Patients' experiences and effects of dietary changes when living with irritable bowel syndrome

Various impacts of dietary treatment

Cecilia Weznaver

Department of Molecular and Clinical Medicine
Institute of Medicine, Sahlgrenska Academy
University of Gothenburg

UNIVERSITY OF GOTHENBURG

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cecilia.weznaver@gu.se, cecilia.weznaver@vgregion.se

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"An apple a day keeps the doctor away."

Walesiskt ordspråk

"Ibland bota, oftast lindra, alltid trösta."

Hippokrates

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Department of Molecular and Clinical Medicine, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ABSTRACT

Irritable bowel syndrome (IBS) is a complex disorder of gut-brain interaction. The causal explanations for this condition remain unclear, however, dietary factors appear to play a significant role in symptom generation and alleviation for these patients. The aim of this thesis was to gain more knowledge about the role of diet concerning the severity of IBS symptoms and the patients' perceived experiences to implement the requested dietary changes to achieve alleviation in IBS.

In Paper I, we compared two restrictive dietary treatments and medical treatment for patients with IBS in a 4-week randomized controlled trial (RCT) including 294 participants. Although all three treatments showed significant alleviation in the severity of IBS symptoms, both dietary groups showed a more pronounced effect than in the medical treatment. The dietary groups also presented a lasting effect on improvements in gastrointestinal (GI), extraintestinal, and psychological symptoms over 6 months. **In Paper II**, inductive content analysis was used to investigate the participants' experience of implementing the dietary changes included in the dietary treatments in the RCT (Paper I). Three themes describe the dietary changes as *Supportive, educational, and motivating, Multidimensional challenges, and Reflective and developing.* The need for support to initiate the dietary changes became clear. Despite structured support, the dietary changes were experienced as challenges and were related to the participants' personal life situation. Going through the dietary changes started a process that resulted in more than a reduction in the severity of GI symptoms, it also gave new knowledge and diet-related reflections, and where maintained dietary changes were related to what was perceived to be practical and healthy habits.

In summary, the results from this thesis confirm that diet plays an important role in the treatment of IBS. Restrictive dietary treatments reduce the burden of symptoms in IBS. With the support to implement the dietary changes for patients with IBS, a process can be initiated that leads to individualized adjusted dietary changes that are varied and can be maintained in the long term.

Keywords: Irritable bowel syndrome, FODMAP, dietary changes, IBS symptom severity, patient´s experiences, qualitative.

SAMMANFATTNING PÅ SVENSKA

Irritabel bowel syndrom (IBS), eller irritabelt tarm-syndrom på svenska, är en term för olika funktionella mag-tarmsjukdomar som kan beskrivas som komplexa störningar av tarm-hjärninteraktionen. IBS påverkar tarmens funktion men orsakar inte någon mätbar skada. Det är en kronisk sjukdom som kännetecknas av en kombination av buksmärtor och förändrade tarmvanor d v s diarré och/eller förstoppning. Orsakerna till IBS är oklara, men kostfaktorer verkar spela en betydande roll som både utlösande och symtomlindrande för dessa patienter. Denna avhandling syftar till att utöka kunskapen om kostens roll när det gäller graden av lindring av IBS-symtom samt patienternas upplevda erfarenheter av att genomföra de kostförändringarna som behövs för att uppnå an lindring av IBS symtom.

I första delarbetet (I) jämfördes två restriktiva kostbehandlingar och medicinsk behandling för patienter med IBS i en 4-veckors randomiserad kontrollerad studie som inkluderade 294 deltagare. Alla tre behandlingarna påvisade en tydlig lindring av IBS-symtomen, men effekten var större i båda kostgrupperna än i gruppen som fick medicinsk behandling. Kostgrupperna hade också en kvarstående god effekt på gastrointestinala (GI), extraintestinala och psykologiska symptom över en period på 6 månader. **I andra delarbetet (II)** användes induktiv innehållsanalys för att undersöka deltagarnas upplevelser av att genomföra de kostförändringar som ingick i behandlingsstudiens kostbehandlingar. Tre teman beskriver kostförändringarna som *Stödjande, utbildande och motiverande, Multidimensionella utmaningar och Reflekterande och utvecklande*. Behovet av stöd för att kunna påbörja kostförändringarna blev tydligt. Trots strukturerat stöd upplevdes kostförändringarna som utmaningar och var relaterade till deltagarnas personliga livssituation. Genom att genomgå kostförändringarna påbörjades en process som resulterade i mer än en lindring av GI symptom, utan även ny kunskap och kostrelaterade reflektioner, där de kostförändringarna som bibehölls var kopplade till det som upplevdes vara de mest praktiskt utförbara samt hälsosamma.

Sammanfattningsvis bekräftar resultaten från denna avhandling att kosten spelar en viktig roll i behandlingen av patienter med IBS. Fyra veckors restriktiva kostbehandlingar minskar symptombördan vid IBS. Med stöd för att implementera kostförändringar kan en process startas som leder till individualiserade kostjusteringar som utökar kosten och kan bibehållas på lång sikt.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. *Contributed equally.

I. Nybacka S, Törnblom H, Josefsson A, Hreinsson J.P, Böhn L, Frändemark Å, Weznaver C, *Störsrud S, *Simrén M.

A low FODMAP diet plus traditional dietary advice versus a low-carbohydrate diet versus pharmacological treatment in irritable bowel syndrome (CARIBS): a single-centre, single-blind, randomised controlled trial.

Lancet Gastroenterology & Hepatology. Published Print: 2024-04.

II. Weznaver C, Nybacka S, Simrén M, Törnblom H *Jakobsson S, *Störsrud S.

Patients' experiences of dietary changes during a structured dietary intervention for irritable bowel syndrome.

Under review for publication in Journal of Human Nutrition and Dietetics, 2024.

CONTENT

ABBREVIATIONS

BDA	British dietetic association
BMI	Body mass index
BSF	Bristol stool form
CA	Content analysis
DGBI	Disorders of gut-brain interaction
FODMAP	Fermentable oligo-, di-, monosaccharides, and polyols
GSRS-IBS	Gastrointestinal Symptoms Rating Scale for IBS version
GI	Gastrointestinal
HAD	Hospital Anxiety and Depression scale
HDL	High density lipoprotein
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with predominant constipation
IBS-D	Irritable bowel syndrome with predominant diarrhea
IBS-M	Irritable bowel syndrome with mixed bowel habits
IBS-U	Unsubtyped irritable bowel syndrome
IBS-SSS	Irritable bowel syndrome severity scoring system
LCD	Low carbohydrate diet
LCHF	Low carbohydrate high fat
LDL	Low density lipoprotein
LFTD	Low FODMAP traditional diet

NICE	National Institute of Health and Care Excellence
NNR	Nordic Nutrition Recommendations
OMT	Optimized medical treatment
PHQ-12	Patient health questionnaire -12
QoL	Quality of life
RCT	Randomized controlled trial
SD	Standard deviation
TDA	Traditional dietary advice

1 INTRODUCTION

1.1 PURPOSE OF THE THESIS

The purpose of this thesis is to gain more knowledge about the role of diet in gastrointestinal (GI) symptoms and the patients' experience of dietary treatment for people living with irritable bowel syndrome (IBS). The thesis combines quantitative measures with perceived experiences of dietary changes explored with qualitative methods. Interweaving these different approaches to gather new knowledge will hopefully further improve the IBS treatment.

1.2 DISORDERS OF GUT-BRAIN INTERACTION

Disorders of gut-brain interaction (DGBI) was previously referred to as functional GI disorders (FGID). DGBI have a world-wide prevalence around 40% in the general population and with a predominance of women (1). No identifiable structural or biochemical cause of the symptoms can be identified during routine clinical investigations or tests. Having a DGBI is associated with poorer quality of life, increased healthcare use and psychological distress (1, 2). There has been an expansion in the scientific understanding of these disorders, and the term DGBI describes the basic underlying pathophysiology with complex neurologic interactions between the gut and the brain even if it is still not yet fully understood (3-5).

The DGBI includes six groups of disorders (for adult) and two (for children). The bowel disorders are the most prevalent and includes irritable bowel syndrome (IBS) (1). All DGBI are presented in Table 1.

Table 1. Overview of the eight groups of disorders of gut-brain interaction (DGBI) according to the Rome IV criteria.

GROUPS of disorders of gut-brain interaction
A. Esophageal Disorders
B. Gastroduodenal Disorders
C. Bowel Disorders
D. Centrally Mediated Disorders of GI Pain
E. Gallbladder and Sphincter of Oddi Disorders
F. Anorectal Disorders
G. Childhood Functional GI Disorders: Neonate/Toddler
H. Childhood Functional GI Disorders: Child/Adolescent

Abbreviation: Gastrointestinal, GI

1.3 IRRITABLE BOWEL SYNDROME (IBS)

IBS is part of the bowel disorders and is defined by recurrent abdominal pain linked to altered bowel habits of long duration (3, 6). IBS itself consists of four subtypes (Table 2) and has a global prevalence of 4.1% (1). The disorder is more common in individuals under the age of 50 years and women are affected to a larger extent (1, 7). Additionally, co-existing GI and non-GI symptoms are common comorbidities in IBS and particularly more common in patients with severe IBS and have an impact on overall quality of life (3, 8, 9). The diagnosis is based on symptoms compatible with the diagnostic criteria (Table 3) where the exclusion of alarm symptoms reduces the extent of investigations needed. The symptoms can cause great suffering for many of those affected and sometimes lead to social isolation. Having IBS symptoms is a common reason for seeking healthcare and therefore also leads to significant costs for the society (9, 10).

Table 2. Overview of the bowel disorders according to the Rome IV criteria.

BOWEL DISORDERS
C1. Irritable bowel syndrome (IBS)
IBS with predominant constipation (IBS-C)
IBS with predominant diarrhea (IBS-D)
IBS with mixed bowel habits (IBS-M)
IBS unclassified (IBS-U)
C2. Functional constipation
C3. Functional diarrhea
C4. Functional abdominal bloating/distension
C5. Unspecified functional bowel disorders
C6. Opioid-induced constipation

1.3.1 DIAGNOSTIC CRITERIA FOR IBS

IBS is defined by the Rome IV criteria (3) by recurrent or chronic abdominal pain associated with changes in frequency and form of stool, shown in Table 3. These symptoms must be present at least one day a week and with a duration after onset of at least 6 months. Based on the clinical history and limited testing, celiac disease, thyroid dysfunction, unintended weight loss, GI bleeding and signs of intestinal inflammation must be excluded (11).

The Rome criteria for DGBI has been revised during the last twenty years and the definition of IBS in the current Rome IV definition is stricter compared with earlier editions and is the one used in this thesis. The changes in the latest edition include removing the symptom abdominal discomfort, to retain only abdominal pain as a qualifying symptom. The changes also included increased abdominal pain frequency threshold and a change from abdominal pain being improved by defecation to being related to defecation. These changes have led to a decrease in prevalence from 10-15 % to 4 % in the general population (12).

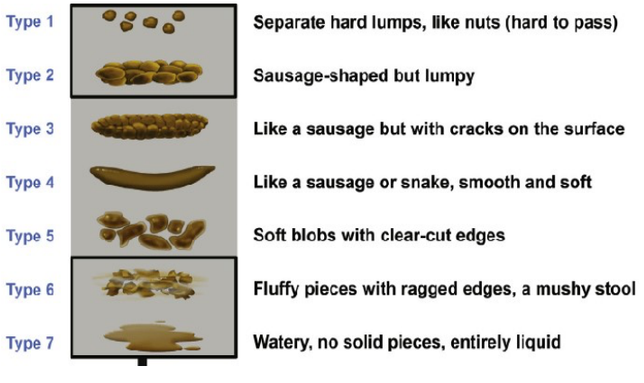
Table 3. Rome IV diagnostic criteria for irritable bowel syndrome

Rome IV diagnostic criteria
Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

1.3.2 SUBTYPES OF IBS

IBS is divided into four subtypes based on the predominant bowel habit, IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits and unsubtyped (IBS-U), shown in Table 2. To determine the subtype, the Bristol stool form (BSF) scale is used, preferably recorded in a daily diary for 10-14 days. The dominant stool form, defining the subtype, must be present in > 25% of stools and < 25% of the opposite stool type, described in Figure 1 B. The BSF scale includes seven stool forms, where 1-2 are considered as constipation and 6-7 as diarrhea (3) (Figure 1 A).

A



B

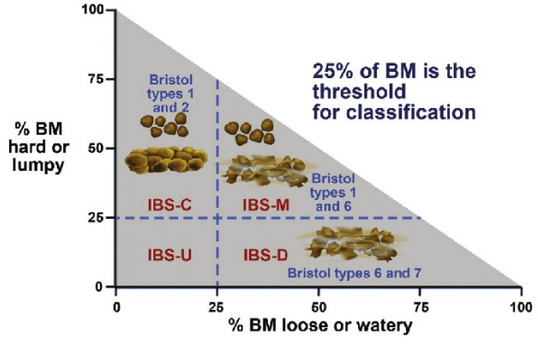


Figure 1. A) Bristol Stool Form (BSF) scale with B) IBS subtyping graph. (Adapted from Lacy et al. Bowel Disorders. Gastroenterology. 2016 Feb 18; S0016-5085(16)00222-5, reprinted with permission). Bowel movements, BM.

1.4 PATHOGENESIS AND PATHOPHYSIOLOGY IN IBS

As with all DGBI, the pathogenesis and pathophysiology of IBS is complex and still only partly understood. Research have been focusing on genetic predisposition, motility disturbances, mucosal immune function, psychological distress, gut-brain signalling, gut microbiota composition, and the central nervous system (1, 5, 13). Some of the most related topics will be briefly reviewed below.

Disturbances in intestinal motility

Abnormal gut transit and irregular bowel contractions are described in some patients with IBS (14, 15). An accelerated transit time is associated with loose and more frequent stools and a slow transit is associated with hard and less frequent stools (14, 16). Bowel movements can be affected by different meal factors such as volume and caloric load. Several beverages and foods have been suggested to influence GI motility for example coffee (17), alcohol (18) and spicy food (capsaicin) (19, 20). Both fat and carbohydrates can affect the gastric reflex and intestinal motility (21).

Immunologic factors

In a subpopulation of patients there is a pathogenesis involving an increased immune activity in the intestinal mucosa after an acute gastroenteritis. This is known as post-infection IBS (PI-IBS) and can occur in 3-36% of cases (22-24). A ”leaky gut”, or an increased intestinal permeability have been shown to be linked to activation of intestinal immune cells and plays a part in a mucosal barrier disruption that increases luminal antigens in to the mucosa (25). These factors may be involved in a low-grade inflammation in the gut in patients with IBS (26).

Altered sensory function

An increased pain perception in the GI tract is often referred to as visceral hypersensitivity and is more prevalent in patients with IBS (27). Intestinal distention could be one explanation to a triggered abdominal pain and intestinal distention could be induced by foods. Carbohydrates not fully digested in the small intestine may cause intraluminal gas and thereby abdominal pain in patients with visceral hypersensitivity. Foods rich in fibre, i.e., bran, whole grain products, lentils as well as some fruits and vegetables are foods that also could cause GI symptoms by this mechanism (28, 29).

Gut microbiota

Prebiotics are indigestible fibres and are an important factor in our diet that favours gut microbiota in the colon and has been shown to provide health benefits in humans (30). In terms of food sources, fiber from grain and fruit seem to offer a significant impact on microbiota composition (31). The gut microbiota has an impact on the mucosal integrity and are producing short-chain fatty acids and vitamins with a beneficial effect in colon (32). The gut microbiota in patients with IBS has been found to have a reduced gut microbial diversity compared to healthy subjects. Research suggest that the composition of the gut microbiota can have an influence in food-related symptoms (33, 34). Since abnormalities in intestinal bacteria have been detected, it is likely that treatments that modify the intestinal microbiota may influence symptoms. Beside fibres, probiotics seem to have a therapeutic role and an effect is suggested to be seen within weeks of treatment (35, 36). Further research in microbiota and optimal probiotic treatments in IBS are needed.

Food hypersensitivity and intolerance

Receptors along the GI mucosa layer detect nutrients and through neural pathways send signals to the brain (37, 38). Findings indicate that 11 % of the global population associate food intake with abdominal pain (39). The self-reported intolerance to foods in patients with IBS is higher, 60-80%, which indicates the significance of dietary factors in IBS (17, 19, 40). There are also theories about allergy-like reactions in the GI tract (duodenum), with no connection to allergies elsewhere in the body, as some research has been able to demonstrate acute changes in the duodenal mucosa associated with certain food intake (41). However, more studies are required to understand the association with IBS symptoms.

Maldigestion of lactose due to lack of the enzyme lactase (42, 43) or malabsorption of fructose in the absence of glucose (44-46), does not seem to be more common in IBS patients, however they may have a greater sensitivity to carbohydrates entering the colon because of maldigestion or malabsorption. Resent research have highlighted that a defective sucrase-isomaltase gene could be more common in a subgroup of IBS patients, particularly IBS-D, and contribute to a sucrose intolerance (47, 48). Reduction of lactose, fructose, sucrose, or starch in the diet can be used when patients clearly experience improvement of GI symptoms as these carbohydrates are reduced in the diet (49). However, there is not sufficient evidence to routinely suggest these exclusion diets for all patients with IBS.

Psychosocial factors

Periods of stress and life crises seem to frequently precede IBS. However, population studies show that mental illness in general is not more common in IBS compared to the general population. Nevertheless, a mental illness seems to be decisive how the patient experiences her or his GI symptoms (50).

Disordered Gut-Brain Interaction

In the healthy state, important information such as satiety and hunger are signalled via the enteric' nervous system to the brain while unimportant information is filtered out. Patients with IBS seem to have a disturbed filter where more and stronger nerve signals come through to conscious perceptions.

Some IBS patients also seem to react more easily to stress, and this may indicate more sensitive reaction pattern in various stress systems in both the body and brain that cause increased IBS symptoms (5, 29).

1.5 MANAGEMENT IN IBS

Since dietary management in IBS is the main focus of this thesis, pharmacological, and behavioural therapies will be discussed briefly, and dietary treatment will receive more attention.

