response independently of treatment-related factors, providing insights that may inform clinical decision-making prior to program initiation. The second model included both baseline predictors and treatment-related variables. This approach aimed to identify patient characteristics associated with treatment response given patient engagement during the program, providing insights that may guide program optimization.

A significance level of $p < 0.05$ was applied in all regression analyses. Each regression model used a binomial distribution with a logit link function. The statistical significance of individual predictors was assessed using Wald tests, and corresponding p-values were reported for their associated odds ratios (OR). For categorical predictors, ORs represent the relative odds of being classified as a responder compared with the reference category. For continuous predictors, ORs represent the multiplicative change in odds of response for each one-unit increase in the predictor. Odds ratios and their 95% confidence intervals (CIs) were obtained by exponentiating model coefficients and their confidence limits. Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test, with nonsignificant results indicating adequate fit. Discrimination was assessed by the area under the receiver operating characteristic curve (AUC) with 95% CI estimated using the DeLong method. The AUC reflects the model's ability to discriminate between responders and non-responders. An AUC of 0.5 indicates performance equivalent to chance, whereas an AUC of 1.0 indicates perfect discrimination. Nagelkerke's pseudo-$R^2$ was assessed as an indication of the proportion of variance explained by the model with higher values reflecting greater explanatory power. Multicollinearity was assessed using

variance inflation factors (VIF) with values > 5 considered to indicate problematic levels of collinearity. All VIF values for the selected predictors were below this threshold.

# 3 Results

# 3.1 Descriptive statistics

Descriptive statistics for all predictor variables are shown in Table 2. In total, 350 participants were included. The sample was predominantly female (87%), had a high educational level (70% had a college or university education), and most participants were working or studying (79%).

Table 2
Baseline Characteristics

| Characteristic | Overall (n = 350) |
|---|---|
| IBS-SSS Baseline | 295.91 (73.95); 120.00–479.00 |
| Baseline IBS- QOL | 47.55 (20.63); 3.68–97.06 |
| Sex | |
| Female | 305 (87%) |
| Male | 45 (13%) |
| Age | 40.65 (12.72); 18.00–69.00 |
| Education Level | |
| Higher | 251 (72%) |
| Lower | 99 (28%) |
| Work Status | |
| Working | 276 (79%) |
| Out of work | 74 (21%) |
| Marital | |
| Married | 135 (39%) |
| Cohabitant | 96 (27%) |
| Single | 119 (34%) |
| Rome IV IBS Type | |
| Rome IV IBS negative | 75 (21%) |
| Rome IV IBS positive | 275 (79%) |
| Years with GI Complaints | 18.38 (12.68); 0.00–65.00 |
| IBS Subtype | |
| IBS-M | 145 (41%) |
| IBS-C | 77 (22%) |
| IBS-D | 128 (37%) |

Mean (SD); range for continuous variables, n (%) for categorical variables; IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Characteristic | Overall (n = 350) |
|---|---|
| Treatment Credibility | 6.05 (1.59); 1.00–9.00 |
| Treatment Expectancy | 5.33 (1.47); 1.00–9.00 |
| Anxiety Score | 9.35 (4.22); 0.00–21.00 |
| Depression Score | 5.33 (3.34); 0.00–16.00 |
| Previous or current experience with the FODMAP diet | |
| No experience | 100 (29%) |
| Experienced poor effect | 74 (21%) |
| Experienced good effect | 176 (50%) |
| Adherence patient education, yes | 220 (63%) |
| Adherence CBT, yes | 51 (15%) |
| Adherence FODMAP, yes | 31 (8.9%) |
| Sent any messages, yes | 121 (35%) |

Mean (SD); range for continuous variables, n (%) for categorical variables; IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

## 3.2 Predictors of response defined by a ≥ 50-point reduction on the IBS-SSS

158 out of 350 participants (45%) experienced a clinically meaningful response, defined by a ≥ 50-point reduction in IBS-SSS. Results from the univariable and multivariable regression analyses are presented in Table 3.

Univariable analyses identified two significant predictors: previous poor treatment effect of the FODMAP diet was associated with reduced odds of improvement compared to FODMAP-naïve participants, while more severe IBS-symptoms at baseline was associated with increased odds of improvement.

The multivariable model including baseline predictors showed good calibration ($\chi^2(8) = 2.4015$, $p = 0.9662$) and moderate discrimination (AUC = 0.733; 95% CI: 0.681 to 0.785), but explained only a modest proportion of the variance (Nagelkerke pseudo-$R^2 = 0.22$). Having higher baseline IBS-QoL and more severe IBS-symptoms at baseline were uniquely associated with increased odds of responding, while having longer duration of gastrointestinal symptoms and previous poor treatment effect of the FODMAP diet were uniquely associated with decreased odds of responding.

When treatment-related predictors were added, the same baseline predictors remained significant. In addition, adherence to patient education was uniquely associated with increased odds of responding. This extended model showed good calibration ($\chi^2(8) = 4.9946$, $p = 0.7582$) and moderate discrimination (AUC = 0.750; 95% CI: 0.699 to 0.801), but still only explained a modest proportion of variance (Nagelkerke pseudo-$R^2 = 0.246$).