Whereas IBS is of a chronic character, the treatment should aim at identifying effective strategies to alleviate symptom burden and a holistic treatment approach is considered the most effective. Most guidelines recommend a stepwise treatment approach (51). Initial management that is of concern in all patients with IBS is to establish a good doctor-patient relationship. This includes thorough explanation of the diagnose, deciding on a mutually agreed treatment plan, and also reassurance of the benign course of IBS from a medical point of view.

Alterations in lifestyle can improve both GI and extraintestinal symptoms (9) which motivates advice about stress management, sleep, physical activity, smoking and basic dietary advice (first line treatment) (51-53). Information should be given verbally but can be supported with written information material. The initial management has shown to be sufficient for around 40-50% of patients with IBS (54, 55). For some patients a more advanced treatment strategy concerning medical, behavioral, and dietary therapies are needed (second line treatment).

Pharmacological management

The pharmacological approach is based on identifying dominant GI symptoms and aiming at acceptable symptom improvements. The number of pharmacological treatment interventions should be limited to one at a time and with a specified follow-up interval. Constipation is most often treated with bulking agents and diarrhea with loperamide, but with the possibility of bile acid diarrhea in mind also with bile acid sequestrants. For temporary abdominal pain, antispasmodics are an alternative, and for more continuous pain, neuromodulators, where tricyclic antidepressants have the most evidence.

(51, 56). Probiotics and bulking agents like fibers are other options beside the pharmacological management. Recommended medications according to the predominant symptoms are presented in Figure 2.

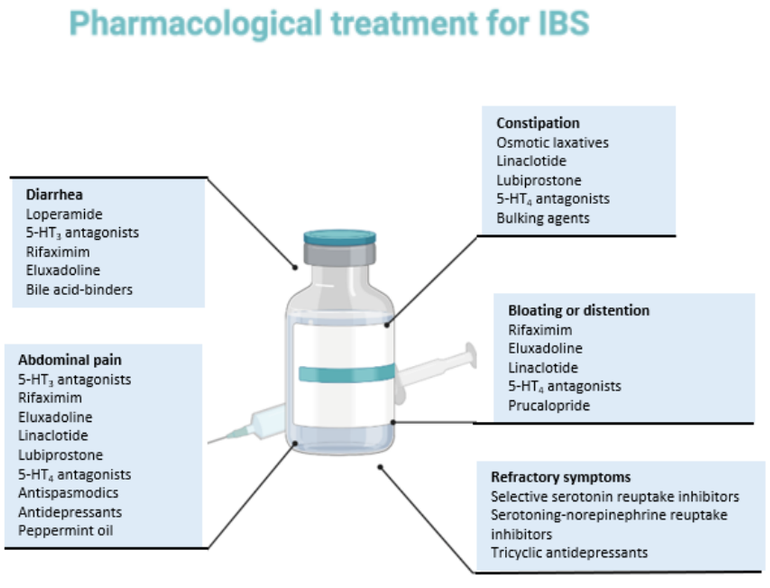


Figure 2. The pharmacological management based on the dominant symptoms in irritable bowel syndrome (IBS). Image created with BioRender.com.

Behavioral treatments

Psychological comorbidity, such as depression and anxiety, is common among patients with IBS and can worsen GI symptoms (57). This understanding has led to various psychological treatment options that have shown to be successful in alleviating IBS symptoms. The most well-studied, effective, and used are cognitive behavioral therapy (both self-administered and face-to-face), and gut-directed hypnotherapy (58, 59). Hypnotherapy, has demonstrated to similar efficacy as a low FODMAP diet (60).

Multidisciplinary approach

A challenge in the management of IBS is that the predominant symptoms can vary in time and from person to person. Therefore, management must be symptom-based, and personalized. The multidisciplinary care model promotes equal prominence to patient education, lifestyle and dietary modifications, pharmacotherapy, and behavioral interventions, with different effectiveness in specific subgroups (56, 61). For patients with severe and refractory symptoms a combination of medications may be required together with dietary and behavioral treatment, in what can be called a multidisciplinary approach (51). Figure 3.

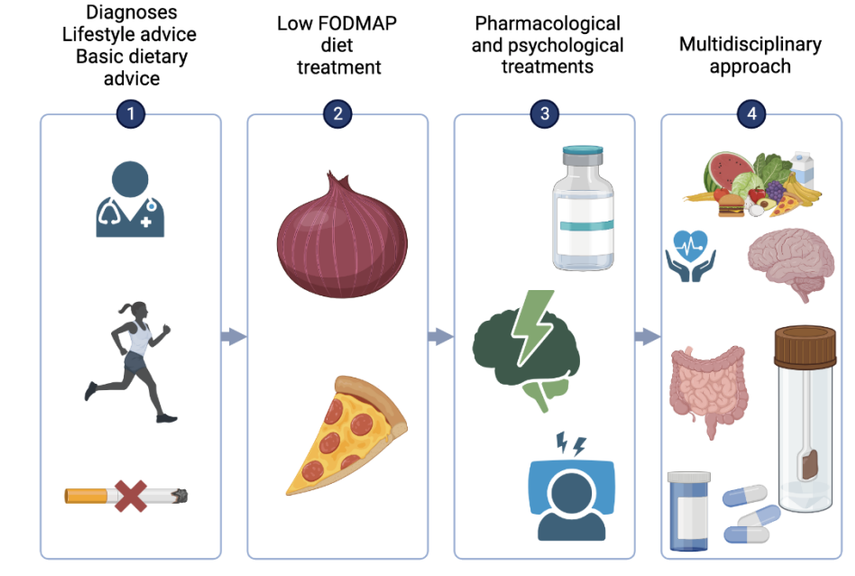


Figure 3. Management of IBS symptoms in a stepwise and multidisciplinary approach. Image created with BioRender.com. FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet.

1.5.1 DIETARY ASPECTS IN IBS

It is known that both subjects in the general population and patients with IBS report an association between food intake and GI symptoms. However, a larger proportion of the IBS patients report food related symptoms, around 60-80% compared to 11% in the general population (17, 19, 39). In previous research patients with IBS have self-reported trigger foods to be fatty or fried foods, dairy products, caffeine, gas-producing foods (onions, legumes) and certain fruits (plum, apple) in these publications (17, 19, 40, 62-64).

However, we also know that it is difficult to identify single food components involved in IBS symptoms because of the complexity of food composition as well as GI physiology. For example, in the case of reported sensitivity to bread, it can be difficult to assess whether it could be the content of FODMAP, fibers, gluten or other components found in cereals that causes symptoms (65). Some individuals with IBS report feeling better when avoiding gluten, even in the absence of celiac disease (65, 66). Non-celiac gluten sensitivity (NCGS) describe individuals who experience symptoms like those of celiac disease when consuming gluten, in the absence of celiac disease or a wheat allergy (67). It is important to recognize that NCGS and IBS are distinct conditions, although they may share overlapping symptoms. For individuals with IBS, it is likely multiple factors involved in the generation of symptoms when consuming gluten-containing products (65), and there are currently no dietary guidelines according to whether or not gluten should be excluded from the diet. More research is required for association with IBS symptoms in this area (36).

Women with IBS have been shown to use a trial and error-strategi that excludes certain foods but reintroduces them to the diet again if symptoms are not improved (68). Nevertheless ,there is a risk for excluding more or too many foods from the diet when symptoms increase, which could lead to poor diet quality and even malnutrition in the long term (40, 53, 69-72). However, there are also contrary findings that do not demonstrate lower nutrient intake in patients with IBS (73). Many patients with IBS seek for online information about dietary treatments themselves and there is a risk of receiving unreliable information from and non-scientific sources (63, 74). To avoid negative consequences from incorrect information, a need for patient education in IBS management has been identified (74, 75). Dietary treatment is ideally given to patients who have difficulties to implement dietary changes themselves and are motivated to follow suggested dietary advice (75). For optimized and safe dietary treatment of IBS a referral to a registered dietitian is recommended (75, 76).

1.5.2 TRADITIONAL DIETARY ADVICE IN IBS – THE NICE GUIDELINES

The traditional dietary advice (TDA) for patients with IBS are funded on the National Institute for Health and Care Excellence (NICE) guidelines (52) together with the systematic reviews by the British dietetic association (BDA) that also added the role of FODMAP in the revised version 2016 (53) and presented in Table 4. These are appointed as the basic dietary advice and are known as the first line dietary treatment options.

The NICE and BDA dietary recommendations in IBS are referred to as “the traditional dietary advice” in both study I and II.

Implementation and potential risks

The TDA are mostly focusing on eating behaviour and limiting the intake of foods considered causing bloating, such as onions, carbonated drinks etc. They can be used in primary care to promote self-management. (Table 4) This diet strategy is considered nutritionally safe, not too restrictive, and without potential risks such as malnutrition. The BDA state that the addition of probiotics is considered safe but with inconclusive efficacy (35) and no general recommendations can yet be made (53).

Mechanism

Certain mechanisms may explain why some food might worsen IBS symptoms. Dietary fiber has a beneficial effect related to stool consistency, bowel passage and the intestinal microbiota (77). However, a high fiber intake can increase IBS symptoms and can be explained by some fibers, mostly insoluble fiber, as abrasive and irritating to the digestive tract, stimulating bowel contractions and fermentation process in the gut (69, 78). Therefore, benefits and risk factors of fiber intake must be considered for each symptom profile regarding GI symptoms and IBS subtype. If an increase in fiber in the diet is needed, an addition of a wide variety of foods rich in fiber including both insoluble and soluble fibers is recommended (79). Furthermore, studies show that fat affects small intestinal motility (80), stimulates the gastrocolic reflex, exaggerates a sensory duodenal response, and may promote pain in IBS

(81, 82) and delay transit of intestinal gas (83). The explanatory beneficial mechanism behind a regular meal pattern, taking time for meals and chewing properly is related to what is acknowledged as a healthy diet and lifestyle. The benefits of a regular meal pattern, taking time for meals and chewing properly come at a fairly low level of evidence but are explained by the practical considerations in the BDA as being a foundation of a healthy diet and lifestyle (84-86).

Table 4. Presentation of the National Institute for Health and Care Excellence (NICE) guidelines together with the systematic reviews by the British dietetic association (BDA).

Traditional dietary advice
Focus on how, and when, to eat, instead of what
Regular meals
Chew properly
Sufficient fluid intake (8 cups/day)
Never feel too full
Probiotics - limited evidence but safe
Specific dietary advice that may apply to some patients. **Potential triggers** - if it is associated with symptoms:
Restrict coffee and tea consumption to max 3 cups/day
Fizzy drinks, alcohol, – with in safe national limits
High-fiber foods (as bran, whole grains) with moderation, resistant starch to be avoided
A low lactose diet can be considered
Fat intake – align to national healthy eating guidelines
Spicy foods – limited consumption
Fruit – limited to 3 servings/day
Artificial sweetener, sorbitol – limited consumption
Gluten - insufficient evidence, no recommendation

Level of Evidence

It has been shown that 40-50 % of patients with IBS find NICE guidelines effective, relatively simple, and not too restrictive (54, 55). A recent study compared TDA, low FODMAP diet and a gluten-free diet and found that all diet approaches were equally effective in non-constipated IBS, however, the TDA was considered as the most user-friendly by the participants in terms of

convenience and affordability (66). In addition, a gluten-free diet (65, 66, 87) have been proposed as a potential dietary treatment in IBS, however, the NICE guidelines state that the evidence is inconclusive and at this point of time no general recommendations can be made (53).

1.5.3 LOW FODMAP DIET

The abbreviation FODMAP is used to compile a group of short-chain carbohydrates not entirely absorbed in the small intestine. These carbohydrates include disaccharides (lactose), monosaccharides (fructose in excess of glucose), oligosaccharides (fructans, fructo-oligosaccharides and galacto-oligosaccharides) and polyols (mannitol and sorbitol) (88). Thresholds set by the Monash University defines if the content of FODMAP is high or low and is based on standard serving sizes of separate foods (89). Estimating the exact amount of FODMAP in the general population can be challenging because it depends on individual dietary habits and variations in food consumption (90). A Swedish study has shown a mean total FODMAP intake to 19 g/day in the general population (91). The reported habitual intake of FODMAP has shown to vary between patients with IBS as some patients who experience symptoms from specific food items, some high in FODMAP, seem to have reduced the intake (90).

Mechanism

Not all short-chain carbohydrates are absorbed in the small intestine. Some of them have complex structures and are more difficult to digest, this could lead to increased water content in the lumen and promotes a quick passage through the small intestine. When short-chain carbohydrates reach colon, they undergo fermentation by gut microbiota, which leads to production of gas (92, 93). This fermentation process can cause symptoms like abdominal pain, flatulence, bloating and diarrhea in individuals sensitive for FODMAP (94). Studies have shown that most healthy individuals do not experience symptoms when eating FODMAP, so the symptom aggravation in patients with IBS may be explained by several interacting factors. Individual variation in enzyme activity, variation in sensitivity to absorption capacity, variation in eating habits and alteration in gut microbiota can be reasons for exceeding the individual FODMAP tolerance limit (29, 95, 96).

Implementation

Treatment with the low FODMAP diet is structured into three phases. It begins with a strict elimination phase for 4-6 weeks, where high FODMAP food should be replaced with low FODMAP equivalents (88). In this phase, food lists, smart phone applications and cookbooks can be used to facilitate the process. In the second phase, for those who experienced an improvement in symptoms the reintroduction of foods high in FODMAP should be systematically and gradually tested in their diet the following 6-10 weeks (97). During this phase the patients will try to identify their trigger foods and

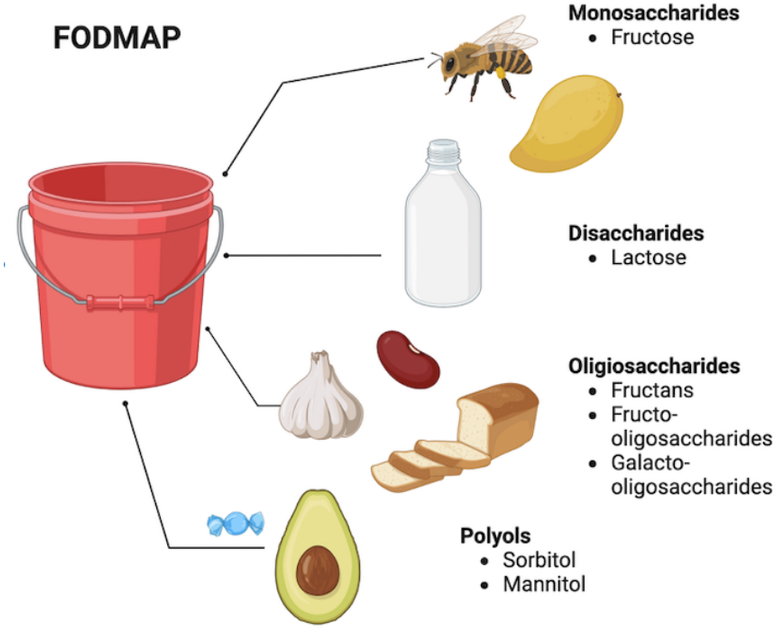


Figure 4. The "bucket" concept. FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet. Image created with BioRender.com.

estimate tolerance levels. This is done by evaluating each FODMAP one by one with increasing amounts for three executive days with a wash-out period in between. During the third phase, a personalized long-term dietary strategy should be implemented that promote flexibility without overly restrictive restrictions on food choices or lifestyle (97). The metaphor of a "bucket" is often used to represent the cumulative threshold of FODMAP that an individual can tolerate without experiencing symptoms related to IBS. When overfilling the bucket, symptoms may start to appear. Explanations for this could be that different combinations of foods produce different effects and that patients with IBS have different tolerance levels. (Figure 4).

Level of Evidence

A diet low in FODMAP has showed effectiveness in several controlled studies (54, 94, 98, 99) but should be suggested when the TDA does not provide a sufficient symptom relief. Around 60% of treated patients have reported low FODMAP diet to be effective in reducing GI symptoms (100). However, dietary studies can be difficult to compare given different design and execution, which must be taken into account evaluating true efficacy. Recently a meta-analysis found the FODMAP diet as the most effective dietary alternative for reducing global IBS symptoms (101), but concluded that the quality of evidence is low. However, most trials have mainly focused on the first and strict elimination of FODMAP alone. There are limited amounts of studies that have investigated the reintroduction phase and a longer follow-up period. Nonetheless, these few studies do conclude that the symptom reduction is sustainable (101-103) and that an adequate nutrient intake is maintained after reintroduction (104) but more research in this field is needed.

Potential risks

A low FODMAP diet does not only come with benefits to all patients with IBS, therefore understanding for whom the low FODMAP diet is the best approach is essential (75, 105). A diet rich in FODMAP are high in vitamins, minerals, antioxidants, prebiotics, and dietary fibre and needs to be adequately replaced by other options if reduced due to a diet advice (106). Following a strict low FODMAP diet have been demonstrated to alter the gut microbiota, rising questions about long-term safety of this dietary regime (95, 107, 108). Around 30% of the patients on the restrictive diet seem to apply an extended

elimination phase, reduce their caloric intake, and start avoiding other foods (109). Over time, this could lead to risk of nutritional deficiencies, negative impact on intestinal microbiota and limitations when eating in social contexts. However, this seems more unlikely as a short-term treatment. Not suitable candidates for the low FODMAP diet are those patients with a current or previous eating disorder, unwanted weight-loss, failure to gain weight, or are already on a restrictive diet (110). Also, patients with GI-specific anxiety have a risk of poorer response to the low FODMAP diet (111). In these cases, the TDA or a diet known as a "gentle" low FODMAP diet, focusing on reducing top trigger foods and not a total elimination could be preferred (55, 110). To mitigate the risk of failure when adhering to the low FODMAP diet, it is advisable to seek guidance from a qualified dietitian (76). Nonetheless, further research is needed in this field.

1.5.4 LOW CARBOHYDRATE DIET

A diet known as low carbohydrate high fat (LCHF) has been anecdotally reported to give symptom relief in patients with GI problems when trying to lose weight or controlling blood glucose level (112). The LCHF diet, also known as ketogenic diet, is a diet where the overall carbohydrate intake is limited and protein-rich foods, fats and vegetables should compensate for this (113). LCHF can be eaten with different degrees of carbohydrate restriction. The general level of macronutrients differs but often mentioned levels are about 70 energy percent (E%) fats, 20 E% proteins and 5-10 E% carbohydrates (114).

Mechanism

The LCHF diet impact in IBS is unknown. A few exploratory explanations may help create a better understanding. Recent discussions propose that a reduced amount of carbohydrates, in particular sugary and starch-rich foods could potentially have a beneficial effect in IBS. This is suggested to be related to the sucrase-isomaltase enzyme complex or fructose malabsorption (47-49, 115). If the sucrase-isomaltase enzyme complex is defective, it can affect the digestion and absorption of both sucrose and starch. Other potential proposed mechanisms is a low-grade gut inflammation related to overconsumption of fructose that could affect bowel function and contribute to GI symptoms, especially in individuals who already suffer from IBS (95, 116), Also, a subsequent accelerating GI transit caused by a high-fat diet that has been

observed in some males (117). LCHF diet contains less carbohydrates but usually no less lactose than a general diet. These are all theories that needs further exploring in the future.

Level of Evidence and potential risks

The LCHF diet has mainly been investigated in studies concerning obesity and/or diabetes and the diet has been considered somewhat controversial regarding health effects. Research have shown reduction of body fat, reduced hunger, improved type 2 diabetes and metabolic syndrome (118). Simultaneously, studies have shown that the LCHF diet increase LDL-cholesterol, and thereby indicate increased risk of dyslipidemia and cardiovascular disease (113). Only a few small studies have investigated the effectiveness of a diet with a reduced total carbohydrates content in patients with IBS-D (119), and in IBS in general (49), however with promising results. There is also poor information about how gut microbiome is affected by this diet, a reduce in diversity has been suggested but a better understanding is needed (120).

1.6 RESEARCH ON PATIENTS' EXPERIENCES OF LIVING WITH IBS

Prior qualitative research studies concerning patients' experience of living with IBS reveal substantial interindividual differences within the IBS patient population. Factors as life situation and gender identity influences the GI symptoms (121, 122). Evidence suggests that engaging in physical activity can empower patient with IBS, and a key is to promote the patient's individual resources into physical activity in the clinic (123). Improved patient management correlates with the provision of supportive and educationally focused person-centered care. A successful approach has been to highlight the importance of the patients' appreciation for attentive healthcare, acquiring more knowledge about IBS and the need for personal solutions to cope with everyday life (124).

Patients with IBS often describe their health status as characterized by fluctuating periods of well-being and illness. Taking control of IBS symptoms comes with both heightened self-awareness and the importance of finding social support. Controlling symptoms are compatible with a long-term learning

process and the beneficial impact of individualized support in health care is once again lifted (125). Several qualitative studies involving both patients with IBS and inflammatory bowel disease, highlight potential risks associated with adverse dietary behaviours, such as restrictive eating patterns, among individuals living with IBS (126). IBS is described as affecting overall quality of life and as a feeling of being held hostage by their disease (127). Again, the healthcare management and support is highlighted to play an important role in the care of patients with IBS (128). A qualitative study of 8 people with the FODMAP diet as primary treatment found that the dietary advice received from gastroenterologists was correct but general and did not meet personal needs and everyday situations. The dietary information provided was also particularly difficult to interpret in family and social situations. Their findings reinforce NICE/BDA guidelines and point out the low FODMAP diet to be dietitian-led (129).

To summarize, the patients' perspectives of undergoing restrictive dietary changes has not previously been investigated in patients with IBS and highlights an additional important area to be able to improve the dietary treatment of these patients. We found it interesting to further explore LCHF diet in relation to IBS. In our studies we refer to it as low carbohydrate diet – LCD – since it is the carbohydrates that has been the main focus. The effects of a combination of the two most acknowledged dietary treatments in IBS, the TDA and low FODMAP diet, have to our knowledge never been studied on IBS symptoms, neither been compared to optimized medical treatment and is a research area that needs to be further explored.

2 AIM

The overall aim of this thesis was to examine the effects of reducing carbohydrates in dietary treatment strategies in IBS and to gain a better understanding of the patients' experiences of implementing the recommended dietary changes. The specific aims were to:

I. Comparing three treatment options for IBS during a four-week intervention; 1*) a combination of the low FODMAP diet and the traditional dietary advice in the NICE guidelines, 2) a low total carbohydrate diet and 3) pharmacological treatment based on predominant GI symptoms*, with the primary aim to evaluate the effect on IBS symptoms during the intervention period, and the dietary effectiveness up to six months in each dietary treatment as a secondary aim.

II. To qualitatively explore patients' experiences of implementing restrictive dietary changes to alleviate IBS symptoms. The participants had undergone a structured dietary intervention that included two restrictive low-carbohydrate diets to alleviate GI symptoms.

3 PATIENTS AND METHODS

3.1.1 STUDY PARTICIPANTS

STUDY I

All patients with IBS included in this thesis were from the same study cohort. The two studies were both part of a large randomized controlled trial (RCT) conducted in an outpatient clinic specialized in DGBI at Sahlgrenska University Hospital, Gothenburg, Sweden (130).

The patients were recruited through referrals to a dietitian or physician at the clinic from e.g., primary care or by advertising via newspaper and social media platforms. Patients asked to participate in study I were given oral and written study information and provided informed consent before any study related actions were undertaken. The trial was carried out between 2017 – 2022.

STUDY II

Participants who were included in the two dietary intervention groups in study I were informed about the qualitative study covering the experience of adhering to the dietary advice given in study I. By a purposive selection based on the general composition of the patient group with IBS shown in current research (in terms of age, gender, duration in years of IBS, subtype of IBS) and which dietary intervention group they entered, were later asked to participate in study II. The recruited participants all agreed to an audio-recorded interview led by a dietitian. This trial lasted between 2018 and 2020.

3.1.2 OVERVIEW OF DESIGN

A comprehensive overview of the two studies (I and II), including study designs, types of data collected, and analytical methods covered in this thesis are presented in Table 5.

Table 5. An overview of the designs of the two studies included in the thesis.

Study	Participants	Design	Data	Data analysis
I	294	Quantitative Single center, singled-blinded, RCT Including 3 treatment arms	Questionaries Food records Blood samples	Analysis of variance Chi-square test Paired-sampled *t* test Wilcoxon signed-rank test Mixed linear regression
II	19	Qualitative Including 2 dietary treatment arms from the RCT	Individual Semi-structured interviews	Content Analysis

Abbreviations: RCT, Randomized controlled trial.

Inclusion and exclusion criteria

Table 6. Inclusion and exclusion criteria for participation in the two studies included in the thesis.

Inclusion criteria	Exclusion criteria
IBS according to ROME IV IBS-SSS ≥175 ≥18 years BMI 18-35 Region of Gothenburg	Any other serious disease or illness, GI disease, including celiac disease, and bariatric surgery, allergy, or food hypersensitivity (other than lactose intolerance), any dietary restrictions (as vegetarian), pregnant or breast feeding Previously treated with any of the dietary interventions or tested all of the pharmacological options Inability to communicate in Swedish

Abbreviations: IBS, irritable bowel syndrome; IBS-SSS, IBS severity scoring system; BMI, body mass index; GI, gastrointestinal.

Characteristics of the study participants

Characteristics of the participants in the two studies are described in Table 7.

Table 7. Overview of the characteristic of the participants in each study at baseline. Mean is presented with (standard deviation) and median with (range).

Baseline	Study I	Study II
N Participants total	294	19
Intervention diet LCD LFTD OMT	 97 96 101	 9 10
Age, years *Mean/**median	*39 (13)	**40 (20-68)
Women, %	82	74
BMI, kg/m^2 *Mean/**median	*25.3 (4.2)	**23.4 (18.8-31.1)
Duration of IBS, years Median	12.5 (1-63)	20 (1-45)
N IBS-subtype C/D/M	 33/39/16	 6/6/7

Abbreviations: IBS, irritable bowel syndrome; C, constipation; D, diarrhea; M; BMI, body mass index; N; numbers; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet; LFTD, low FODMAP traditional IBS diet; LCD, low carbohydrate diet; OMT, optimal medical treatment.

Research ethics approval and consent

Both studies were approved by the Regional Ethical Review Board in Gothenburg, Sweden, approved 2016 (Dnr 278-16), and with an amendment for the qualitative study 2017 (Tnr 1079-17). The studies were conducted according to the Declaration of Helsinki. All participants gave written and oral informed consent prior collection of data. The participants were de-identified with a code and could withdraw from participation at any time.

3.1.3 OVERVIEW OF TIMELINE AND STUDY VISITS

STUDY I

The two dietary treatment intervention groups in the RCT included 1) a combined low FODMAP and traditional IBS diet (LFTD), and 2) a low-carbohydrate diet (LCD). Participation included 5 visits. The third group were given an optimized medical treatment (OMT) grounded on primary GI symptoms. In this group, participants were scheduled to 3 visits and an additional letter at the six-month follow-up. (130) (Figure 5)

STUDY II

Pre-planned semi-structured interviews were conducted at visits 4 or 5 in a selected group of those who completed the dietary interventions. Consideration was given to variation in age, gender, duration in years of IBS, subtype of IBS and intervention diet. (Figure 5)

Figure 5. Overview of timeline and study visits.

Short presentation of the content of the study visits in study I

STUDY I

Visit 1: Study information to participants was given and informed consent was obtained. A physician examined the patient and when the diagnosis of IBS (Rome IV) was confirmed, and inclusion criteria fulfilled, the patient could continue with the 10-day screening period containing questionnaires and 4-day food records.

Visit 2: In order to be included in the RCT, the participant had to report IBS symptom severity ≥175 (IBS-SSS) and if so, the randomization took part. An external web-randomization program (Gothia Forum) was used with the randomization ratio of 1:1:1. Patients randomized to one of the dietary interventions were given oral and written dietary information and material from a study dietitian. Patients randomized to the OMT were given information and prescription of medication from a physician. Fasting blood samples was taken, and questionnaires were filled out. The interventions lasted for 4 weeks (28 days), and all foods included in the intervention was delivered home free of charge and the cost for the medication was reimbursed. The participants in the dietary treatment arms were informed that additional food or drinks consumed should be avoided, if possible, otherwise registered on a deviation list each day.

Visit 3: After completed interventions the participants in the LFTD group were informed about FODMAP reintroduction. It followed the recommendations available in the literature (67, 82) and the participants were given a structured schedule to test tolerance to individual FODMAP. Both diet groups were informed that the food deliveries ended and that the degree of continued adherence to the allocated diet was voluntary during the next six months. The formal participation in the OMT arm ended but participants were offered a regular visit to a dietitian. Fasting blood samples, questionnaires, and 4-day food records were collected.

Visit 4 and 5: The participants in the dietary interventions had structured follow-up meetings scheduled at three and six months. Fasting blood samples, questionnaires, and 4-day food records were collected. The participants in the OMT group were contacted by mail after six months concerning the severity of IBS symptoms and whether they currently used IBS treatments.

Short presentation of the content of the study visits in study II

STUDY II

Visit 1: When the study I information was given, the participants were also informed about the possibility to be invited to a qualitative interview study later on.

Visit 3: A purposive selection of participants was invited to participate in the interview study. Of the participants who were asked, all agreed to an interview which was scheduled at one of the follow-up visits.

Visit 4 and 5: The semi-structured interviews were led by a dietitian (CW) and were conducted in a relaxed setting conducive to conversation during one of the follow-up visits.

3.1.4 THE THREE INTERVENTIONS

The two RCT intervention diets were isocaloric but differed significantly in macronutrient composition, in particular in carbohydrates and FODMAP content. In addition, the LFTD follows the Nordic Nutrition Recommendations (NNR) (131) in macronutrients, but both intervention diets can be described as restrictive diets due to their food composition.

Information about the two dietary treatments was provided by a dietitian. Oral and written information of the intervention was given, but neither the name nor detailed information about the composition of the diet were mentioned. Detailed meal plans, recipes, list of option for allowed food were handed out. All foods included were delivered to the participants home once a week by a home delivery service supplier. The participants were advised to reduce or increase their food intake as necessary to maintain stable weight throughout the intervention. If the patient had to deviate from the meal plan everything had to be reported in a diary.

Table 8. The composition of low FODMAP traditional diet in study I.

Low FODMAP traditional IBS diet, LFTD
The composition of the diet:
The average energy level was 2380 kcal and the macronutrients 264 g carbohydrates, 88 g fat and 99 g protein
46 E% carbohydrates, 34 E% fat, 17 E% protein 3.4 g FODMAP and 29 g of dietary fiber/day
The diet matches the Nordic Nutrition Recommendation for a healthy intake*
Distribution of the diet: Three main meals and three snacks/day. Advised small meals on regular basis, slowly and properly chewed.
Limited intake of triggers like coffee, alcohol, fizzy drinks, some sweeteners, spicy and fatty foods. Food low in FODMAP, lactose free, gluten- and wheat-free bread, mainly soluble fibers from oats, chia seeds, vegetables and fruit, to be peeled or boiled.

Abbreviation: FODMAP, fermentable oligo-, di-, monosaccharides and polyols; Energy percent, E%. *Nordic Nutrition Recommendations 2012, (131).

Table 9. The composition of the low carbohydrate diet in study I.

Low carbohydrate diet, LCD
The composition of the diet:
The average energy level was 2350 kcal and the macronutrients 50 g carbohydrates, 175 g fat and 132 g protein
9 E% carbohydrates, 67 E% fat, 23 E% protein 17.1 g FODMAP (lactose, 6.1 g / lactose free, 0.8 g) and 24 g of dietary fiber/day
Distribution of the diet: Three main meals and one snacks/day.
Mainly dietary fibers from nuts, seeds, and low-carbohydrate bread (with fibers from e.g. pea-and soybeans and wheat bran), and specific vegetables and berries.

Abbreviation: LCD, low carbohydrate diet; Energy percent, E%.

The extensive description of the two intervention diets can be seen in the original paper of study I, supplementary appendix, Table 2: Energy and nutrient content.

The OMT was managed by a physician who provided information about the intervention and the prescribed medical treatment based on the predominant symptom and on accordance with national guidelines (Table 10). If participants already had medications or probiotics given at a stable dose for at least six weeks prior to randomization, the participant could continue with this. The interventions lasted for 4 weeks (28 days).

Table 10. The optimized medical treatment (OMT) during intervention in study I.

Optimized medical treatment, OMT		
Only one medication was prescribed per participant and after two weeks the physician contacted the participant to assess the effect, adherence and to adjust dosage if needed.		
The evidence-based medical treatment options followed a pre-defined list of medication based on predominant GI symptoms, where the medications mentioned first were chosen if not tested before:		
Constipation	**Diarrhea**	**Abdominal pain**
Bulking Agent	Loperamide	Chronic pain: Amitriptyline
Osmotic laxative	Cholestyramine	Episodic pain: Hyoscyamine
Linaclotide	Ondansetron	Pain with constipation: Linaclotide
		Pain with diarrhea: Amitriptyline

3.2 DATA COLLECTION

3.2.1 STUDY I

Self-reported questionnaires were used in all three treatment arms at baseline and after four weeks of intervention. In the two diet groups the questionnaires were also completed at the three- and six-month follow-up.

ASSESSMENTS

GI symptoms

The IBS severity scoring system (IBS-SSS), (132), evaluates the severity of IBS symptoms. Five questions are included; pain severity, distension, bowel habit dissatisfaction and life interference are rated with visual analogue scales (VAS) (0-100 points each), whereas pain frequency is defined as the number of days with pain during the last 10 days multiplied by 10 (0-100 points). Patients with IBS-SSS <175 are defined as having mild IBS, 175-300 moderate IBS, and ≥300 severe IBS.

Bristol Stool form scale (BSF) (133) was used as a stool diary where each stool was reported to define stool frequency and consistency. Using BSF scale, normal stools were defined as 3-5, hard as 1-2 and loose as 6-7.

GI Symptom Rating Scale version (GSRS-IBS) (134), evaluates the severity of IBS symptoms, including a total score (1-7), as well as domain scores for the severity of abdominal pain, bloating, satiety, diarrhea, and constipation. A higher score indicates more severe symptoms. A higher score implies more severe symptoms.

The GI symptom assessments were performed during the screening period, throughout the intervention period, and one week before visits 4 and 5.

Extraintestinal symptoms

Patient Health Questionnaire (PHQ)-12*,* is an abbreviated version of PHQ-15 (135), without the three GI symptoms, assesses the non-GI somatic symptom severity. The higher score between 0-12 meaning more severe symptoms.

Psychological symptoms

The Hospital Anxiety and Depression (HAD) scale (136), was used to assess the severity of anxiety and depression and to identify participants with clinically significant anxiety and depression. It has a score between 0-12, where a higher score means more pronounced symptoms.

IBS-Quality of Life (IBS-QoL) questionnaire (137) evaluates the effect of IBS symptoms on quality of life. It has a score between 0-100, where a low score implies less quality of life.

These assessments were performed at each visit from 2 to 5.

Dietary assessment

Food records (4 days). Written and verbal instructions were given to the participants to maintain their regular diet and to complete the food records during consecutive days. Quantities referring to household utensils or standard measures, cooking methods, food labels and brands were noted for all foods and drinks consumed. The nutrient calculation software Dietist XP version 3.1 (kostdata.se) and a Swedish database for FODMAP content in foods were used for calculation (91). The food record was carried out 4 days before visits 2, 4 and 5.

Dietary adherence assessments. During the dietary intervention periods the participants noted any deviation from their diet in a diary. Adherence to the diet was calculated for each week and carried out though the whole intervention.

Treatment satisfaction questionnaire. With this questionnaire the participants could evaluate various aspects regarding perceived satisfaction/dissatisfaction of the intervention diet period. Agreed statements of following aspects were ticked in a box.

What was good about your intervention diet?
The diet has improved my IBS-symptoms
The diet has improved my overall health
The food tasted good
The recipes were simple
The food is affordable
I am used to cook my own food
The rest of my family can eat the same food
It is easy to find options while eating out

What was bad about your intervention diet?
The diet worsened my IBS-symptoms
The diet worsened my overall health
The food did not taste good
The recipes were difficult
The food is too expensive
I am not used to cook my own food
The rest of the family would not eat the same food
It is difficult to find options while eating out

Blood samples. Cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides were analyzed before and after the intervention. During the follow-up visits in the dietary treatment groups, hemoglobin A1c, glucose, and blood lipids were followed to assess potential negative effects of the intervention diets. At visit 1, routine clinical blood samples were also taken to other diseases.