Table 3
Results from univariable and multivariable models of predictors for ≥ 50-point reduction in IBS-SSS

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| **Demographic** | | | | | | |
| Sex | | | | | | |
| *Female (ref.)* | | | | | | |
| *Male* | 1.32 [0.70, 2.48] | 0.395 | 1.27 [0.61, 2.65] | 0.529 | 1.27 [0.60, 2.69] | 0.526 |
| Education level | | | | | | |
| *University or college (ref.)* | | | | | | |
| *Primary or high school level* | 0.92 [0.57, 1.47] | 0.719 | 0.85 [0.49, 1.47] | 0.566 | 0.86 [0.49, 1.49] | 0.581 |
| Age | 1.01 [0.99, 1.02] | 0.533 | 1.01 [0.99, 1.04] | 0.304 | 1.01 [0.99, 1.04] | 0.337 |
| Work status | | | | | | |
| *Part-time, full-time or studying (ref.)* | | | | | | |
| *Retired or disability pension* | 1.05 [0.62, 1.75] | 0.859 | 1.05 [0.55, 1.99] | 0.881 | 1.11 [0.58, 2.11] | 0.759 |
| Marital status | | | | | | |
| *Married (ref.)* | | | | | | |
| *Cohabitant* | 0.90 [0.53, 1.52] | 0.686 | 0.73 [0.39, 1.36] | 0.318 | 0.72 [0.38, 1.36] | 0.314 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| *Single* | 0.93 [0.56, 1.52] | 0.765 | 0.84 [0.46, 1.55] | 0.587 | 0.87 [0.46, 1.61] | 0.651 |
| **IBS characteristics** | | | | | | |
| Baseline IBS-SSS | **1.01 [1.00, 1.01]** | **< 0.001** | **1.01 [1.01, 1.02]** | **< 0.001** | **1.01 [1.01, 1.02]** | **< 0.001** |
| Rome IV positive | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.61 [0.96, 2.77] | 0.077 | 1.55 [0.84, 2.90] | 0.169 | 1.52 [0.81, 2.89] | 0.197 |
| Rome IV subtype | | | | | | |
| *IBS-M (ref.)* | | | | | | |
| *IBS-C* | 1.53 [0.88, 2.68] | 0.133 | 1.58 [0.84, 2.98] | 0.155 | 1.56 [0.82, 2.98] | 0.174 |
| *IBS-D* | 1.17 [0.73, 1.90] | 0.513 | 1.33 [0.78, 2.29] | 0.293 | 1.38 [0.80, 2.38] | 0.247 |
| Duration of gastrointestinal complaints | 0.99 [0.97, 1.00] | 0.143 | **0.97 [0.95, 1.00]** | **0.019** | **0.97 [0.95, 0.99]** | **0.014** |
| **Psychological and dietary characteristics** | | | | | | |
| Baseline IBS-QoL | 1.00 [0.99, 1.01] | 0.723 | **1.02 [1.00, 1.04]** | **0.021** | **1.02 [1.00, 1.04]** | **0.014** |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| HADS anxiety score | 1.01 [0.96, 1.06] | 0.765 | 1.01 [0.94, 1.09] | 0.769 | 1.01 [0.94, 1.08] | 0.856 |
| HADS depression score | 1.00 [0.93, 1.06] | 0.895 | 0.96 [0.88, 1.06] | 0.427 | 0.96 [0.88, 1.06] | 0.434 |
| Credibility score | 1.11 [0.97, 1.28] | 0.118 | 1.05 [0.87, 1.27] | 0.635 | 1.05 [0.87, 1.28] | 0.606 |
| Expectancy score | 1.15 [1.00, 1.34] | 0.053 | 1.07 [0.87, 1.32] | 0.532 | 1.06 [0.86, 1.31] | 0.596 |
| FODMAP experience | | | | | | |
| *No previous or current experience (ref.)* | | | | | | |
| *Experienced no or small effect* | **0.38 [0.20, 0.70]** | **0.002** | **0.35 [0.17, 0.70]** | **0.004** | **0.35 [0.17, 0.71]** | **0.004** |
| *Experienced medium, large or very large effect* | 0.62 [0.38, 1.02] | 0.058 | 0.60 [0.34, 1.05] | 0.076 | 0.66 [0.37, 1.16] | 0.148 |
| **Treatment-related variables** | | | | | | |
| Adherence to the patient education | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.54 [0.99, 2.41] | 0.056 | - | - | **2.00 [1.16, 3.48]** | **0.014** |
| Adherence to the CBT | | | | | | |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | OR [95% CI] | p-value | OR [95% CI] | p-value | OR [95% CI] | p-value |
| module | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.18 [0.61, 2.28] | 0.616 | - | - | 1.08 [0.49, 2.39] | 0.843 |
| Adherence to the FODMAP module | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.06 [0.48, 2.31] | 0.892 | - | - | 0.86 [0.34, 2.17] | 0.757 |
| Use of asynchronous follow-up | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 0.97 [0.62, 1.51] | 0.881 | - | - | 0.69 [0.41, 1.16] | 0.164 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

# 3.3 Predictors of response defined by a ≥ 30% reduction on the IBS-SSS

86 out of 350 participants (25%) experienced a clinically meaningful response, defined by a ≥ 30% reduction in IBS-SSS. Results from the univariable and multivariable regression analyses are presented in Table 4.

Univariable analyses identified two significant variables. Previous poor treatment effect of the FODMAP diet reduced the odds of responding compared FODMAP-naïve participants, while adherence to the CBT module increased the odds of responding when examined separately.

Only one predictor remained significant in the multivariable models. Previous poor treatment effect of the FODMAP diet reduced the odds of responding compared FODMAP-naïve participants. The multivariable model including baseline predictors showed good calibration ($\chi^2(8) = 3.9951$, $p = 0.8576$) and moderate discrimination (AUC = 0.664; 95% CI: 0.595 to 0.733), but only a small proportion of the variance was explained (Nagelkerke pseudo-$R^2 = 0.087$). When adding the treatment-related variables, calibration ($\chi^2(8) = 8.1647$, $p = 0.4175$), discrimination (AUC = 0.681; 95% CI: 0.613 to 0.749) and the explained variation remained similar (Nagelkerke pseudo-$R^2 = 0.108$).

Table 4
Results from univariable and multivariable models of predictors for ≥ 30% reduction in IBS-SSS

| **Predictor** | **Univariate** | | **Multivariate (baseline characteristics)** | | **Multivariate (baseline characteristics and treatment-related variables)** | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| **Demographic** | | | | | | |
| Sex | | | | | | |
| *Female (ref.)* | | | | | | |
| *Male* | 1.31 [0.63, 2.60] | 0.445 | 1.19 [0.53, 2.55] | 0.657 | 1.27 [0.57, 2.76] | 0.547 |
| Education level | | | | | | |
| *University or college (ref.)* | | | | | | |
| *Primary or high school level* | 1.13 [0.65, 1.91] | 0.657 | 1.10 [0.60, 1.96] | 0.757 | 1.05 [0.57, 1.90] | 0.865 |
| Age | 1.00 [0.98, 1.02] | 0.891 | 0.99 [0.97, 1.02] | 0.577 | 0.99 [0.97, 1.02] | 0.676 |
| Work status | | | | | | |
| *Part-time, full-time or studying (ref.)* | | | | | | |
| *Retired or disability pension* | 0.98 [0.53, 1.76] | 0.955 | 1.18 [0.58, 2.35] | 0.639 | 1.16 [0.57, 2.34] | 0.672 |
| Marital status | | | | | | |
| *Married (ref.)* | | | | | | |
| *Cohabitant* | 0.78 [0.42, | 0.416 | 0.75 [0.38, 1.46] | 0.398 | 0.76 [0.38, 1.49] | 0.422 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| | 1.42] | | | | | |
| *Single* | 0.77 [0.43, 1.36] | 0.369 | 0.76 [0.39, 1.48] | 0.422 | 0.77 [0.39, 1.51] | 0.446 |
| **IBS characteristics** | | | | | | |
| Baseline IBS-SSS | 1.00 [1.00, 1.00] | 0.967 | 1.00 [1.00, 1.01] | 0.200 | 1.00 [1.00, 1.01] | 0.167 |
| Rome IV positive | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 0.79 [0.45, 1.44] | 0.436 | 0.84 [0.45, 1.61] | 0.585 | 0.83 [0.44, 1.62] | 0.581 |
| Rome IV subtype | | | | | | |
| *IBS-M (ref.)* | | | | | | |
| *IBS-C* | 1.42 [0.75, 2.66] | 0.280 | 1.51 [0.77, 2.95] | 0.225 | 1.48 [0.75, 2.92] | 0.254 |
| *IBS-D* | 1.18 [0.67, 2.07] | 0.565 | 1.29 [0.72, 2.34] | 0.395 | 1.38 [0.76, 2.52] | 0.291 |
| Duration of gastrointestinal complaints, years | 0.99 [0.97, 1.01] | 0.287 | 0.99 [0.96, 1.01] | 0.323 | 0.98 [0.96, 1.01] | 0.215 |
| **Psychological and dietary characteristics** | | | | | | |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| Baseline IBS-QoL | 1.01 [1.00, 1.02] | 0.056 | 1.01 [1.00, 1.03] | 0.138 | 1.01 [1.00, 1.03] | 0.150 |
| HADS anxiety score | 0.99 [0.93, 1.05] | 0.670 | 1.04 [0.96, 1.12] | 0.378 | 1.03 [0.96, 1.12] | 0.399 |
| HADS depression score | 0.93 [0.86, 1.00] | 0.071 | 0.92 [0.83, 1.02] | 0.124 | 0.92 [0.83, 1.02] | 0.129 |
| Credibility score | 1.13 [0.97, 1.33] | 0.116 | 1.07 [0.88, 1.32] | 0.488 | 1.05 [0.86, 1.30] | 0.621 |
| Expectancy score | 1.15 [0.97, 1.36] | 0.115 | 1.08 [0.86, 1.36] | 0.496 | 1.07 [0.85, 1.35] | 0.553 |
| FODMAP experience | | | | | | |
| *No previous or current experience (ref.)* | | | | | | |
| *Experienced no or small effect* | **0.37 [0.17, 0.78]** | **0.011** | **0.42 [0.18, 0.92]** | **0.036** | **0.42 [0.18, 0.92]** | **0.035** |
| *Experienced medium, large or very large effect* | 0.69 [0.40, 1.20] | 0.186 | 0.70 [0.39, 1.25] | 0.223 | 0.70 [0.39, 1.28] | 0.247 |
| **Treatment-related variables** | | | | | | |
| Adherence to the patient education | | | | | | |
| *No (ref.)* | | | | | | |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| *Yes* | 1.41 [0.85, 2.40]] | 0.193 | - | - | 1.24 [0.68, 2.28] | 0.489 |
| Adherence to the CBT module | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | **2.30 [1.10, 4.76]** | **0.025** | - | - | 2.26 [0.97, 5.27] | 0.058 |
| Adherence to the FODMAP module | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.26 [0.51, 2.92] | 0.604 | - | - | 1.03 [0.38, 2.66] | 0.955 |
| Use of asynchronous follow-up | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.09 [0.65, 1.80] | 0.743 | - | - | 0.86 [0.48, 1.50] | 0.597 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = irritable bowel syndrome; FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

# 3.4 Predictors of response defined by a ≥ 14-point reduction on the IBS-QoL

77 out of 350 participants (22%) experienced a clinically meaningful response defined by a ≥ 14-point reduction in IBS-QoL. Results from the univariable and multivariable regression analyses are presented in Table 5.

Univariable analyses identified five significant predictors: higher baseline IBS-QoL reduced the odds of responding, while more severe IBS-symptoms at baseline, higher baseline anxiety, previous good treatment effect of the FODMAP diet, and higher perceived credibility of the intervention pretreatment all increased the odds of responding when examined separately.

However, in both multivariable models only baseline IBS-QoL remained significant. The multivariable model including baseline predictors showed good calibration ($\chi^2(8) = 8.478$, $p = 0.3882$) and moderate discrimination (AUC = 0.732; 95% CI: 0.668 to 0.796), but only a moderate proportion of the variance was explained (Nagelkerke pseudo-$R^2 = 0.19$). When adding the treatment-related variables, calibration ($\chi^2(8) = 8.1249$, $p = 0.4214$), discrimination (AUC = 0.750; 95% CI: 0.687 to 0.814) and the explained variation remained similar (Nagelkerke pseudo-$R^2 = 0.214$).