A more detailed overview of the data collections during the RCT can be seen in the original paper of study I, supplementary appendix in Figure 1: Overview of the visits and procedures.

3.2.2 STUDY II

Qualitative approach – question guide

The purpose of the interviews was to include the experience both from the intervention period, and the time after the end of the interventions, and therefore planned to be carried out at any of the two follow-up visits. Since most of the respondents were asked to participate at visit 3 (end of intervention), eighteen of the nineteen interviews were performed on the first return visit (visit 4) and only one at the latter (visit 5).

The purposive selection was done to obtain experiences from a group of participants that reflect the general composition of the IBS group in terms of age, gender, duration in years of IBS, subtype of IBS, and which dietary intervention group they entered. All invited participants accepted the invitation and a variation of collected data was reached after 19 interviews.

An interview guide was developed to explore the patients' experience of dietary change when undergoing a restrictive dietary intervention with the goal to alleviate GI symptoms. The semi-structured interviews were conducted with the support of four open-ended questions and/or with varied probes to invite the participants to talk freely. The questions followed an inductive approach and aimed to capture thoughts, feelings, and experiences during and after the dietary intervention. (Figure 6).

Semi-structured interviews

The interviews were all performed by one of the authors (CW) and conducted in a room that was furnished for a more relaxed conversation, likely to encourage narrative. The interviewer summarized the interviews to provide an opportunity for the participant to clarify what had been said. Notes were taken and the latent content was considered through noted sighs, silence, and laughter. The interviews lasted between 24 and 72 minutes and were audio taped. The recordings were transcribed verbatim by a medical secretary and the interviewer.

Interview questions
1. Please, describe how it was for you to change your diet during the four intervention weeks. Participants randomized to the low FODMAP diet, where reintroduction of FODMAP was recommended, were also asked: Please, describe your reintroduction phase. 2. Was there something you were missing, or had needed, to perform the intervention diet? If so, what, why and why not? 3. What are your thoughts about your own ability to make the requested dietary changes? 4. Do you eat differently today than before you participated in the intervention study? If so, or not, please describe why and in what way. **Example of probes used:** Tell me more about X? Can you give me an example of X? Can you describe X? What does X mean to you? In what way? Why, why not? How?

Figure 6. The main questions and following probes in the semi-structured interviews in study II.

3.3 STATISTICS AND DATA ANALYSIS

3.3.1 STUDY I

The expected response rate in the treatment groups on the primary outcome measure was 40% after LCD, 65% after LFTD, and 40% after OMT. These expected response rates were used in a power calculation demonstrating that with 80% power to detect differences between the groups at $\alpha = 0.05$, each cohort would need to consist of 83 patients. The drop-out rate was expected to be approximately 15%, and therefore 100 patients were planned in each of the treatment arms.

For baseline characteristics normally distributed variables were presented as mean± standard deviation (SD) and differences in mean values between the three groups were analyzed with analysis of variance (ANOVA), and proportions with chi square tests. Non-normally distributed variables were presented as median and range. For the absolute change in continuous outcome variables, normally distributed variables, mean and percentage change, were used to analyze within group differences (baseline versus follow-up and end of intervention) with paired-samples *t* tests. For non-normally distributed variables Wilcoxon signed-rank test was utilized. Binary outcome variables (responders/no responders) were compared with chi square test between all three groups and post-hoc analyses with pairwise comparisons. Mixed linear effects regression was used to assess the linear response of IBS-SSS to the interventions. Statistical significance was set to two-tailed p values of <0.05. IBS SPSS statistics version 28.0.1 for Windows (Armonk, NY: IBM Corp.) was used for performing statistical analyses and for programming language R version 4.2.1 (Vienna, Austria) and RStudio 2022.12.0. The statistics were performed by two of the authors (SN, JPH).

Primary outcomes

The participants with a reduction in IBS-SSS ≥ 50 at the end of intervention relative to baseline was defined as a responder to the treatment to, and the same definition was also used during the follow-up visits in the dietary groups. The IBS-SSS threshold of ≥ 50 for defining response is considered to indicate a significant reduction in IBS symptoms and recommended for use in clinical studies (138).

Secondary outcomes

Changes in GSRS-IBS, BSF, IBS-QoL, HAD and PHQ-12 at the end of the intervention period relative to baseline were evacuated for all three treatment options. In the dietary groups, in addition to the questionnaires, differences in intake of energy, macronutrients, FODMAP, blood lipids (cholesterol, triglycerides, LDL, HDL) were also evaluated at the follow-up visits. Participants in the OMT group were analyzed in separate groups with different treatment based on the predominant symptoms, constipation, diarrhea, or abdominal pain.

3.3.2 STUDY II

The collected diet-related experiences that were told during the semi-structured interviews were transformed into text and was analysed with an inductive content analysis (CA) with the approach of Elo et al (139). Elo et al have developed a structured approach to inductive content analysis that provides a systematic framework for analyzing previously unexplored qualitative data and therefore well suited for our purpose (139, 140).

A six-step analysis process was applied for analysing the text moving from specific to the general aspects. Both recordings and written materials were important for achieving an overall understanding and were continually re-assessed during the analysis. The process of open coding commenced by identifying relevant meaning units from the transcribed interviews. The initial abstraction from the original text involved condensing these units of meaning. Subsequently, data were coded and extracted into subcategories and the preliminary subcategories were systematically compared, grouped, and re-grouped. This iterative process deepened the understanding of similarities and differences in the participants' experiences, ultimately leading to the formation of distinct categories. Finally, the categories were ordered into themes that comprehensively described all included data. All steps were needed to be able to formulate general statements summarizing the insights that emerged. (Figure 7)

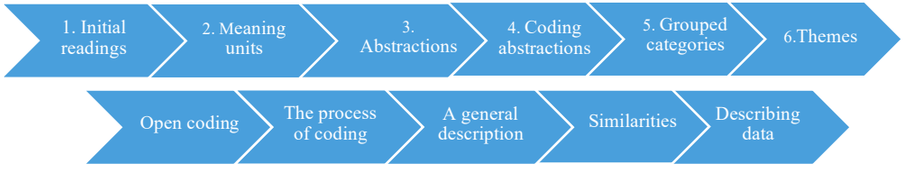


Figure 7. Description of the six-step analysis process of the content analysis following the approach of Elo et al.

To establish trustworthiness, our research group engaged in ongoing discussions related to readings, abstractions, codings and themes. The primary objective was to ensure consistency across various stages of the analysis and enhance the transferability of our findings. The researchers in the discussion group had different professions and research methodological experience that contributed to an open-minded approach during the analytical process.

4 RESULTS

4.1 MAIN FINDINGS OF THE STUDIES

The RCT (study I) included 294 participants divided into three cohorts: two dietary treatment arms with two restrictive diets (LFTD/LCD) and one medical (OMT) arm. After completing the four-week interventions, all three groups had reduced their IBS symptoms, with diet groups having significantly more responders (IBS-SSS reduction ≥50) compared to the medication group. There were no differences in the positive outcome effects between the diet groups and the effects persisted at the six-month follow-up.

From the analysis of the qualitative study (study II), with 19 participants selected from the two dietary treatment groups of the RCT study, three themes evolved. The themes describe the dietary intervention as supportive, challenging and also contributing to reflection. The analysis demonstrated not only a perceived improvement in GI symptoms, but also new dietary learnings and developments related to food intake which led to personalized adjusted dietary changes.

4.1.1 STUDY I

Participants

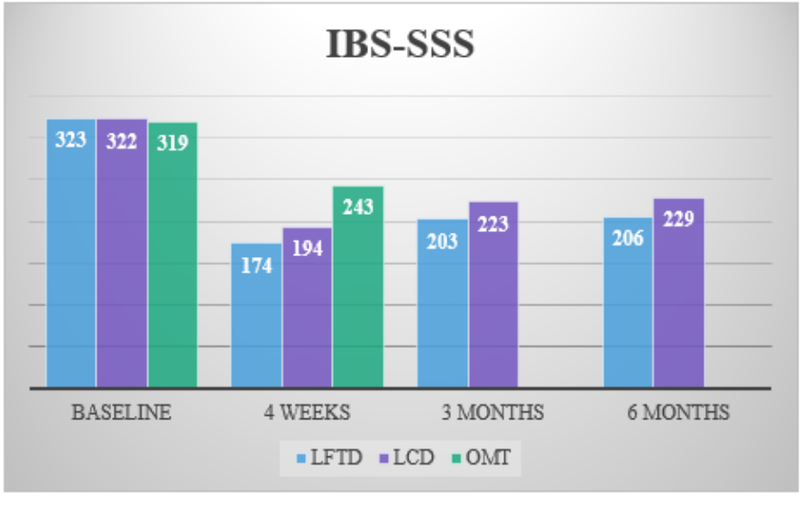
A total of 1104 individuals were approached and asked to participate in the study and 416 came to the screening visit. Of these, 304 individuals (82% females) were randomized. After randomization 10 participants were found to be ineligible and 294 participants were included in the study: 96 in LFTD, 97 in LCD, and 101 in OMT groups. Dropout rates during the intervention did not differ between groups and was 10 in the OMT group and 5 in each of the dietary intervention groups. Baseline characteristics of the participants showed no significant differences between the groups.

For the three- and six months follow-up, 69 (72%) and 56 (58%) in LFTD, and 75 (77%) and 62 (64%) participants in LCD were included. In the OMT 68 participants answered to the follow-up mail. The drop-out rate did not differ between the diet treatments, but was higher than expected, mainly due to the covid-19 pandemic. An extensive description of the number of participants and dropouts during the course of the RCT can be seen in the trial profile in the original paper of study I, Figure 1: Trial profile.

4.1.1.1 IBS SYMPTOM SEVERITY

Intervention period

There was a significant decrease in the total IBS symptom severity score after the intervention period relative to baseline for all three interventions (p<0,0001) (Figure 8). Notably, the reduction was significantly more pronounced in the LFTD (-149±115) and LCD (-128±110) groups compared to the OMT group (-76±94). The individual domains of IBS-SSS (pain intensity, pain frequency, bloating intensity, daily life interference, and bowel habit dissatisfaction), were all significantly lower after intervention than at baseline in all three treatment groups (p<0.001), and as well with more pronounced effects in the dietary interventions than in the medical treatment group.



Abbreviations: IBS symptom severity score, IBS-SSS; LFTD, low-FODMAP traditional IBS diet; LCD, low carbohydrate diet; OMT, optimal medical treatment.

Figure 8. The change of total IBS symptom severity score (IBS-SSS) from baseline to six months for the diet groups and to end of intervention (four weeks) for the OMT group. The reduction is significant from baseline for all treatments follow-ups, (p-values <0.001). Values intention-to-treat.

The proportion of responders (participants with IBS-SSS ≥50 points) in the LFTD n=73 (76.0%) and LCD n=69 (71.1%) groups was larger compared to OMT n=59 (58.4%) (p=0.023). There was no significant difference in the proportion of responders between the two diets (LFTD vs LCD, p=0.44; LFTD vs OMT, p=0.009; LCD vs OMT, p=0.061). Visual diagrams of the proportions of responders to treatment can be seen in the original paper of study I, Supplementary appendix, Figure 2 A.

In the OMT group, there was no difference in the proportion of responders when comparing the predominant symptom groups: constipation (56.5%), diarrhea (55.6%) or abdominal pain (60.0%) (p=0.93). The response to treatment in all three groups did not differ concerning subtype of IBS. (LFTD p=0.089, LCD p=0.48, and OMT p=0.91.)

Three- and six-month follow-up

At the three- and six-month follow-up visit the total IBS-SSS were still significantly lower than at baseline in the dietary groups (Figure 8). The proportion of responders in the dietary groups at the three- and six-month follow-up visits were n=51 (73.9%) and n=38 (67.9%) in the LFTD group and n=48 (64%) and n=37 (59.7%) (completers) in the LCD group. The number of responders were still high at the follow-ups and with no difference in between the two dietary groups. (LFTD and LCD three- and six-month p=0.20, p=0.36, respectively). Extended visual diagrams of the proportions of responders to treatment in the RCT after three- and six months can be seen in the original paper of study I, Supplementary appendix, Figure 2 C and D.

The set up for the six-month follow-ups differs between the OMT and the diet groups and presents separately. The number of participants in the OMT group who completed the six-month follow-up questionnaires were n=68 (67.3%), and of these n=26 (38.6%) had continued to take the prescribed medication. The mean IBS symptom severity was 224±104 and was lower among participants who had continued with their medication versus not (IBS-SSS 166±82 versus 260±101; p<0,001). After six months a majority (66.2%) was still considered as a responder in the medical treatment arm. In addition, n=67 (73.6%) of the OMT completers had received dietary advice post-intervention, but the difference in symptom severity between those who

received dietary advice compared to not (IBS-SSS 227 versus 199) was not statistically significant (p=0.33).

Table 11. An overview of responders in IBS symptom severity score (IBS-SSS) during intervention and follow-ups in the three treatment groups.

IBS-SSS responders	LFTD	LCD	OMT
4 weeks *	76% of 96	71.1% of 97	58.4% of 101
3 months **	73.9% of 69	64% of 75	--------
6 months **	67.9% of 56	59.7% of 62	66.2% of 68

*Abbreviations: IBS-SSS, IBS severity scoring system; LFTD, low-FODMAP traditional IBS diet; LCD, low carbohydrate diet; OMT, optimal medical treatment. * Intention-to-treat, ** Completers.*

4.1.1.2 SECONDARY OUTCOMES

Dietary components

At the six-month follow-up the participants in both dietary groups had adjusted their diets. Adjustments from baseline diets, the respective intervention diets and six-month diets are presented in Table 12. Differences from baseline were more pronounced in the LCD group. Participants in the LCD group had a higher fat E% intake and a lower total carbohydrate E% compared to LFTD (p=0.0002 and p=0.0001, each) at six months. The mean intake of FODMAP in LFTD at six months had increased from the intervention period, but the FODMAP intake still tended to be lower, but not significantly so, compared to baseline. In the participants self-reported reintroduction of FODMAP after 6 months, the majority had reintroduced several of the FODMAP options. Lactose was the least reintroduced FODMAP in the diet. The extensive description of dietary data can be seen in the original paper of study I, Table 2: IBS symptom severity, anthropometry, stool consistency, and dietary and questionnaire data.

Table 12. Energy percentage, E%, from macronutrients in the two RCT dietary groups at baseline, at 4 weeks intervention, and six months follow-up.

Intake E%	LFTD			LCD		
Mean (SD)	Baseline	4 weeks	6 months	Baseline	4 weeks	6 months
Protein	16 (3)	17 (2)	18 (3)**	16 (4)	23 (4)	18 (5)**
Fat	39 (6)	34 (6)	38 (6)	39 (6)	67 (4)	44 (8)**
Carbohydrate	41 (6)	46 (5)	41 (5)	41 (7)	9 (2)	34 (9)*
FODMAP (g)	17 (8.9)	3.4 (0.9)	13.8 (9.6)	17.7 (9.6)	17.1 (7)	14.7 (8.6)*

*Significantly lower than baseline, ** Significantly higher than baseline. Abbreviations: FODMAP, fermentable oligo-, di-, monosaccharides and polyols; LFTD, low-FODMAP traditional IBS diet; LCD, low carbohydrate diet; SD; standard division; E%; energy percentage.

Adherence

In total, 52.7% of the participants in the LFTD and 59.5% in the LCD group reported complete adherence during intervention. The comparable mean number of reported deviations in the final week in both diet groups was 1.4 (±2.2) in LFTD; 1.6 (±2.4) in LCD, range 0-12, (p=0.52).

Treatment satisfaction assessment

As shown in Table 13, a majority of the participants in both dietary groups reported perceived improved IBS symptoms and a perceived improved overall health after the four-week intervention period in the assessment of treatment satisfaction. A predominance of the participants in both diet groups found the recipes to be tasty and easy to cook. Approximately a fifth in both groups stated that their cooking habits were not sufficient for some cooking. The highest reported dissatisfaction factor was difficulty finding options that adhered to the dietary regimen when eating out in the LFTD compared to the LCD group. More of the participants in the LCD group found the intervention food “family

friendly" compared to in the LFTD group. Both dietary groups, reported a low degree of worsening of IBS symptoms or overall symptoms.

Table 13. Presentation of the Treatment satisfaction assessment result in percent, %.

Treatment satisfaction Assessment, %	LFTD Positive	Negative	LCD Positive	Negative
Improved / worsened IBS symptoms	78	4	72	9
Improvements / worsened in overall health	62	3	51	8
The food tasted good / bad	89	0	86	5
The recipes were simple / hard	90	3	95	3
The food is affordable / too expensive	51	2	48	1
Family can eat the same / not used to cook	45	20	59	20
Easy / hard to find options eating out	9	37	27	23

Abbreviations: LFTD, low FODMAP traditional IBS diet; LCD, low carbohydrate diet

Bowel habits

There was a significant improvement in stool consistency for both dietary groups. The LFTD group significantly reduced the proportion of loose stools and increased the proportion of normal stools ($p<0.001$). The LCD group mainly reduced the proportion of hard stools and increased the proportion of normal stools ($p<0.001$). In the OMT cohort the effects on bowel habits differed based on the type of treatment. The statistical changes in stool consistency are presented in the original paper of study I, supplementary appendix, Figure 4: Changes in stool consistency.

Blood samples

The levels of total cholesterol, HDL, LDL and triglycerides were all significantly reduced during the LFTD intervention. In the LCD group the levels of triglycerides and HbA1c were significantly reduced, while total cholesterol and LDL-cholesterol were increased. The presentation of blood values from baseline to 6-month follow-up are presented in the original paper of study I, supplementary appendix, Table 7: Blood lipids and sugars.

Questionnaires

In addition to a symptom relief in IBS-SSS, all three treatment arms showed a significant improvement after the intervention period in the outcome measures concerning overall GI symptoms, non-GI somatic symptoms, quality of life, anxiety and depression during the intervention. For the two dietary arms this was consistent during the follow-up periods. All questionnaire data is presented in the original paper of study I, Table 2: IBS symptom severity, anthropometry, stool consistency, and dietary and questionnaire data.

4.1.2 STUDY II

The participants' experiences of implementing necessary dietary changes as a dietary treatment when living with IBS are represented by three themes.