Table 5
Results from univariable and multivariable models of predictors for ≥ 14-point reduction in IBS-QoL

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | OR [95% CI] | p-value | OR [95% CI] | p-value | OR [95% CI] | p-value |
| **Demographic** | | | | | | |
| Sex | | | | | | |
| *Female (ref.)* | | | | | | |
| *Male* | 1.05 [0.47, 2.18] | 0.898 | 1.46 [0.59, 3.39] | 0.395 | 1.51 [0.61, 3.58] | 0.357 |
| Education level | | | | | | |
| *University or college (ref.)* | | | | | | |
| *Primary or high school level* | 0.80 [0.44, 1.41] | 0.457 | 0.66 [0.33, 1.27] | 0.228 | 0.61 [0.30, 1.21] | 0.168 |
| Age | 0.99 [0.97, 1.01] | 0.410 | 1.00 [0.97, 1.03] | 0.978 | 1.00 [0.97, 1.03] | 0.843 |
| Work status | | | | | | |
| *Part-time, full-time or studying (ref.)* | | | | | | |
| *Retired or disability pension* | 0.49 [0.23, 0.97] | 0.054 | 0.51 [0.22, 1.12] | 0.107 | 0.47 [0.20, 1.05] | 0.077 |
| Marital status | | | | | | |
| *Married (ref.)* | | | | | | |
| *Cohabitant* | 0.92 [0.46, 1.80] | 0.804 | 0.94 [0.44, 2.01] | 0.889 | 0.99 [0.45, 2.13] | 0.972 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** | **OR [95% CI]** | **p-value** |
| *Single* | 1.68 [0.94, 3.04] | 0.083 | 1.53 [0.76, 3.11] | 0.238 | 1.65 [0.80, 3.41] | 0.174 |
| **IBS characteristics** | | | | | | |
| Baseline IBS-SSS | **1.00 [1.00, 1.01]** | **0.046** | 1.00 [1.00, 1.00] | 0.927 | 1.00 [1.00, 1.00] | 0.979 |
| Rome IV positive | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 0.91 [0.50, 1.73] | 0.775 | 0.64 [0.32, 1.32] | 0.217 | 0.60 [0.29, 1.25] | 0.162 |
| Rome IV subtype | | | | | | |
| *IBS-M (ref.)* | | | | | | |
| *IBS-C* | 1.40 [0.73, 2.66] | 0.301 | 1.21 [0.59, 2.45] | 0.592 | 1.15 [0.56, 2.33] | 0.709 |
| *IBS-D* | 0.90 [0.49, 1.62] | 0.725 | 0.77 [0.40, 1.47] | 0.432 | 0.79 [0.41, 1.53] | 0.493 |
| Duration of gastrointestinal complaints, years | 1.00 [0.98, 1.02] | 0.871 | 1.01 [0.98, 1.04] | 0.559 | 1.00 [0.98, 1.03] | 0.751 |
| **Psychological and dietary characteristics** | | | | | | |
| Baseline IBS-QoL | **0.97 [0.96, 0.98]** | **< 0.001** | **0.97 [0.95, 0.99]** | **0.003** | **0.97 [0.95, 0.99]** | **0.003** |
| HADS anxiety score | **1.10 [1.03,** | **0.003** | 1.05 [0.96, | 0.292 | 1.05 [0.96, 1.15] | 0.276 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | OR [95% CI] | p-value | OR [95% CI] | p-value | OR [95% CI] | p-value |
| | **1.17]** | | 1.14] | | | |
| HADS depression score | 1.06 [0.99, 1.15] | 0.111 | 0.99 [0.89, 1.10] | 0.806 | 0.99 [0.89, 1.10] | 0.894 |
| Credibility score | **1.19 [1.01, 1.40]** | **0.042** | 1.14 [0.91, 1.42] | 0.263 | 1.10 [0.88, 1.39] | 0.388 |
| Expectancy score | 1.12 [0.94, 1.33] | 0.213 | 1.00 [0.78, 1.27] | 0.984 | 0.98 [0.77, 1.25] | 0.885 |
| FODMAP experience | | | | | | |
| *No previous or current experience (ref.)* | | | | | | |
| *Experienced no or small effect* | 0.81 [0.33, 1.88] | 0.627 | 0.65 [0.25, 1.62] | 0.359 | 0.57 [0.21, 1.46] | 0.248 |
| *Experienced medium, large or very large effect* | **2.16 [1.17, 4.15]** | **0.017** | 1.81 [0.93, 3.66] | 0.090 | 1.74 [0.88, 3.57] | 0.121 |
| **Treatment-related variables** | | | | | | |
| Adherence to the patient education | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.31 [0.77, 2.28] | 0.322 | - | - | 1.10 [0.57, 2.15] | 0.775 |
| Adherence to the CBT module | | | | | | |
| *No (ref.)* | | | | | | |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

| Predictor | Univariate | | Multivariate (baseline characteristics) | | Multivariate (baseline characteristics and treatment-related variables) | |
|---|---|---|---|---|---|---|
| | OR [95% CI] | p-value | OR [95% CI] | p-value | OR [95% CI] | p-value |
| *Yes* | 1.96 [0.93, 4.06] | 0.071 | - | - | 1.83 [0.75, 4.44] | 0.183 |
| Adherence to the FODMAP module | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 2.12 [0.89, 4.90] | 0.080 | - | - | 1.96 [0.70, 5.32] | 0.190 |
| Use of asynchronous follow-up | | | | | | |
| *No (ref.)* | | | | | | |
| *Yes* | 1.27 [0.75, 2.14] | 0.367 | - | - | 1.17 [0.63, 2.14] | 0.611 |

Note: All models adjusted for treatment arm. Predictors significant at P < 0.05 are shown in bold. IBS = FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Score; IBS-QoL = Irritable Bowel Syndrome Quality of Life; HADS = Hospital Anxiety and Depression Scale; CBT = cognitive behavioral therapy; IBS-M = IBS mixed/unclassified; IBS-C = IBS constipation; IBS-D = IBS diarrhea

# 4 Discussion

This secondary analysis aimed to explore baseline characteristics and treatment-related variables associated with clinical meaningful improvements in IBS symptoms and IBS-QoL. Using data from an RCT of a multidisciplinary internet-delivered intervention for patients with IBS, several associations were observed between predictors and treatment response. However, only previous poor treatment effect of the FODMAP diet was consistently associated with reduced odds of improvement in IBS-SSS, and higher baseline IBS-QoL was consistently associated with reduced odds of improvement in IBS-QoL. Across all models, overall predictive power was low.

Taken together, these findings suggest that neither currently measured baseline characteristics, nor treatment-related variables assessed in this study, provided meaningful predictive utility for identifying responders to a multidisciplinary internet-delivered intervention for patients with IBS. This highlights the complexity of forecasting treatment response in IBS and suggests that factors not captured in the

current analysis may be relevant to understanding who benefits from digital interventions. Based on our interpretation of the findings, we will highlight several important implications for clinical practice and future research.

# 4.1 The role of previous experiences

Previous poor treatment effect of the FODMAP diet was the only predictor that remained consistently among models for improvement in IBS symptoms. This finding suggests that previous treatment effects matter and aligns with research indicating that patient reactions to self-management interventions are shaped by previous successes and failures in managing their condition (44).

It is not possible to draw firm conclusions from the current study, but several mechanisms may explain this association. First, previous poor treatment effect of a highly structured intervention, such as the FODMAP diet, may undermine self-efficacy for future behavioral change. Self-efficacy is shown both to increase during internet-delivered interventions and to mediate treatment outcomes of mental health interventions (44). Second, participants with previous poor dietary treatment effect may have thought of the internet-delivered intervention as one of the few remaining avenues for symptom management, resulting in expectations that could not be fully realized. Notably, in line with previous research on internet-delivered treatments for IBS, baseline expectancies and perceived credibility were not identified as predictors in our study (18). However, these dimensions were assessed only before participants accessed their treatment, meaning they were unaware of the content of the treatment when responding. Third, previous poor treatment effect of the FODMAP diet may indicate greater clinical complexity and a more extensive treatment history. IBS patients commonly describe repeated treatment attempts, with one study in tertiary care reporting an average of 12 different treatment modalities tried (45). In addition, longer symptom duration was associated with reduced odds of improvement in our study. The pattern of long-standing symptoms and previous treatment failure may reflect a subgroup that could need additional attention or more intensive treatment approaches.

While internet-delivered interventions represent a promising and scalable option, our findings indicate that they may not be sufficient for a subgroup of IBS patients with previous treatment failure. Clinically, these findings highlight the importance of acknowledging the complex interplay between previous treatment experiences, self-efficacy, and expectancies. They also underscore the potential value of offering evidence-based internet-delivered interventions as an early treatment option, thereby reducing the risk of repeated unsuccessful self-management attempts. Given the considerable individual and societal burden associated with IBS, earlier access to effective internet-delivered treatment may help improve patient trajectories while easing pressure on already strained healthcare systems.

# 4.2 Predictors of symptomatic improvement

Higher baseline IBS severity was associated with improvement when defined as an absolute ≥ 50-point reduction in IBS-SSS, consistent with previous research on IBS interventions (21–23, 28). This association did not remain significant when response was defined as a relative ≥ 30% reduction in IBS-

SSS, suggesting that the initial finding reflects greater potential for absolute change among those with higher baseline scores rather than a true differential treatment effect (46).

Consistent with previous research on IBS interventions, higher baseline IBS-QoL was associated with symptomatic improvement when defined as an absolute ≥ 50-point reduction in IBS-SSS (20, 25). One possible explanation is that patients with better quality of life at baseline may have been less burdened by their symptoms, enabling greater engagement with behavioral strategies and treatment content. However, this interpretation should be made cautiously, as the association did not remain significant when response was defined as a relative ≥ 30% reduction in IBS-SSS.

Beyond baseline characteristics, adherence to the general patient education was associated with increased odds of improvement when defined as an absolute ≥ 50-point reduction in IBS-SSS. This finding resonates with psychological literature, where adherence is consistently identified as a predictor of treatment success in internet-based interventions (29). Interestingly, we did not identify adherence to the CBT module or the FODMAP module as predictors. This may be related to the more intensive content of those interventions implying that adherence, measured as module completion, may not have fully captured meaningful engagement with these modules.

Taken together, neither baseline IBS symptoms nor baseline IBS-QoL was consistently associated with treatment response across outcome definitions. These findings suggest that patient selection should not be based on currently measured baseline characteristics and highlight the need for identifying more robust predictors. The mixed adherence results further indicate that module completion may not adequately capture meaningful patient engagement. Future research should therefore focus on exploring how to enhance engagement, support active participation, and clarify mechanisms of change in internet-delivered interventions for patients with IBS.

## 4.3 The importance of looking beyond symptom change

While symptom improvement is often reported as the primary outcome of treatment success in IBS trials, it is important to acknowledge that improvement in quality of life is a meaningful outcome itself. Previous research in integrated care has shown that quality of life may improve independently of symptom reduction (47). In the present study, higher baseline IBS-QoL was the only variable associated with reduced odds of improvement in IBS-QoL. This aligns with previous research showing baseline quality of life as the most prominent predictor of subsequent improvement (25). The findings for IBS-QoL diverge from the predictors of symptomatic improvement, suggesting that independent processes may underly improvement in IBS-QoL.

Clinically, this pattern indicates that patients who may be less likely to experience symptomatic benefit still can achieve meaningful improvements in quality of life. This highlights the importance of managing expectations for both clinicians and patients by recognizing that improvements in IBS-QoL represent a valuable treatment outcome, particularly within integrated care approaches.