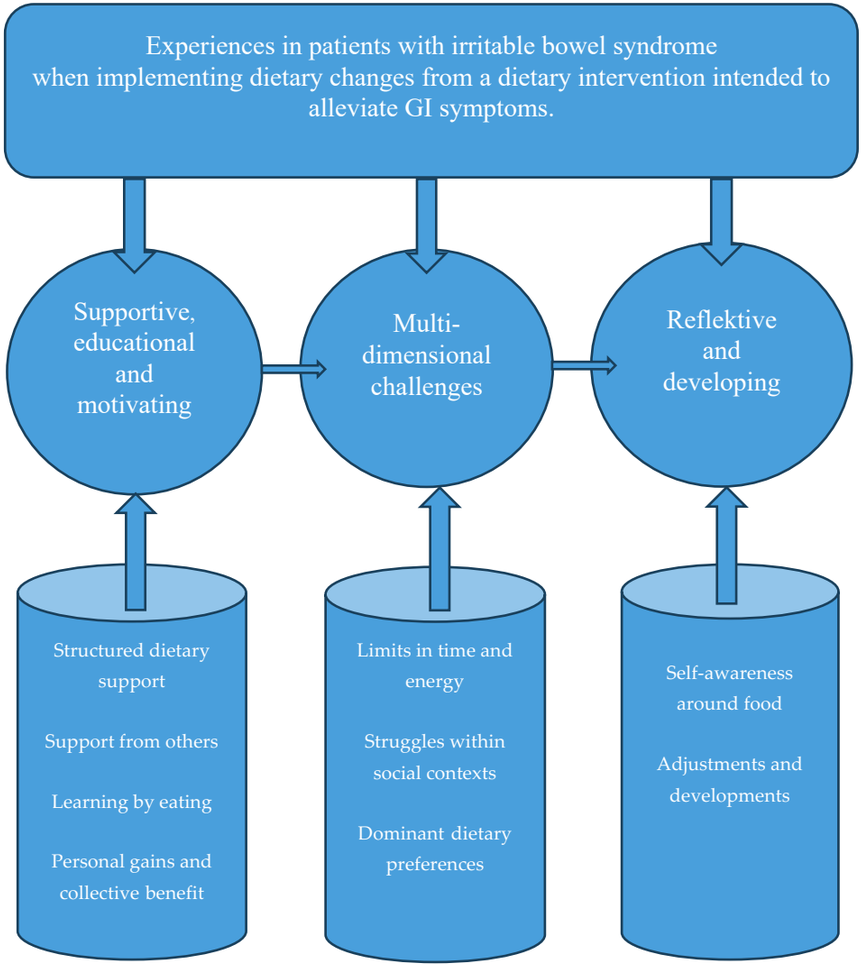


Figure 9. Themes and subordinated categories of experiences of structured dietary interventions to alleviate GI symptoms in patients with irritable bowel syndrome (IBS).

The qualitative analysis extracted from transcripted interviews identified three main themes, “Supportive, educational and motivating”, “Multidimensional challenging”, and “Reflective and developing”. Nine obtained categories together with the participants' quotes clarify and describe the themes in a more detailed way. A visual overview of the results can be seen in Figure 9.

A structured dietary support helped the participants to implement and adhere to the new dietary changes requested from the intervention protocol. Gaining access to professional help and being part of the research were perceived as motivating factors. By performing the intervention diets, participants tried new foods that demonstrated both positive and negative effects on symptoms. The adherence to the intervention diet was taken seriously and facilitated in that way their dietary learnings. Although the reintroduction of FODMAP into everyday life was perceived as difficult and with a fear of increased symptoms, the FODMAP reintroduction was experienced as a process of learning-by-eating that ultimately offered a more varied diet.

Despite support in various forms (menus, groceries bags, and access to feedback from dietitians responsible for the diet intervention), the implementation of the dietary changes was experienced as multidimensionally challenging in many ways. The challenges were individual and depended on the participants' lifestyle and personal needs. Social context and family life could interfere with the dietary implementations. Limitations of everyday time and energy and not being used to cooking were pointed out as demanding conditions. For some participants, previously learned dietary habits or learnings seemed to be dominant and sometimes difficult to change although it could be beneficial for achieving symptom relief in IBS, for example changing one's opinion of what constitutes a healthy diet.

By going through the dietary intervention with its support and challenges, a reflective and developing process arose regarding previous eating behaviors, strategies, and an awareness around food intake. New insights led to new ways for realistic and personalized dietary changes, adapted and developed according to the needs of each individual participant. Dietary changes that were maintained were not always the most symptom relieving, but those that were considered the most practical and that fitted into everyday life. In addition, according to the participants' own perceptions of maintained dietary changes post-intervention was a decrease of total carbohydrates, an increased intake of vegetables and a feeling of eating a more versatile and healthy diet.

Descriptive quotes from the theme Supportive, educational, and motivating:

"You [*the study staff*] *are interested and do everything to make it work* [*the intervention diet*]. *It feels great not to fight this all by myself."* (p18, LFTD)

"But many [*work colleagues*] *were very understanding /…/ And many had the same problem! They thought it was interesting and wanted to look at the book* [*intervention menus*] *and to understand."* (p5, LFTD)

"But I didn´t think that diet was so significant. But now with this [*experiences from the intervention diet*]*! /…/ But now, I realize that for me it´s important to have these fixed mealtimes. "* (p7, LCD)

"If I want to try something new [foods], I will do as I did with this [reintroducing FODMAP]; I test a little and then a little bit more and a little bit more." (P2, LFTD)

Figure 10. Visualization of supportive, educational, and motivational conversations in IBS care. Image created with BioRender.com.

Descriptive quotes from the theme Multidimensional challenges:

"It is required that you are reasonably alert and active, both physically and mentally, in order to have the energy to get through it [*coping with the intervention diet*]*."* (p14, LCD)

"It's my boyfriend who thinks I'm very awkward [*with food*]. *Therefore, it felt very nice that I got this* [*intervention diet*]. *But he still thought it was hard."/… /"It's tough to feel that it´s a big conflict at home because I have special things* [*issues*] *with food."* (p5, LFTD)

"… And too much fat! It feels weird to eat such fatty foods [*the intervention diet*]. *For a long time… or forever!"/… /"I try to eat… choose foods that are good for health"* (p6, LCD)

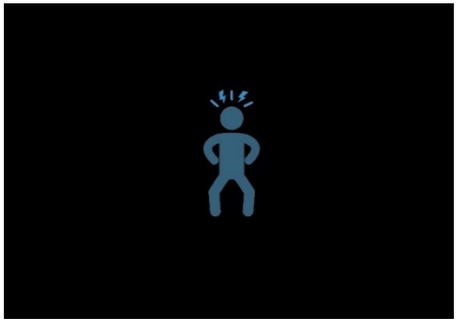


Figure 11. Visualization of going through challenges in dietary changes when living with IBS. Image created with BioRender.com.

Descriptive quotes from the theme Reflective and developing:

"I´ve been rethinking - not binge eating just because it's good for the moment, and then there's a price to pay afterwards." (p13, LFTD)

"But towards the end [*of the dietary intervention*], *from thinking that this was nice… I felt towards the end, that now I understand the concept, now I want to make*

my own schedule, so that I can do what I really feel good about in terms of fiber, what works and what is easy." (p5, LFTD)

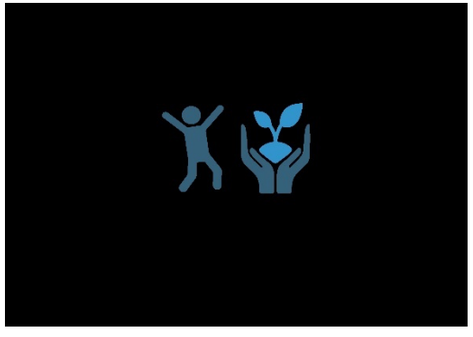


Figure 12. Visualization of the process of reflection and development when changing diet when living with IBS. Image created with BioRender.com.

5 DISCUSSION

5.1 WHAT DO OUR FINDINGS MEAN FROM A DIETARY TREATMENT PERSPECTIVE?

Our studies showed that diet matters for patients living with IBS. All three treatments in the RCT showed significant improvements in IBS symptoms, but the two dietary treatments showed a notably increased positive effect compared to the medication alternative. This is supported by several findings from our two studies and includes the measurements of GI symptoms (IBS-SSS, GSRS-IBS), assessment of treatment satisfaction and the semi-structured interviews. Previous research has shown evidence for an effect of a low FODMAP diet in the short (54, 55, 94, 98, 99), and to some extent, longer term (101-104). This is consistent for the TDA, recommended as the first dietary option in the BDA/NICE guidelines (52, 53) and also considered the most patient-friendly option (66). The effects of combining the low FODMAP diet and traditional IBS diet, referred as the LFTD in our studies, have not been studied before and contributes with additional important insight in dietary treatment in IBS. However, given previous research, it was not unexpected to observe a positive result with the LFTD. Conversely, the LCD represented an unexplored dietary paradigm with uncertain expectations for IBS patients.

Given our results, where the LCD showed comparable symptom efficacy to LFTD and a greater efficacy compared to symptom-oriented medical treatment, a few contributing factors could be discussed for the favorable outcome of the diet. Some of these factors could relate to the diet's low carbohydrate content. A lower sucrose and starch intake have shown promising results for some individuals in previous studies (47-49), as well as the potential involvement of sugars in low-grade intestinal inflammation has been mentioned (95, 116). However, according to the BDA/NICE guidelines, a high-fat diet may potentially increase GI symptoms (52, 53) and the high fat content in LCD could possibly affect GI transit (117). These different aspects of LCD may indicate different effects on different IBS symptoms, alleviating or worsening depending on the IBS subtype. Our study found no significant differences in number of responders between IBS subtypes, nevertheless, when comparing the percentages of the stool consistencies (C and D) at baseline and post intervention, interesting patterns emerged. Hard stools decreased with LCD, while loose stools were decreased with LFTD. Both diets led to an increase in number of stools with normal stool consistency**.** This outcome seems though to be inconsistent with the results of a study that reported

positive impact of LCD in IBS-D (119). These divergent results suggest that the two dietary interventions may have varying benefits for different IBS subtypes and could therefore be a valuable indicator for a more personalized dietary treatment in the future. Further research is needed to comprehensively understand the potential mechanism behind these dietary indications.

The two dietary interventions differed in macronutrient- and FODMAP composition. Our RCT demonstrated that the LCD group maintained its intervention dietary profile with lower intake of E% carbohydrate and higher intake of E% fat throughout the six-month follow-up, while the LFTD group did not exhibit equivalent consistency regarding FODMAP content. The inclusion phase of FODMAP reintroduction in the LFTD group may explain this discrepancy. Adding different FODMAP in an individualized manner appears to have formed a personal expanded diet with continued positive impact on the GI symptoms. Here, the qualitative analysis provides additional insights into the process of how participants integrate FODMAP into their daily lives. Experienced positive impacts were the personal dietary learnings, and a less restrictive diet. Encountered challenges were described as a lack of motivation for this assignment, and fear of increased symptoms. The selected reintroduced foods were also stated to be those that added quality of life more than symptom relief. These intertwining results suggests that the individual reintroduction of FODMAP was implemented successfully in our study and counteracts an unwanted strict adherence to the LFTD diet. Our finding validates the current recommended approach of FODMAP reintroduction (88, 97, 109). However, since the LCD group showed an increased intake of carbohydrates after six months compared to the intervention diet, it could be suggested that this diet was also gradually adapted to an individual level of carbohydrates without increasing severity of GI symptoms.

Dietary intake in the LCD group showed a remaining higher fat content at the follow-up visits compared to baseline intake. In the interviews some participants who received the LCD perceived the intervention diet as too high in fat content and this contributed to a concern about perceived health risks and potential negative effects on blood lipids. When analysing the blood lipids, the mean total cholesterol and LDL-cholesterol (known as the 'bad' cholesterol) were increased in this group. This is most likely an adverse effect of the diet and demonstrate that their concerns about these effects were reasonable (113). It should also be noted that our study's LCD contained a good fat quality compared to a traditional ketogenic diet where often saturated fats such as animal and coconut fat are the main fat sources and may pose be an even larger health risk. The blood lipid levels in the LFTD group showed significantly lowered blood lipids and highlights the positive impact of a balanced diet in

macronutrient and fat composition and therefore LFTD again emerges as a favourable dietary option in IBS (141). However, different personalized low FODMAP diets may not be as well composed as our intervention diet (follows the recommendations of NNR(131) and are not generally transferable to all low FODMAP diets.

The treatment satisfaction assessment reported that the participants perceived the dietary treatment to also have improved their general health status. This finding could be reinforced by both the narratives from the qualitative study and the questionnaire assessments of non-GI symptoms, anxiety and depression, and quality of life. Patients with IBS describe a presence and impact of non-GI symptoms as common and aggravating (1, 2, 8, 9, 50, 142). It should be reasonable to assume that reduced IBS symptoms lead to a generally better well-being. Thus, our treatments show an improvement in the psychosocial aspects. It is an important outcome to demonstrate that dietary changes can contribute to better overall well-being, which also in the long run could lead to a better ability to manage IBS.

The interviews of the participants at the follow-up visits reveal a feeling of perceiving their diet as healthier and more diverse than before. Even participants who did not experience improvements in IBS symptoms maintained some dietary changes that they associated with healthier choices. This perception may have been influenced by new dietary knowledge, increased dietary self-awareness, and the introduction of novel foods in both diets. Nevertheless, practical dietary challenges, such as difficulties in preparing intervention food due to time constraints or cooking experience were reported. Thus, the dietary changes that persisted were not always the most symptom-relieving but rather the most practical for everyday life. To further facilitate dietary changes, one approach could involve encouraging the food industry to produce IBS-adapted food bags, recipes, and IBS-friendly fast-food options. Additionally, to facilitate family-related challenges, involving partners in visits to dieticians could help address dietary complications and enhance understanding.

In addition, the result of the dietary deviations report shows strong adherence and therefore reinforces reliable results. Although a six-month follow-up period may not fully capture long-term dietary changes, this period of time offers insights into immediate dietary post-intervention changes and could indicate potential persistence of dietary modifications. Investigating sustained long-term dietary effects for more than six months is rarely done but has been highlighted in a few studies and needs to be expanded (101-103).

Quantitative research has predominantly characterized investigations in IBS. However, by integrating qualitative insights, we aim to enhance our comprehension and understanding, and improve patient care. Our qualitative analysis mainly concentrates on the experience of performing dietary changes and not specifically on the diets themselves. The analysis reveals the dietary changes as a process involving learning, self-awareness, and dietary developments. Patients desire for more IBS-related knowledge and investing in education has previously been noticed and are being reinforced in our findings (74, 75, 143). IBS treatment with physical activity has been suggested to lead to a stronger "self" that contributes to new self-management ways, and positive parallels can be drawn to the performance of the dietary changes (123). Furthermore, our participants expressed the importance of having social support, in addition to professional help, which is consistent with established findings in previous research (125, 129). Challenges experienced by our participants in managing the IBS can also be confirmed in previous findings highlighting the difficult maneuvering and poorer quality of life (126-128). The participants in our study showed great ingenuity that led to personal dietary changes adapted to their unique life circumstances, which is a positive result as life situational factors are known to have a large impact on GI symptoms (125).

The described dietary process provides an insight into the multifaceted layers of dietary change and challenges faced by patients with IBS as they strive for symptom improvement. Our structured dietary intervention designed for IBS patients, can be seen as not only a dietary treatment, but as a personal dietary educational journey. Not all patients with IBS have the opportunity to undergo a similar dietary intervention, but parallels from this could be drawn to dietary treatment in practice. Dietary management should firstly support the patient to begin their dietary adjustment, and ongoing follow-up visits provide continued assistance during subsequent challenges. To facilitate the initiation of suitable dietary changes, it is important to highlight that dietary changes involve a learning process. Emphasize that the initial dietary changes must be adjusted, expanded, and personalized, but to know how and in what way the patient must make the dietary changes to learn their own best working long-term dietary plan. Our findings both show and reinforce previous findings of the need of robust support mechanisms of the management of dietary treatment in health care for patients with moderate to severe symptoms (125, 128, 143). In addition, our findings support the generally recognized need of dietitian guidance for dietary treatment with restrictive diets to fulfill good patient support (75, 76). Our results also contribute to the interest to invest in education for this patient group (61, 63). However, the challenge persists with the limited resources available within healthcare settings, but it is important to

keep on spreading the knowledge about the best possible care around these patients. It should be recalled that lifestyle information and first line dietary advice seem to be good initial treatment for a group of IBS patients (46, 49-52)

In summary, LCD demonstrated comparable efficacy in symptom reduction to the LFTD in IBS. The LCD may be more beneficial for patients who experience a sensitivity to foods containing sugars and starches and could from our findings be assumed to be more suitable for patients that have a problem with hard stools. Because LCD increased LDL-cholesterol, blood lipid monitoring and lipid quality adjustments may be considered to provide LCD as a safe dietary treatment for specific patients. If suggesting LCD, it should be to a patient with a healthy blood lipid profile and positive dietary preferences for this dietary regime. LCD could have a more prominent role for future interventions and needs to be further studied and compared to established dietary treatments before it could be used in clinical settings. Both low FODMAP diet (including the reintroduction) and the traditional NICE guidelines have previously been shown to be effective separately (54, 94). In the present studies, our results suggest that the diets are equally effective at alleviating GI symptoms, non-somatic burden and providing a healthy intake as a combination together. The low FODMAP diet may also be more suitable for patients who are concerned by loose stools.

Our research contributes to new findings about the effect of unproven diets. More research is needed in the long-term effect and carbohydrate content, but a combined NICE guideline and low FODMAP dietary treatment emerges as an effective and safe dietary treatment alternative. The dietary treatment should be delivered from health care with the management of a clear dietary support, encouraging initiation of dietary changes, and for personal dietary developments.

5.1.1.1 LIMITATIONS AND STRENGTHS

Both studies include only Swedish speaking patients which might limit the generalizability to patients with a different food culture. IBS symptoms at recruitment were set to moderate or severe and is not representative for patients with milder symptoms. The studies use delivery of free grocery bags, which probably improved adherence but is not possible in the clinical practice. Additionally, a so-called Hawthorne effect, where subjects may unconsciously change behaviour when being observed, can occur and should be considered in dietary studies involving active treatments.