## 4.4 Limitation

In the interpretation of the results from this study, several limitations should be considered. First, this was a secondary analysis of data from an RCT, which was not designed a priori as study of predictors. Consequently, the results should therefore be interpreted with caution and considered explorative. Second, the current study did not impute missing data, and thus caution should be taken in generalizing the findings to participants who do not provide data following internet-delivered interventions. Third, the exploratory power of all our models was small to moderate, indicating that the variables accounted for in our models accounted for little variability in the treatment response. This suggests that factors that were not measured in our study may pose as more robust predictors of treatment effect. Notably, the only measure of previous treatment experiences in our study was experiences with the FODMAP diet. As this was the only consistent predictor of symptomatic effect, it would be of interest to know if treatment experiences with psychological or pharmacological treatments shared the same associations. Fifth, the current study focused on symptomatic improvement and IBS-QoL as outcomes. Although these are key outcomes in IBS research, the study did not examine other clinically relevant outcomes, among others intervention satisfaction, potential negative effects, and changes in healthcare or medication use. Future research should therefore explore predictors of a wider range of outcomes. As more trials of internet-delivered IBS interventions are published, individual patient data meta-analytic approaches may also be valuable to identify more robust predictors across studies. Taken together, the limitations of the current study highlights the need for more research exploring the predictors of response to complex and multidisciplinary internet-delivered interventions for patients with IBS.

# 5 Conclusion

This study is the first to explore predictors of clinical meaningful improvements in IBS symptoms and IBS-QoL from a multidisciplinary internet-delivered intervention for adults with IBS. Although no predictor was consistently identified across all outcomes, previous poor treatment effect of the FODMAP diet was consistently associated with reduced odds of symptomatic improvement, suggesting that previous treatment experiences may influence symptomatic improvement and highlighting the potential benefit of offering internet-delivered interventions as an early treatment option.

Overall, these results highlight the limited utility of the assessed variables for forecasting individual treatment response and underscore the need for future research to identify more robust predictors and explore mechanisms of change in internet-delivered interventions for patients with IBS.

# Abbreviations

IBS: irritable bowel syndrome; FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; CBT: Cognitive Behavioral Therapy; IBS-SSS: IBS severity scale; RCT: randomized controlled trial; IBS-QoL: Irritable bowel syndrome quality of life; HADS: Hospital Anxiety and Depression Scale; CEQ: Credibility/Expectancy scale

# Declarations

Ethics approval and consent to participate: This study was reviewed and approved by the Regional Committees for Medical and Health Research Ethics Western Norway, Bergen, Norway, ID # 630038. The participants provided their written informed consent to participate in this study.

Consent for publication: Not applicable.

Availability of data and materials: De-identified data and statistical code can be provided from the corresponding author upon a reasonable request.

Competing interests: BB has developed and is the managing director of the internet-delivered intervention but derives no financial benefits from it. The other authors have no competing interests to declare.

Funding: This publication presents independent research funded by the Research Council of Norway (Grant reference number: 309264). Haukeland University Hospital is the project owner. The views expressed are those of the author(s) and not necessarily those of the Research Council of Norway or Haukeland University Hospital. This study was undertaken as part of the main author’s PhD.

Authors' contributions: CT, BB, EKS and GAL were involved in early-stage idea generation and informal discussions prior to the initiation of the original study. CT and BB developed and refined the study protocol for the original study and applied to the ethical committee. While BB was responsible for overseeing the project, CT executed the study including recruitment, randomization, follow-up of participants, statistical analyses, and drafting the manuscript. BD contributed to the idea generation and discussions about statistical analyses in this secondary analysis, and interpretation of outcomes. CT, RMFK, BB, EKS, LASV, GAL and BD critically reviewed and approved the final manuscript.

Acknowledgements: We would like to acknowledge all clinicians involved in the development of the digital treatment program, all participants for their involvement and feedback throughout the study, the patient organization involved in the recruitment and the patient representatives for their feedback throughout the study. The statistical analysis was carried out with support from generative AI tools. Claude AI and ChatGPT were used to assist with R code development, debugging, and documentation. All code was critically reviewed, edited and approved by CT. During the preparation of this manuscript CT used Microsoft Copilot (institutional license) to help organize and structure ideas, generate some text, and improve the readability of the manuscript. All content has been critically reviewed, edited and approved by the authors. No personal or sensitive data was entered into any AI tool. All authors take full responsibility for the academic integrity and the content of the published article.

# References

1. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. The Lancet. 2020;396(10263):1675–88. https://doi.org/10.1016/S0140-6736(20)31548-8

2. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology. 2016;150(6):1257–61. 10.1053/j.gastro.2016.03.035
3. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(10):908–17. https://doi.org/10.1016/s2468-1253(20)30217-x
4. Camilleri M. Diagnosis and Treatment of Irritable Bowel Syndrome: A Review. Jama. 2021;325(9):865–77. https://doi.org/10.1001/jama.2020.22532
5. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel Disorders. Gastroenterology. 2016. 10.1053/j.gastro.2016.02.031
6. Tornkvist NT, Aziz I, Whitehead WE, Sperber AD, Palsson OS, Hreinsson JP, et al. Health care utilization of individuals with Rome IV irritable bowel syndrome in the general population. United European Gastroenterol J. 2021;9(10):1178–88. 10.1002/ueg2.12153
7. Flacco ME, Manzoli L, De Giorgio R, Gasbarrini A, Cicchetti A, Bravi F, et al. Costs of irritable bowel syndrome in European countries with universal healthcare coverage: a meta-analysis. Eur Rev Med Pharmacol Sci. 2019;23(7):2986–3000. 10.26355/eurrev_201904_17580
8. El-Salhy M, Johansson M, Klevstul M, Hatlebakk JG. Quality of life, functional impairment and healthcare experiences of patients with irritable bowel syndrome in Norway: an online survey. BMC Gastroenterol. 2025;25(1):143. 10.1186/s12876-025-03685-6
9. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021;116(1):17–44. 10.14309/ajg.0000000000001036
10. Vasant DH, Paine PA, Black CJ, Houghton LA, Everitt HA, Corsetti M, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut. 2021;70(7):1214–40. 10.1136/gutjnl-2021-324598
11. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. N Engl J Med. 2017;376(26):2566–78. 10.1056/NEJMra1607547
12. Chey WD, Keefer L, Whelan K, Gibson PR. Behavioral and Diet Therapies in Integrated Care for Patients With Irritable Bowel Syndrome. Gastroenterology. 2021;160(1):47–62. 10.1053/j.gastro.2020.06.099
13. D'Silva A, Hua N, Modayil MV, Seidel J, Marshall DA. Digital Health Interventions Are Effective for Irritable Bowel Syndrome Self-Management: A Systematic Review. Dig Dis Sci. 2025;70(2):644–64. 10.1007/s10620-024-08672-7
14. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Short-term and Long-term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2016;14(7):937–47 e4. 10.1016/j.cgh.2015.11.020
15. Dimidi E, McArthur AJ, White R, Whelan K, Lomer MCE. Optimizing educational methods for the low FODMAP diet in disorders of gut-brain interaction: A feasibility randomized controlled trial. Neurogastroenterol Motil. 2023;35(10):e14640. 10.1111/nmo.14640