The drop-out rate in study I were low during the intervention phase and included all subtypes of IBS. During the follow-up periods the covid-19 pandemic resulted in an increased number of dropouts from the study. The foods included were not blinded, but specific nutrient composition was not discussed or revealed to reduce placebo effects. The offered dietary treatment post-intervention provided for the OMT group made it difficult to interpret the mean IBS-SSS at six months for comparing the IBS-SSS with the two dietary groups. Study II highlights an unexplored area of research, includes a large amount of interview material, and includes a variation of the patients with IBS characteristics.

6 CONCLUSION AND FUTURE PERSPECTIVES

Our findings shows that diet plays a big role in the treatment of patients with IBS. We contribute with one of the largest studies to evaluate the effectiveness of restrictive dietary treatments versus an OMT strategy and experience in the required dietary change for patient with IBS. All three treatments showed reduction in IBS symptoms with a higher proportion in the dietary treatment groups. The diets LFTD and LCD differ in composition but led to equal symptom severity improvement.

Implementing of restrictive diets such as LFD and LCD appear to benefit from structured dietary support. Ultimately, the dietary changes that were maintained were not only related to a relief in IBS symptoms but to dietary changes that were not too challenging to maintain in the patients´ current life situation and consistent with the personal view of overall health. New dietary learning and self-awareness served as motivation and led to further dietary developments.

Our findings support previous research regarding the TDA (NICE guidelines) and low FODMAP diet as a primary and effective dietary option. Our result also reinforces the already known fact about the need for good support, education and dietary treatment by a dietitian for this patient group in healthcare. However, more research is needed within the concept of LCD for further use in patients with IBS.

Moving forward, to investigate more about how patients with IBS in general perceive the role of diet and what constitutes their view of healthy food could enrich our findings. Identification of predictive factors, examining food intake and microbiota composition are additional useful knowledge that could contribute to a better treatment effect and optimize the clinical use of these treatment strategies for patients with IBS.

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Hjärtans tack till min kära familj och vänner för ert stöd och alltid glada tillrop.

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Paper I

A low FODMAP diet plus traditional dietary advice versus a low-carbohydrate diet versus pharmacological treatment in irritable bowel syndrome (CARBIS): a single-centre, single-blind, randomised controlled trial

Sanna Nybacka, Hans Törnblom, Axel Josefsson, Johann P Hreinsson, Lena Böhn, Åsa Frändemark, Cecilia Weznaver, Stine Störsrud, Magnus Simrén**

Summary

Background Dietary advice and medical treatments are recommended to patients with irritable bowel syndrome (IBS). Studies have not yet compared the efficacy of dietary treatment with pharmacological treatment targeting the predominant IBS symptom. We therefore aimed to compare the effects of two restrictive dietary treatment options versus optimised medical treatment in people with IBS.

Methods This single-centre, single-blind, randomised controlled trial was conducted in a specialised outpatient clinic at the Sahlgrenska University Hospital, Gothenburg, Sweden. Participants (aged ≥18 years) with moderate-to-severe IBS (Rome IV; IBS Severity Scoring System [IBS-SSS] ≥175) and no other serious diseases or food allergies were randomly assigned (1:1:1) by web-based randomisation to receive a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) plus traditional IBS dietary advice recommended by the UK National Institute for Health and Care Excellence (hereafter the LFTD diet), a fibre-optimised diet low in total carbohydrates and high in protein and fat (hereafter the low-carbohydrate diet), or optimised medical treatment based on predominant IBS symptom. Participants were masked to the names of the diets, but the pharmacological treatment was open-label. The intervention lasted 4 weeks, after which time participants in the dietary interventions were unmasked to their diets and encouraged to continue during 6 months' follow-up, participants in the LFTD group were instructed on how to reintroduce FODMAPs, and participants receiving pharmacological treatment were offered diet counselling and to continue with their medication. The primary endpoint was the proportion of participants who responded to the 4-week intervention, defined as a reduction of 50 or more in IBS-SSS relative to baseline, and was analysed per modified intention-to-treat (ie, all participants who started the intervention). Safety was analysed in the modified intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02970591, and is complete.

Findings Between Jan 24, 2017, and Sept 2, 2021, 1104 participants were assessed for eligibility and 304 were randomly assigned. Ten participants did not receive their intervention after randomisation and thus 294 participants were included in the modified intention-to-treat population (96 assigned to the LFTD diet, 97 to the low-carbohydrate diet, and 101 to optimised medical treatment). 241 (82%) of 294 participants were women and 53 (18%) were men and the mean age was 38 (SD 13). After 4 weeks, 73 (76%) of 96 participants in the LFTD diet group, 69 (71%) of 97 participants in the low-carbohydrate diet group, and 59 (58%) of 101 participants in the optimised medical treatment group had a reduction of 50 or more in IBS-SSS compared with baseline, with a significant difference between the groups (p=0·023). 91 (95%) of 96 participants completed 4 weeks in the LFTD group, 92 (95%) of 97 completed 4 weeks in the low-carbohydrate group, and 91 (90%) of 101 completed 4 weeks in the optimised medical treatment group. Two individuals in each of the intervention groups stated that adverse events were the reason for discontinuing the 4-week intervention. Five (5%) of 91 participants in the optimised medical treatment group stopped treatment prematurely due to side-effects. No serious adverse events or treatment-related deaths occurred.

Interpretation Two 4-week dietary interventions and optimised medical treatment reduced the severity of IBS symptoms, with a larger effect size in the diet groups. Dietary interventions might be considered as an initial treatment for patients with IBS. Research is needed to enable personalised treatment strategies.

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*Contributed equally

Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (S Nybacka PhD, H Törnblom MD, A Josefsson MD, J P Hreinsson MD, L Böhn PhD, Å Frändemark MD, C Weznaver MSc, S Störsrud PhD, Prof M Simrén MD)**; Center for Functional GI and Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA** (Prof M Simrén)

Correspondence to:
Dr Sanna Nybacka, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg S-405 30, Sweden
sanna.nybacka@gu.se

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Research in context

Evidence before this study

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal disorder with few effective treatment options. Dietary advice and pharmaceutical treatment options benefit some patients with IBS, but few studies have directly compared these treatment options. We searched PubMed from database inception to Nov 30, 2023, using the search terms "irritable bowel syndrome" AND "FODMAP" AND ("NICE" OR "traditional IBS diet") for "randomised controlled trials", "meta-analyses", or "systematic reviews" published in English, which yielded ten results. The most recent systematic review and meta-analysis concluded that the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet was superior to all other dietary interventions in all outcomes studied. However, it concluded that there is a shortage of studies on the reintroduction and personalisation of the FODMAP diet. No studies evaluating a combined low FODMAP diet and traditional IBS diet were found. A search for "irritable bowel syndrome" AND "low carbohydrate diet" filtering for randomised controlled trials yielded four results, of which one was a small randomised controlled trial in patients with diarrhoea-predominant IBS receiving a very low carbohydrate diet. The efficacy of a diet low in total carbohydrates as a treatment option in IBS has therefore not previously been fully evaluated in a randomised trial. A search for "irritable bowel syndrome" AND "diet" AND ("pharmacological treatment" OR "medication") filtering on "randomised controlled trials" yielded ten search results, in which one was a direct comparison between a specific pharmacological agent and a low FODMAP diet within a primary care setting. Thus, no previous studies have evaluated symptom-targeted medical treatment versus dietary treatment among patients with IBS.

Added value of this study

To our knowledge, this randomised controlled trial is the first in IBS to compare the efficacy of these three treatment options: a diet combining low FODMAPs and traditional IBS dietary advice; a fibre-optimised diet low in total carbohydrates and high in protein and fat; and optimised medical treatment targeting the predominant IBS symptom. We found that the two dietary interventions outperformed the medical treatment option at improving IBS symptom severity after 4 weeks of intervention. In the low FODMAP and traditional IBS diet intervention, a FODMAP reintroduction was successfully carried out during the follow-up period. The positive effects of the interventions, in terms of improvements in global IBS symptoms, non-gastrointestinal somatic symptoms, psychological symptoms, and quality of life, largely persisted over a 6-month follow-up period, providing evidence for long-term benefit.

Implications of all the available evidence

Although we found evidence that dietary treatments were more efficacious than medical treatment after 4 weeks, all three treatment options showed significant and clinically meaningful efficacy. The sustained positive effects of dietary interventions suggest their potential as first-line treatments for IBS, although patient preference, compliance, cost-effectiveness, and effects on nutritional status and the gut microbiota would need to be accounted for. Considering the different treatment options in IBS, of which several show good effectiveness, future research is needed to identify possible predictors of treatment outcomes to enable personalised treatment strategies in the future.

Introduction

Irritable bowel syndrome (IBS) is a disorder of gut–brain interaction affecting approximately 4% of adults.[1] IBS is characterised by chronic or recurrent abdominal pain associated with abnormal bowel habits[2] with normal clinical routine tests and investigations. The pathophysiology of IBS is incompletely understood but can partly be explained by gut-related mechanisms[3,4] and disordered gut–brain interactions.[5] Most patients with IBS report that symptoms might be triggered by eating specific foods.[6] Thus, dietary modifications are often advocated as first-line treatment in IBS[7] along with other lifestyle adjustments. Due to the heterogeneity of symptoms in IBS, pharmacological treatment is recommended to target the predominant issue (eg, abdominal pain, constipation, or diarrhoea) for which evidence-based pharmacological treatments exist.[8] To date, few studies have compared dietary treatments and pharmacological treatments in IBS.[9]

Current IBS clinical dietary guidelines from the UK National Institute for Health and Care Excellence (NICE) emphasise the importance of healthy eating patterns as first-line dietary advice.[10] These recommendations include having a regular meal intake, taking time to eat, and restricting intake of coffee, tea, fizzy drinks, alcohol, and whole grains. For patients who do not get adequate symptom relief by these initial dietary modifications, a more restrictive dietary approach, known as the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet, might be used.[11] The low FODMAP diet limits the intake of short-chain carbohydrates that are poorly digested and osmotically active, thus reducing the delivery of fermentable substrates and water to the colon.[12] Initial FODMAP reduction should be followed by a systematic reintroduction of the different types of FODMAPs to evaluate individual tolerance. A 2022 meta-analysis showed that the low FODMAP diet was the most efficacious dietary intervention to improve global IBS symptoms,[13] but evidence on its long-term effectiveness is still scarce. To our knowledge, no study has evaluated whether a combination of traditional IBS dietary advice, with emphasis on healthy and regular meal intake, and a low FODMAP diet could provide additional benefit for people with IBS. It has also been proposed that people with IBS might have a reduced tolerance for foods rich in sugar and starch, partly due to variations in the sucrase-isomaltase enzyme complex.[14] Reducing the total amount of carbohydrates in the diet could thus potentially have a beneficial effect in IBS. A few studies have investigated the efficacy of a diet low in total carbohydrates[15] or reduced in starch and sucrose[16] in IBS with promising results. However, to our knowledge, a low-carbohydrate diet has not been compared with other dietary interventions in IBS.

In this study, we therefore aimed to compare three different treatment options in IBS: a combination of two currently recommended dietary strategies, the low FODMAP diet and traditional IBS dietary advice recommended by NICE (hereafter the LFTD diet); a diet low in total carbohydrates and high in protein and fat content, with optimised fibre intake (hereafter the low-carbohydrate diet); and pharmacological treatment based on the predominant gastrointestinal symptom. We hypothesised that the diet combination would be superior to both other treatment options in reducing IBS symptoms.

Methods

Study design and participants

This single-centre, single-blind, randomised controlled trial was conducted in an outpatient clinic specialised in disorders of gut–brain interactions at the Sahlgrenska University Hospital, Gothenburg, Sweden. Participants were recruited via social media advertisement, local newspaper advertisements, or by clinical referrals to a dietitian or physician at the clinic. Eligible participants were adults (aged ≥18 years) with IBS (any subtype), defined by Rome IV criteria,[2] with moderate-to-severe symptom severity according to the IBS Severity Scoring System[17] (IBS-SSS; score ≥175) and a BMI of 18–35 kg/m², without other serious diseases or food allergies, and residing in the Gothenburg region. A full list of inclusion and exclusion criteria is in the appendix (p 2). Participants provided written informed consent before study procedures.

The study protocol and all research procedures performed in this study were done in accordance with the ethical guidelines outlined in the Declaration of Helsinki. The study was approved by the regional ethics committee in Gothenburg (DNR 278–16). A detailed study protocol has been published previously.[18]

Randomisation and masking

Participants were randomly assigned (1:1:1) to the LFTD diet, the low-carbohydrate diet, or optimised medical treatment. The randomisation process was carried out by one of the dietitians (SN, SS, LB, and CW) using participant initials using a web-based randomisation software (dsharprandomization, version 2016) provided by an external regional coordinating research unit (Gothia Forum). The randomisation sequence was generated consecutively using a block-based algorithm. The block sizes were randomly ordered and could either be 1+1+1 or 2+2+2. There were no further stratification factors in the randomisation process.

Participants allocated to dietary treatment received oral and written information about the diet from a study dietitian, without disclosing the names of the diets (eg, LFTD or low-carbohydrate diet). Foods were not labelled as being low in FODMAPs or carbohydrates. The pharmacological treatment was open-label, per real-world practice. The study dietitians and physicians, as well as the investigators analysing the data, were not masked to group assignment. All data were entered into a database by staff masked to group assignment and not involved in the analyses or interpretation of the study results.

Procedures

The study encompassed a 10-day screening period, a 4-week intervention (28 days), and a 6-month follow-up, with five visits for participants assigned to dietary treatments (–10 days, 0 days, 4 weeks, 3 months, and 6 months) and three visits for those on optimised medical treatment (day –10, day 0, and 4 weeks; appendix p 3). At screening visit 1, a physician confirmed the IBS diagnosis by detailed clinical history, physical examination, and appropriate tests, as needed. Participant sex (options of male and female) was identified by the Swedish social security number. If all inclusion criteria were met, a 10-day screening period followed. The IBS-SSS was completed on the last day of screening to assess the severity of IBS symptoms during the past 10 days.

For more on the **social media recruitment platform** see https://www.trialy.se/en/home/

At visit 2, participants who still fulfilled the inclusion criteria were informed that all three interventions aimed to reduce symptoms of IBS, and none were believed to cure IBS. A study dietitian provided oral and written information about the diet to people in the dietary treatment groups, including a recipe booklet with detailed meal plans for the 4 weeks of intervention, diet-specific recommendations, and lists of foods that were allowed and not allowed during the intervention. All foods included in the recipes were provided for free once per week by use of a home delivery service from a conventional grocery supplier. Participants receiving dietary treatment were informed to continue with prescribed medications and probiotics at a stable dose if the treatment had started at least 6 weeks before randomisation. The study physician chose the optimised medical treatment, per participant agreement, without cost to the participant. No dietary or lifestyle advice was given before the medical intervention. Participants were asked not to make any changes to their diet or physical activity level during the intervention period.

See **Online** for appendix

The LFTD diet matched the Nordic Nutrition Recommendations[19] for a healthy dietary intake, with a macronutrient composition of 50% energy from carbohydrate, 33% from fat, and 17% from protein, and a mean

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total FODMAP content of 3·4 g/day (SD 0·9). Mean daily intake of dietary fibre was 29·3 g (4·6), mainly from soluble fibre (eg, oats, gluten-free bread, chia seeds, vegetables, and fruits). The daily meal plan consisted of breakfast, lunch, dinner, and three snacks in between larger meals. The advice also included sitting down during meals to eat, chewing foods thoroughly, and avoiding excessive intake of coffee (maximum three cups a day), alcohol (maximum one unit per drinking occasion), fizzy drinks, fatty foods, and spicy foods. Foods low in FODMAPs (eg, rice, potatoes, quinoa, pasta based on rice flour, and wheat-free and gluten-free bread) and a variety of vegetables and fruits (eg, carrots, aubergine, orange, kiwi, and raspberries) were used. If the intake of fresh fruits and vegetables was difficult to tolerate, participants were recommended to consume them peeled or boiled (or both). All dairy products were low-fat and lactose-free. Approximately three main meals per week consisted of fish and shellfish, and three main meals per week were based on plant-based protein.

The low-carbohydrate diet was based on a mean carbohydrate intake of 50 g/day (SD 9·0), with a macronutrient composition of 10% energy from carbohydrate, 67% from fat, and 23% from protein. Mean daily intake of dietary fibre was 23·9 g (SD 5·6), mainly derived from nuts, seeds, and low-carbohydrate bread. The daily meal plan was divided into breakfast, lunch, dinner, and one snack. The diet was based on vegetables and berries (eg, aubergine, squash, cauliflower, tomatoes, onions, olives, avocado, blueberries, and raspberries). It also contained dairy products, fish, shellfish, eggs, chicken, pork, and beef. Approximately three main meals per week consisted of fish and shellfish, and three main meals per week were based on plant-based protein. Participants who reported being on a lactose-free diet before the study were offered lactose-free dairy products during the intervention; hence, nutritional composition differed in lactose content and total FODMAPs for a subgroup of participants. The low-carbohydrate diet had a mean lactose content of 6·1 g (SD 3·8) and a mean total FODMAP content of 18·9 g (7·1), whereas the lactose-free version of this diet had a mean lactose of 0·8 g (0·9) and a mean total FODMAP of 13·4 g (6·7).

Although recipes for the LFTD and low-carbohydrate diets were based on a standardised energy content, participants were instructed to either add or reduce portion sizes to suit personal needs and maintain weight balance while still following the principles of the dietary intervention. A detailed list of included foods and the nutritional composition of the diets is provided in the appendix (pp 5–7).

The optimised medical treatment group received free pharmacological treatment according to evidence-based guidelines and resembling current clinical practice.[8] The decision was made on the basis of a predefined list of medications based on predominant gastrointestinal symptom, with preference for first-line options if they had not been used before (appendix p 8). Only one type of medication was allocated per participant during the intervention.

Participants were contacted via telephone or email after 2 weeks to establish potential adverse events and need for dose adjustment of study medication. Compliance to medications was assessed during a medical consultation at the end of the intervention period.