16. Carbone F, Van den Houte K, Besard L, Tack C, Arts J, Caenepeel P, et al. Diet or medication in primary care patients with IBS: the DOMINO study - a randomised trial supported by the Belgian Health Care Knowledge Centre (KCE Trials Programme) and the Rome Foundation Research Institute. Gut. 2022;71(11):2226–32. 10.1136/gutjnl-2021-325821
17. Pathipati MP, Scott LL, Griser AC, Staller K. Real-world outcomes for a digital prescription mobile application for adults with irritable bowel syndrome. Neurogastroenterol Motil. 2024;36(7):e14811. 10.1111/nmo.14811
18. Ljotsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, et al. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am J Gastroenterol. 2011;106(8):1481–91. 10.1038/ajg.2011.139
19. Wallen H, Ljotsson B, Lindfors P, Forsell E, Hesser H, Svanborg C. Internet-Delivered Exposure-Based Cognitive Behavior Therapy for Irritable Bowel Syndrome: A Clinical Effectiveness Study. Am J Gastroenterol. 2025;120(4):856–63. 10.14309/ajg.0000000000003059
20. Devenney J, Hasan SS, Morris J, Whorwell PJ, Vasant DH. Clinical trial: predictive factors for response to gut-directed hypnotherapy for refractory irritable bowel syndrome, a post hoc analysis. Aliment Pharmacol Ther. 2024;59(2):269–77. 10.1111/apt.17790
21. Manning LP, Tuck CJ, Biesiekierski JR. Predicting response to the low FODMAP diet in irritable bowel syndrome: Current evidence and clinical considerations. Asia Pac J Clin Nutr. 2025;34(3):373–85. 10.6133/apjcn.202506_34(3).0012
22. Algera JP, Demir D, Tornblom H, Nybacka S, Simren M, Storsrud S. Low FODMAP diet reduces gastrointestinal symptoms in irritable bowel syndrome and clinical response could be predicted by symptom severity: A randomized crossover trial. Clin Nutr. 2022;41(12):2792–800. 10.1016/j.clnu.2022.11.001
23. Rometsch C, Martin A, Cosci F. Predictors of Treatment Success of Psychotherapy in Functional Disorders: A Systematic Review of the Literature. Clin Psychol Psychother. 2025;32(2):e70075. 10.1002/cpp.70075
24. Manning LP, Van Den Houte M, Tuck CJ, Van Oudenhove L, Biesiekierski JR. Psychological Factors Predict Response to a Low Fermentable Oligo-, di-, Monosaccharide and Polyol Dietary Intervention in Irritable Bowel Syndrome: A Prospective Cohort Study. United European Gastroenterol J. 2026;14(3):e70204. 10.1002/ueg2.70204
25. Blanchard EB, Lackner JM, Gusmano R, Gudleski GD, Sanders K, Keefer L, et al. Prediction of treatment outcome among patients with irritable bowel syndrome treated with group cognitive therapy. Behav Res Ther. 2006;44(3):317–37. 10.1016/j.brat.2005.01.003
26. Creed F, Fernandes L, Guthrie E, Palmer S, Ratcliffe J, Read N, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology. 2003;124(2):303–17. 10.1053/gast.2003.50055
27. Drossman D, Morris CB, Hu Y, Toner BB, Diamant N, Whitehead WE, et al. Characterization of Health Related Quality of Life (HRQOL) for Patients With Functional Bowel Disorder (FBD) and Its Response

to Treatment. Official journal of the American College of Gastroenterology | ACG. 2007;102(7):1442–53.

28. Ljotsson B, Andersson E, Lindfors P, Lackner JM, Gronberg K, Molin K, et al. Prediction of symptomatic improvement after exposure-based treatment for irritable bowel syndrome. BMC Gastroenterol. 2013;13:160. 10.1186/1471-230X-13-160
29. Haller K, Becker P, Niemeyer H, Boettcher J. Who benefits from guided internet-based interventions? A systematic review of predictors and moderators of treatment outcome. Internet Interv. 2023;33:100635. 10.1016/j.invent.2023.100635
30. Thuen CK, Robin; Assmus, Jörg; Steinsvik, Elisabeth Kjelsvik; Vikøren, Linn Anja Slåke; Arslan, Gülen; Berentsen, Birgitte. Internet-delivered cognitive behavioral therapy and FODMAP diet for adults with irritable bowel syndrome: A randomized controlled trial (preprint). 2026. 10.2139/ssrn.6282914
31. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997;11(2):395–402. 10.1046/j.1365-2036.1997.142318000.x
32. Bosman M, Elsenbruch S, Corsetti M, Tack J, Simren M, Winkens B, et al. The placebo response rate in pharmacological trials in patients with irritable bowel syndrome: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(6):459–73. 10.1016/S2468-1253(21)00023-6
33. (CDER)" USDoHaHSFaDACfDEaR. Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment. 2012. https://www.fda.gov/media/78622/download
34. Scott AJ, Walker J, Karin E, Gandy M, Dudeney J, Heriseanu AI, et al. Exploring predictors of clinical response to a transdiagnostic, internet-delivered psychological intervention for people with chronic health conditions. Health Psychol. 2025;44(6):653–63. 10.1037/hea0001454
35. Moore AR, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain--establishing best practice in the reporting of systematic reviews. Pain. 2010;150(3):386–9. 10.1016/j.pain.2010.05.011
36. Dear BF, Titov N, Perry KN, Johnston L, Wootton BM, Terides MD, et al. The Pain Course: a randomised controlled trial of a clinician-guided Internet-delivered cognitive behaviour therapy program for managing chronic pain and emotional well-being. Pain. 2013;154(6):942–50. 10.1016/j.pain.2013.03.005
37. Dear BF, Staples L, Nielssen O, Titov N. Examining the Effectiveness and Acceptability of Internet-Delivered Psychological Pain Management for Regional and Rural Australians With Chronic Pain. Aust J Rural Health. 2025;33(1):e70008. 10.1111/ajr.70008
38. Drossman D, Morris CB, Hu Y, Toner BB, Diamant N, Whitehead WE, et al. Characterization of health related quality of life (HRQOL) for patients with functional bowel disorder (FBD) and its response to treatment. Am J Gastroenterol. 2007;102(7):1442–53. 10.1111/j.1572-0241.2007.01283.x
39. Palsson OS, Whitehead WE, van Tilburg MA, Chang L, Chey W, Crowell MD, et al. Development and Validation of the Rome IV Diagnostic Questionnaire for Adults. Gastroenterology. 2016. https://doi.org/10.1053/j.gastro.2016.02.014

40. Drossman DA, Patrick DL, Whitehead WE, Toner BB, Diamant NE, Hu Y, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol. 2000;95(4):999–1007. 10.1111/j.1572-0241.2000.01941.x
41. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70. 10.1111/j.1600-0447.1983.tb09716.x
42. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry. 2000;31(2):73–86. 10.1016/s0005-7916(00)00012-4
43. Dear BF. Credibility and expectations: Important factors for understanding clinical response, treatment completion, and dropout in internet-delivered psychological interventions. J Consult Clin Psychol. 2025;93(9):595–608. 10.1037/ccp0000969
44. Rogers A, Lee V, Kennedy A. Continuity and change? Exploring reactions to a guided self-management intervention in a randomised controlled trial for IBS with reference to prior experience of managing a long term condition. Trials. 2007;8:6. 10.1186/1745-6215-8-6
45. Dong Y, Baumeister D, Berens S, Eich W, Tesarz J. High Rates of Non-Response Across Treatment Attempts in Chronic Irritable Bowel Syndrome: Results From a Follow-Up Study in Tertiary Care. Front Psychiatry. 2019;10:714. 10.3389/fpsyt.2019.00714
46. Olsen MF, Bjerre E, Hansen MD, Tendal B, Hilden J, Hrobjartsson A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. J Clin Epidemiol. 2018;101:87–106 e2. 10.1016/j.jclinepi.2018.05.007
47. Kruimel J, Leue C, Winkens B, Marcus D, Schoon S, Dellink R, et al. Integrated medical-psychiatric outpatient care in functional gastrointestinal disorders improves outcome: a pilot study. Eur J Gastroenterol Hepatol. 2015;27(6):721–7. 10.1097/MEG.0000000000000335

## Figures

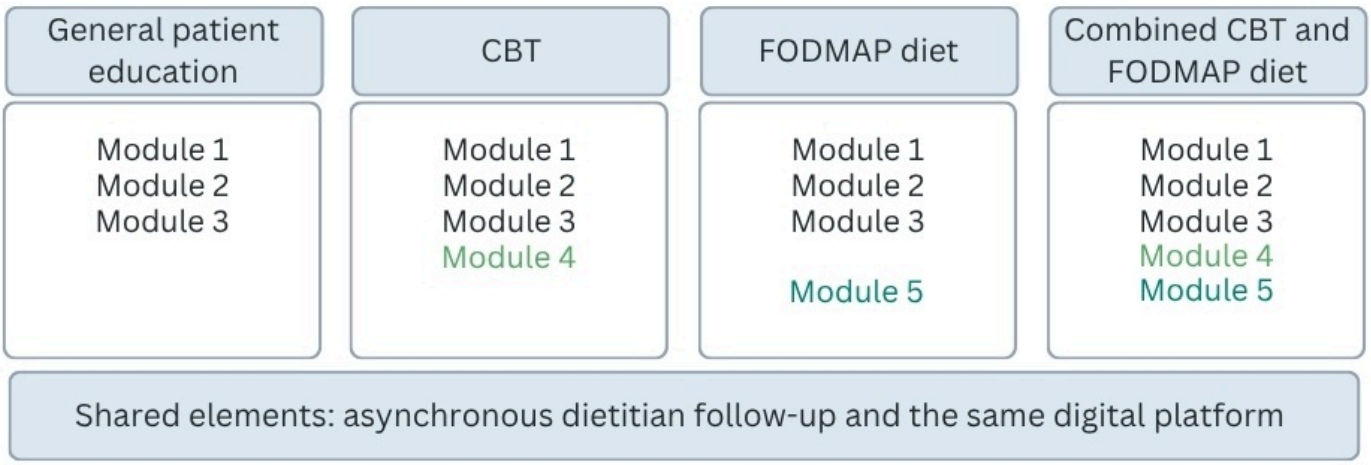


**Figure 1**

Description of study groups. Reproduced from Thuen et al (30), licensed under CC BY 4.0.