At 4 weeks (visit 3; end of intervention), participants receiving pharmacological treatment were offered voluntary, personalised dietary counselling and to continue with the medication. Participants in the dietary interventions were introduced to the concepts of their diet and encouraged to continue with their allocated diet during the 6-month follow-up. Participants on the LFTD diet were instructed on how to reintroduce FODMAPs, guided by individual tolerance. The reintroduction schedule included a comprehensive list of food items within each FODMAP category (ie, galacto-oligosaccharides, fructo-oligosaccharides, fructose, lactose, sorbitol, and mannitol) and instructions on how to re-challenge. In short, one of the FODMAPs was evaluated each week. Participants increased the amount of the selected FODMAP in their diet during a 3-day period to evaluate tolerance levels, while continuing to limit intake of the other FODMAPs. After all categories had been tested in the re-challenge, participants were encouraged to continue eating well tolerated FODMAPs. At 3 months (visit 4) and 6 months (visit 5), a study dietitian interviewed participants to assess FODMAP reintroduction. To aid the assessment, a questionnaire listing the individual FODMAP categories was used, with the response options of: yes, I do eat; yes, I eat to some extent; no, I do not eat; I have yet not evaluated; or do not know.

Participants completed the IBS-SSS and the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) at the last day of screening, day 7, day 14, day 21, day 28, 3 months, and 6 months. Participants completed the IBS Quality of Life Questionnaire (IBS-QoL), the Hospital Anxiety and Depression (HAD) scale, and the Patient Health Questionnaire 12 (PHQ-12) on day 0, day 29, 3 months, and 6 months. The Bristol Stool Form (BSF) scale was completed daily during screening and intervention, and for 7 days before each follow-up. Participants completed a 4-day food record before visits 2, 4, and 5. All potential deviations from the meal plan were reported in a diary, which was used to assess adherence by use of a scoring system we developed. At follow-up visits, adherence to diets was assessed by use of questionnaires. Participants allocated to dietary treatment filled out an in-house treatment satisfaction questionnaire to assess potential positive and negative aspects of the diets. More information on the assessments and questionnaires completed during the visits is in the appendix (p 4). The optimised medical treatment group was followed up by regular mail using a prepaid return envelope at 6 months, with questions regarding the severity of IBS symptoms and the current treatments being used.

Outcomes

The primary outcome was the proportion of participants who responded to treatment after 4 weeks, defined as those having a reduction in IBS-SSS of 50 or more compared with baseline, which is considered to represent a clinically relevant symptom reduction.[17] The IBS-SSS assesses the severity of IBS symptoms in five domains: pain severity, pain frequency, bloating severity, bowel habit dissatisfaction, and daily life interference (0–100 points each). The secondary outcomes reported herein are the proportion of patients with score reductions of 100 or more or 50% or more in IBS-SSS from baseline to 4 weeks; the absolute and percentage change in IBS-SSS and GSRS-IBS from baseline to 4 weeks; changes in nutrient intake (energy, macronutrients, and FODMAPs); change in quality of life due to IBS (IBS-QoL); change in psychological factors (anxiety and depression, per HAD); and changes in extra-intestinal somatic symptoms (PHQ-12). This study was also designed to address the following secondary outcomes, which will be presented elsewhere: a qualitative assessment of patients' experiences with a restrictive dietary treatment; the effect of treatment on gut microbiota composition, metabolites, and immunological markers; treatment compliance in relation to treatment outcome; maintained adherence to dietary intervention at 3-month and 6-month follow-up; exploration of factors predicting a positive treatment outcome and long-term adherence to diet; determinants of gastrointestinal symptoms (IBS-SSS and GSRS-IBS); and IBS-related Work Productivity and Activity Impairment.[18] The post-hoc outcomes reported herein are: changes in individual IBS symptoms (using the individual IBS-SSS questions for pain severity, pain frequency, bloating severity, bowel habit dissatisfaction, and daily life interference); IBS-SSS reductions of 50 or more, 100 or more, or 50% or more from baseline to 3-month and 6-month follow-up; the absolute and percentage change in IBS-SSS and GSRS-IBS from baseline to 3-month and 6-month follow-up; changes in stool form (proportions of hard, normal, and loose stools); differences in adherence between the two dietary interventions; changes in bodyweight; and changes in blood lipids and blood glucose concentrations. We partially reported patients' experiences with a restrictive dietary treatment in this study, and this outcome will be fully reported elsewhere. Safety and adverse events were assessed in the modified intention-to-treat population.

Statistical analysis

We hypothesised that the LFTD diet would be superior to both other treatment options in reducing IBS symptoms. Thus, the power calculation was based on an expected response rate of 65% (LFTD diet), 40% (low-carbohydrate diet), and 40% (optimised medical treatment) in the respective intervention groups.[20–23] With 80% power to detect differences between groups and an α of 0·05, 83 participants were needed in each group. To account for a 15% dropout rate, 100 participants were planned for random assignment to each group.

All participants who started treatment after randomisation were included in the modified intention-to-treat analysis and missing data were imputed using the last-observation-carried-forward principle. Participants who completed the respective assessments at each timepoint were included in the completers population. In the modified intention-to-treat and completers populations, we analysed the absolute and percentage change in IBS-SSS from baseline to 4 weeks, 3 months, and 6 months, and the proportion of patients with reductions in IBS-SSS of 50 or more, 100 or more, or 50% or more from baseline to 4 weeks, 3 months, and 6 months, as well as safety and adverse events. All other outcomes were analysed in the completers population.

For baseline characteristics, normally distributed variables are presented as mean (SD) and non-normally distributed variables as median (IQR). Comparisons of means between the three intervention groups were analysed with the ANOVA test for continuous variables, and with the χ^2 test for proportions. For comparisons of the two dietary intervention groups at 3-month and 6-month follow-ups, the independent-samples *t* test was used to compare means for continuous variables and the χ^2 test was used for proportions. For the absolute change in continuous outcome variables, the mean and percentage change were calculated and analysed with paired-samples *t* tests within groups (baseline *vs* end of intervention and follow-up) for normally distributed variables, and Wilcoxon signed-rank tests for non-normally distributed variables. The distribution of the binary outcome of participants who responded and participants who did not respond to treatment was compared with χ^2 tests between all three intervention groups, and post-hoc analyses were performed with pairwise comparisons between two groups.

Post-hoc subgroup analyses of responders and non-responders were performed, stratified by subtypes of IBS, and within the low-carbohydrate diet group for participants receiving a lactose-free versus lactose-containing diet, and in the optimised medical treatment group by the different symptom profiles (ie, constipation, diarrhoea, or abdominal pain). Furthermore, we assessed post hoc the degree to which participants would continue their prescribed medication during 6 months' follow-up and whether continued use of medication had greater efficacy than discontinuing the medical treatment. We also assessed post hoc whether receiving dietary advice after the 4-week medical treatment intervention led to greater symptom reduction at 6 months than not receiving additional dietary advice.

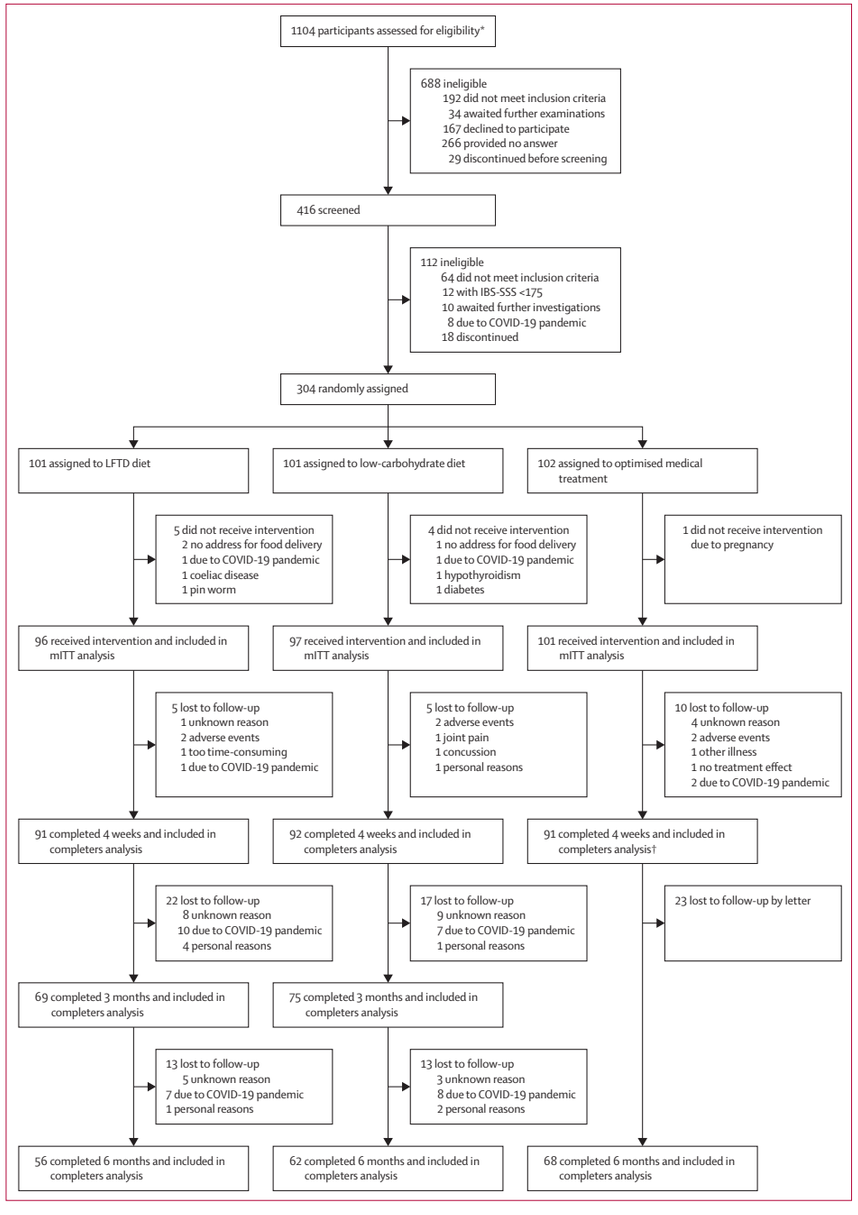

Figure 1: **Trial profile**
Completers were participants who completed the respective assessments at each timepoint. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. LFTD=low FODMAP and traditional irritable bowel syndrome dietary advice. mITT=modified intention to treat. *144 from newspaper advertisement, 248 with referral to the gastroenterology department, and 712 from advertisement in social media. †Formal participation in the study ended. Participants were offered diet counselling, of whom 67 received dietary advice. There was no follow-up of the optimised medical treatment group at 3 months.

To assess whether the linear response of IBS-SSS to intervention was different, and whether it differed with time, prespecified linear mixed-effects regression was used for the 4-week and 6-month data. IBS-SSS (absolute values) was included as a continuous dependent variable, intervention as an independent categorical variable, and patient as a random effect. Models with the same specifications but adding an interaction term between intervention (group) and time were also constructed, in which a significant interaction indicated whether a response in IBS-SSS changed over time by intervention. In these models, time was included as a categorical variable. The timepoints for the 4-week follow-up were baseline, 1 week, 2 weeks, 3 weeks, and 4 weeks, and, for the 6-month follow-up, were baseline, 4 weeks, 3 months, and 6 months.

Two-tailed p values of less than 0·05 were considered statistically significant. Statistical analyses were performed by use of IBM SPSS Statistics (version 28.0.1) for Windows, R (version 4.2.1), and RStudio (2022.12.0). This study did not have a data monitoring committee and was registered with ClinicalTrials.gov, NCT02970591.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Jan 24, 2017, and Sept 2, 2021, of 1104 individuals assessed for eligibility, 304 (27·5%) were randomly assigned: 101 to the LFTD diet, 101 to the low-carbohydrate diet, and 102 to optimised medical treatment (figure 1). After randomisation, three participants were unable to start the diet intervention due to not having a permanent address for food delivery, two were unwilling to participate because of the COVID-19 pandemic, three were excluded due to abnormal laboratory test results (one diabetes, one hypothyroidism, one coeliac disease), and one was excluded due to pin worm. In the optimised medical treatment group, one participant did not receive intervention due to pregnancy. Therefore, the modified intention-to-treat population comprised 294 participants, of whom 96 were in the LFTD diet group, 97 were in the low-carbohydrate diet group, and 101 were in the optimised medical treatment group. During the intervention period, five (5%) of 96 participants in the LFTD diet group, five (5%) of 97 participants in the low-carbohydrate diet group, and ten (10%) of 101 participants in the optimised medical treatment group were lost to follow-up. The dropout rate did not differ between the groups.

Of 294 participants, 241 (82%) were women and 53 (18%) were men (table 1). The mean age was 38 (SD 13) years. No differences in baseline characteristics were noted between the groups (table 1). Eight individuals with a BMI of 35 kg/m² or more (range 35·3–43·3) were mistakenly included but were allowed to complete the intervention and are included in the analyses (one in the LFTD diet group, three in the low-carbohydrate diet group, and four in the optimised medical treatment group).

At 4 weeks in the modified intention-to-treat population, 73 (76%) of 96 participants in the LFTD diet group, 69 (71%) of 97 participants in the low-carbohydrate diet group, and 59 (58%) of 101 participants in the optimised medical treatment group had a reduction of 50 or more in IBS-SSS compared with baseline, with a significant difference between the groups (p=0·023; post-hoc analyses between LFTD *vs* optimised medical treatment, p=0·0086 low-carbohydrate diet *vs* optimised medical treatment, p=0·061; LFTD *vs* low-carbohydrate diet, p=0·44; table 2; appendix p 9). When stricter endpoint cutoffs were applied (ie, score reduction of 100 or more), the proportions of participants who

	LFTD diet (n=96)	Low-carbohydrate diet (n=97)	Optimised medical treatment (n=101)
Sex			
Women	82 (85%)	76 (78%)	83 (82%)
Men	14 (15%)	21 (22%)	18 (18%)
IBS subtype (Rome IV)			
Constipation	41 (43%)	43 (44%)	30 (30%)
Diarrhoea	32 (33%)	36 (37%)	48 (48%)
Mixed	21 (22%)	11 (11%)	16 (16%)
Unclassified	2 (2%)	7 (7%)	7 (7%)
Age, years	38 (13)	39 (14)	40 (13)
Weight, kg	74·0 (14·3)	73·0 (13·8)	72·6 (14·1)
BMI, kg/m²	25·4 (3·9)	25·3 (4·2)	25·0 (4·4)
IBS duration, years	13 (6–25)	12 (6–21)	15 (8–25)
Onset of IBS symptoms			
Post-infection	8 (8%)	6 (6%)	9 (9%)
Stress or trauma	31 (32%)	24 (25%)	28 (28%)
After taking antibiotics	0	1 (1%)	1 (1%)
Other reasons or unknown	57 (59%)	66 (68%)	63 (62%)
Education, university degree	52 (54%)	43 (44%)	56 (55%)
Occupation			
Student	15 (16%)	18 (19%)	11 (11%)
Employed	74 (77%)	71 (73%)	79 (78%)
Retired	2 (2%)	3 (3%)	5 (5%)
Sick leave	1 (1%)	0	3 (3%)
Other	4 (4%)	5 (5%)	3 (3%)
Lactose-free version of diet	NA	32 (33%)	NA
Predominant symptom for treatment targeting			
Constipation*	NA	NA	23 (23%)
Diarrhoea†	NA	NA	18 (18%)
Abdominal pain‡	NA	NA	60 (59%)

Data are n (%), mean (SD), or median (IQR). FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. IBS=irritable bowel syndrome. LFTD=low FODMAP and traditional IBS dietary advice. NA=not applicable. *In the constipation predominant group, ten participants received a bulking agent, three received an osmotic laxative, and ten received linaclotide. †In the diarrhoea predominant group, 11 received loperamide, five received cholestyramine, and two received ondansetron. ‡In the abdominal pain predominant group, 38 received amitriptyline, 15 received hyoscyamine, and seven received linaclotide.

Table 1: **Baseline characteristics in the modified intention-to-treat population**

responded were 59 (61%) of 96 participants in the LFTD diet group, 56 (58%) of 97 participants in the low-carbohydrate diet group, and 39 (39%) of 101 participants in the optimised medical treatment group (p=0·0025; table 2; appendix p 9).

The total IBS-SSS was reduced in all groups at 4 weeks (p<0·0001; table 2; figure 2). The mean change in IBS-SSS was significantly larger for the LFTD diet (–149 [SD 115]; p<0·0001) and low-carbohydrate diet (–128 [110]; p=0·0004) than for optimised medical treatment (–76 [94]). All individual domains of IBS-SSS were significantly reduced at 4 weeks in all three groups compared with baseline (all p<0·0001). At 4 weeks, between-group comparisons showed significant differences in pain severity, pain frequency, bloating severity, and daily life interference, but not in bowel habit dissatisfaction (p=0·062; table 2; appendix p 10). Linear mixed-effects regression showed that the overall magnitude of IBS-SSS reduction at 4 weeks was greater with the LFTD diet (β coefficient –47·1 [95% CI –69·4 to –24·9]; p<0·0001) and the low-carbohydrate diet (–36·4 [–58·6 to –14·1]; p<0·0001) than with optimised medical treatment. When testing for interaction between treatment and time, the reduction of symptoms was greater over time with the LFTD diet (p<0·0001) and low-carbohydrate diet (p<0·0001) than with optimised medical treatment, but with no difference between the diets (p=0·35).

In post-hoc analyses, no significant differences in the proportion of participants who responded to the intervention at 4 weeks across IBS subtypes were noted in any of the groups (appendix p 11). There was also no significant difference in the proportion of responders to the low-carbohydrate diet with lactose (48 [74%] of 65 participants) versus without lactose (21 [66%] of 32 participants; χ^2 p=0·40) at 4 weeks in the modified intention-to-treat population. In the optimised medical treatment group, the proportion of responders did not differ when comparing predominant symptom groups: 13 (57%) of 23 participants with predominant constipation responded, ten (56%) of 18 with predominant diarrhoea responded, and 36 (60%) of 60 with predominant abdominal pain responded (χ^2 p=0·93).

At group level, stool consistency improved significantly from baseline to 4 weeks with both diets, but not with optimised medical treatment (table 2; appendix p 12). The LFTD diet mainly reduced the frequency of loose stools (p<0·0001), whereas the low-carbohydrate diet reduced the frequency of hard stools (p=0·0001). In the optimised medical treatment group, the effects of intervention on stool consistency differed depending on the type of treatment (appendix p 12).

All three interventions significantly reduced total GSRS-IBS compared with baseline (all p<0·0001; table 2). For the individual domains of the GSRS-IBS, all were significantly reduced from baseline except for constipation with optimised medical treatment (table 2). Quality of life significantly improved in all groups compared with baseline, with significant between-group differences after 4 weeks (p=0·0029). HAD scores were significantly reduced from baseline in all three groups at 4 weeks, but with no significant difference between groups (p=0·27). Non-gastrointestinal somatic symptoms were also significantly reduced from baseline in all three groups at 4 weeks (all p<0·0001) with significant between-group differences (p=0·0003; table 2).

During the last week of the intervention, the mean number of deviations from the meal plan reported were similar with both diets (post-hoc analysis; 1·4 [SD 2·2] deviations [range 0–12] with the LFTD diet and 1·6 [SD 2·4] deviations [range 0–12] with the low-carbohydrate diet; p=0·52). 48 (53%) of 91 participants in the LFTD diet group and 45 (49%) of 92 participants in the low-carbohydrate diet group reported complete adherence. In the 4-week treatment satisfaction questionnaire, 71 (78%) of 91 participants on the LFTD diet reported improvements in IBS symptoms and 56 (62%) reported improvements in overall health; whereas, for the 92 participants on the low-carbohydrate diet, the corresponding respective numbers were 66 (72%) and 47 (51%; appendix p 13). More participants in the LFTD diet group than in the low-carbohydrate diet group reported that it was difficult to find options that adhered to the dietary regimen when eating out (34 [37%] of 91 participants *vs* 21 [23%] of 92 participants; p=0·012).

Of participants who were lost to follow-up at week 4, two individuals in each of the intervention groups stated they had discontinued due to adverse events. Of 91 participants who returned after the 4-week intervention in the optimised medical treatment group, five (5%) had discontinued treatment prematurely due to side-effects. No serious adverse events or treatment-related deaths occurred. At 4 weeks, the treatment satisfaction questionnaire revealed that four (4%) of 91 participants on the LFTD diet reported worsening of IBS symptoms versus eight (9%) of 92 participants on the low-carbohydrate diet, and three (3%) of 91 reported worsening of overall health versus seven (8%) of 92 (appendix p 13). Fasting blood concentrations of total cholesterol, HDL, LDL, and triglycerides were significantly reduced with the LFTD diet at 4 weeks compared with baseline (appendix p 14). From baseline to 4 weeks, fasting blood concentrations of triglycerides and glycated haemoglobin were significantly reduced with the low-carbohydrate diet, whereas total cholesterol and LDL concentrations were significantly increased (appendix p 14).

32 participants could not attend follow-up visits due to the COVID-19 pandemic (17 in LFTD group and 15 in the low-carbohydrate diet group). At the 3-month follow-up in the completers population, 51 (74%) of 69 participants on the LFTD diet and 48 (64%) of 75 participants on the low-carbohydrate diet were still considered responders to treatment (p=0·20). At 6-month follow-up, the respective proportions were

	LFTD diet				Low-carbohydrate diet				Optimised medical treatment				Between-group comparison (p value*, 4 weeks)
	Baseline (n=96)	4 weeks (n=96)	3 months (n=96)	6 months (n=96)	Baseline (n=97)	4 weeks (n=97)	3 months (n=97)	6 months (n=97)	Baseline (n=101)	4 weeks (n=101)			
IBS symptom severity													
Total IBS-SSS	323 (66)	174 (112)†	203 (109)†	206 (108)†	322 (69)	194 (108)†	223 (108)†	229 (110)†	319 (71)	243 (108)†			<0·0001
Absolute change IBS-SSS	..	-149 (115)	-120 (106)	-117 (111)	..	-128 (110)	-99 (109)	-93 (112)	..	-76 (94)			<0·0001
Percentage change in IBS-SSS	..	-45·3% (33·8)	-36·9% (31·1)	-35·0% (32·7)	..	-38·7% (32·3)	-28·6% (32·9)	-27·5% (33·8)	..	-23·9% (32·7)			<0·0001
Proportion with ≥50 score reduction	..	73 (76%)	68 (71%)	67 (70%)	..	69 (71%)	59 (61%)	57 (59%)	..	59 (58%)			0·023
Proportion with ≥100 score reduction	..	59 (61%)	50 (52%)	48 (50%)	..	56 (58%)	46 (47%)	44 (45%)	..	39 (39%)			0·0025
Proportion with 50% score reduction	..	45 (47%)	34 (35%)	32 (33%)	..	38 (39%)	26 (27%)	23 (24%)	..	25 (25%)			0·0047
Completers population	n=96	n=91	n=69	n=56	n=97	n=92	n=75	n=62	n=101	n=91			..
Total IBS-SSS	323 (66)	163 (106)†	202 (103)†	206 (107)†	322 (69)	183 (99)†	216 (98)†	221 (108)†	319 (71)	233 (108)†			<0·0001
Absolute change IBS-SSS	..	-158 (112)	-116 (95)	-106 (110)	..	-137 (108)	-97 (104)	-92 (115)	..	-86 (95)			<0·0001
Percentage change in IBS-SSS	..	-48·4% (32·7)	-36·6% (29·3)	-32·5% (33·9)	..	-41·3% (31·2)	-29·4% (32·6)	-27·3% (35·5)	..	-27·1% (33·6)			<0·0001
Pain severity	56 (22)	29 (27)†	33 (26)†	34 (28)†	55 (21)	32 (26)†	33 (25)†	38 (23)‡	55 (21)	43 (27)†			0·0018
Pain frequency	56 (27)	27 (28)†	31 (27)†	31 (29)†	60 (28)	30 (24)†	33 (27)†	36 (26)†	62 (28)	40 (29)†			0·0026
Bloating severity	65 (25)	27 (25)†	42 (30)†	41 (29)†	68 (24)	33 (27)†	49 (27)†	46 (30)†	63 (25)	48 (30)†			<0·0001
Bowel habit dissatisfaction	69 (24)	39 (27)†	47 (27)†	52 (26)‡	63 (27)	43 (28)†	49 (27)†	48 (29)‡	67 (23)	49 (25)†			0·062
Daily life interference	77 (19)	41 (27)†	49 (28)†	49 (27)†	77 (19)	45 (28)†	52 (28)†	52 (29)†	73 (21)	54 (26)†			0·0073
Proportion with ≥50 score reduction	..	73/91 (80%)	51/69 (74%)	38/56 (68%)	..	69/92 (75%)	48/75 (64%)	37/62 (60%)	..	59/91 (65%)			0·058
Proportion with ≥100 score reduction	..	59/91 (65%)	38/69 (55%)	26/56 (46%)	..	56/92 (61%)	36/75 (48%)	27/62 (44%)	..	39/91 (43%)			0·0025
Proportion with 50% score reduction	..	45/91 (49%)	24/69 (35%)	17/56 (30%)	..	38/92 (41%)	21/75 (28%)	16/62 (26%)	..	25/91 (27%)			0·011
Anthropometry													
Weight, kg	74·0 (14·3)	72·0 (13·3)‡	73·6 (14·7)§	70·4 (12·8)§	73·0 (13·8)	72·0 (13·5)§	71·3 (13·2)§	73·9 (13·5)	72·6 (14·1)	71·3 (12·2)			0·92
BMI, kg/m²	25·4 (3·9)	24·9 (3·9)‡	25·1 (3·8)§	24·3 (3·3)§	25·3 (4·2)	25·0 (4·0)‡	24·8 (4·0)‡	25·4 (4·4)	25·0 (4·4)	24·6 (3·9)			0·77
Stool consistency¶													
Hard stools, %	26·7 (25·6)	25·1 (23·1)	24·3 (28·6)	23·4 (26·4)	25·0 (26·0)	15·0 (17·6) †	16·5 (22·0)‡	17·6 (23·4)‡	20·9 (24·8)	17·1 (21·3)			0·0028
Loose stools, %	20·2 (21·7)	10·5 (14·2)†	8·8 (11·4)‡	10·1 (17·2)§	21·0 (24·2)	21·1 (23·0)	16·0 (21·4)§	18·8 (26·5)	26·5 (22·9)	26·2 (22·3)			<0·0001
Normal stools, %	53·1 (24·7)	64·4 (21·4)†	66·9 (27·1)‡	66·5 (29·3)§	54·1 (24·6)	63·9 (23·1) ‡	67·6 (25·7) †	63·6 (29·6)§	52·6 (24·7)	56·7 (23·4)			0·040

(Table 2 continues on next page)

	LFTD diet				Low-carbohydrate diet				Optimised medical treatment		Between-group comparison (p value*, 4 weeks)
	Baseline (n=96)	4 weeks (n=96)	3 months (n=96)	6 months (n=96)	Baseline (n=97)	4 weeks (n=97)	3 months (n=97)	6 months (n=97)	Baseline (n=101)	4 weeks (n=101)	
(Continued from previous page)											
Dietary data											
Energy, kJ	8352 (1799)	9659 (736)‡	7785 (1656)§	7994 (2285)	8488 (2420)	9740 (786)‡	7597 (2017)§	8331 (2612)	8601 (2056)	..	0·25
Protein, g	81 (22)	99 (15)‡	80 (22)	83 (25)	80 (27)	132 (19)‡	80 (22)	89 (37)	81 (26)	..	<0·0001
Fat, g	86 (24)	88 (19)	80 (22)	80 (24)	87 (27)	175 (22)‡	89 (30)	97 (34)	88 (25)	..	<0·0001
Carbohydrate, g	202 (54)	264 (23)‡	186 (46)§	195 (69)	208 (75)	50 (9)‡	154 (58)‡	170 (72)‡	207 (56)	..	<0·0001
Energy from protein, %	16 (3)	17 (2)	17 (3)	18 (3)§	16 (4)	23 (4)‡	18 (4)‡	18 (5)‡	16 (4)	..	<0·0001
Energy from fat, %	39 (6)	34 (6)‡	38 (6)	38 (6)	39 (6)	67 (4)‡	44 (9)‡	44 (8)‡	39 (6)	..	<0·0001
Energy from carbohydrate, %	41 (6)	46 (5)‡	40 (6)	41 (5)	41 (7)	9 (2)‡	34 (9)‡	34 (9)‡	40 (7)	..	<0·0001
Fibre, g	18·8 (7·4)	29·3 (4·6)‡	17·3 (5·8)	20·1 (10·9)	18·7 (6·8)	23·9 (5·6)‡	16·9 (6·9)§	17·5 (6·3)	19·3 (7·5)	..	0·0003
Lactose, g	8·6 (5·6)	0·2 (0·2)‡	9·1 (5·6)	7·1 (7·0)	8·8 (7·2)	4·5 (3·8)‡,‖	7·7 (5·7)	7·9 (5·6)	8·7 (6·2)	..	<0·0001
Fructan, g	2·5 (1·0)	1·7 (0·3)‡	1·9 (0·9)‡	2·2 (1·7)	2·6 (1·4)	3·3 (1·1)‡	2·1 (1·2)§	2·1 (1·7)	2·5 (1·3)	..	<0·0001
Excess fructose, g	4·5 (3·9)	0·7 (0·9)‡	2·8 (3·1)§	3·5 (2·8)	5·1 (4·7)	2·0 (2·3)‡	2·7 (2·6)‡	3·5 (4·8)§	5·1 (3·7)	..	0·0094
Polyol, g	0·9 (1·7)	0·4 (0·3)§	0·5 (0·8)	0·5 (0·8)§	0·8 (1·5)	6·1 (3·0)‡	0·9 (1·6)	0·7 (1·1)	0·7 (1·0)	..	<0·0001
GOS, g	0·4 (0·3)	0·3 (0·1)‡	0·3 (0·3)	0·5 (0·4)	0·5 (0·3)	1·2 (2·4)‡	0·4 (0·7)	0·4 (0·3)	0·6 (0·6)	..	<0·0001
Total FODMAP, g	17·0 (8·9)	3·4 (0·9)‡	14·8 (7·4)§	13·8 (9·6)	17·7 (9·6)	17·1 (7·0)*	13·9 (7·3)‡	14·7 (8·6)§	17·6 (8·6)	..	<0·0001
Questionnaire data											
Total GSRS-IBS	36·6 (9·2)	20·0 (11·3)†	24·3 (11·4)†	24·4 (11·7)†	36·7 (9·0)	23·1 (11·9)†	26·2 (10·0)†	26·8 (12·1)†	36·5 (9·7)	29·6 (12·4)†	<0·0001
Absolute change in GSRS-IBS	..	−16·3 (13·4)	−11·1 (12·1)	−10·7 (12·2)	..	−13·6 (13·0)	−10·0 (10·5)	−9·2 (13·2)	..	−6·0 (10·9)	<0·0001
Percentage change in GSRS-IBS	..	−42·4% (32·5)	−29·6% (33·7)	−28·2% (33·1)	..	−34·8% (33·6)	−26·1% (25·2)	−22·7% (37·7)	..	−15·9% (35·8)	<0·0001
GSRS-IBS abdominal pain	6·5 (2·0)	3·6 (2·5)†	4·5 (2·6)‡	4·4 (2·3)‡	6·5 (2·0)	4·1 (2·3)†	4·8 (2·2)‡	4·6 (2·2)‡	6·5 (1·9)	5·2 (2·7)‡	<0·0001
GSRS-IBS bloating	11·4 (3·5)	5·5 (3·3)†	7·6 (3·9)‡	7·6 (3·7)‡	11·9 (3·2)	6·5 (4·0)†	8·3 (3·4)‡	8·2 (4·2)‡	11·4 (3·1)	9·3 (3·7)†	<0·0001
GSRS-IBS satiety	3·6 (2·9)	2·0 (2·1)†	2·8 (2·6)‡	2·3 (2·3)‡	3·9 (2·9)	2·8 (2·4)‡	2·8 (2·6)§	2·6 (2·9)§	4·0 (2·8)	3·0 (2·5)‡	0·014
GSRS-IBS diarrhoea	10·2 (4·3)	5·8 (4·3)†	6·7 (4·3)‡	6·5 (4·1)‡	9·7 (4·4)	6·7 (4·4)†	7·2 (4·6)‡	7·9 (4·6)‡	9·7 (4·5)	8·2 (4·8)§	0·0026
GSRS-IBS constipation	4·9 (3·0)	3·0 (2·9)†	3·6 (3·1)‡	3·6 (2·9)§	4·7 (3·2)	3·0 (2·7)†	3·2 (2·8)‡	3·4 (3·1)§	4·9 (3·7)	3·9 (3·0)	0·047
IBS quality of life	65·8 (13·6)	80·1 (13·4)‡	78·3 (13·1)‡	79·7 (13·5)‡	66·2 (14·4)	76·9 (13·9)‡	73·8 (14·6)‡	73·5 (17·5)‡	65·6 (14·8)	72·9 (14·4)‡	0·0029
Total HAD	11·8 (6·8)	8·7 (6·3)†	8·7 (6·1)§	8·5 (5·5)	10·4 (5·3)	6·8 (5·0)‡	9·3 (5·2)‖	9·4 (5·6)	11·1 (6·3)	9·8 (5·8)§	0·27
PHQ-12	7·5 (3·6)	4·8 (3·1)†	5·5 (3·4)‡	5·3 (3·1)§	7·0 (3·3)	4·8 (2·6)†	5·9 (3·0)‡	5·6 (3·1)§	7·6 (3·6)	6·4 (3·3) †	0·0003

Data are n (%), n/N (%), or mean (SD), unless otherwise specified. The optimised medical treatment group did not have data collected after week 4 (end of intervention). BSF=Bristol stool form. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. GOS=galacto-oligosaccharide. GSRS-IBS=Gastrointestinal Symptom Rating Scale-IBS. HAD=Hospital Anxiety and Depression scale. IBS=irritable bowel syndrome. IBS-SSS=IBS Severity Scoring System. LFTD=low FODMAP and traditional IBS dietary advice. PHQ-12=Patient Health Questionnaire 12. *ANOVA comparison between all three intervention groups. †p value less than 0·0001; paired-samples t test relative to baseline. ‡p value less than 0·001. §p value less than 0·05. ¶Calculated on the basis of the BSF stool diary. Based on the total number of stools, the proportions of hard (BSF 1–2), normal (BSF 3–5), and loose stools (BSF 6–7) were calculated. ‖Mean of the lactose-containing and lactose-free versions of the low-carbohydrate diet.

Table 2: **IBS symptom severity, anthropometry, stool consistency, and dietary and questionnaire data**

38 (68%) of 56 participants and 37 (60%) of 62 participants (p=0·36; table 2). In linear mixed-effect regression models, the mean symptom severity (IBS-SSS) during follow-up remained significantly lower than that at baseline in both diet groups (p<0·0001), but symptom severity did not differ significantly between the diets (β coefficient −14·7 [95% CI −37·5 to 8·1]; p=0·21). The results were not significant when testing for interaction between group and time, indicating that the reduction in symptom severity (IBS-SSS) was not different over time for the diet groups p=0·97).

After 6 months, participants in both diet groups had partly returned to their baseline diets. Compared with the LFTD diet, changes in nutrient intake at 6 months, relative to baseline, were more pronounced with the low-carbohydrate diet, in which there was a significantly lower mean percentage of energy that came from carbohydrates and a significantly higher mean percentage of energy that came from protein and fat, as well as a significantly lower total intake of FODMAPs (table 2). In the LFTD diet group, percentage from protein was significantly higher and polyol intake was significantly lower at 6 months than at baseline. Of 46 participants with data in the LFTD diet group, the FODMAP categories that most participants had reintroduced by 6 months were fructose (41 [89%] participants), followed by sorbitol (36 [78%] participants), fructans (33 [72%] participants), and mannitol (30 [65%] participants; appendix p 15).

In the optimised medical treatment group, 67 (74%) of 91 participants received dietary advice after the 4-week intervention period. Of 68 (67%) of 101 participants who returned follow-up questionnaires after 6 months, 26 (38%) reported that they were still taking prescription medicine. The mean IBS-SSS was 224 (SD 104), and 45 (66%) of 68 participants were considered responders to treatment. In post-hoc analyses, symptom severity was lower among individuals who had continued with their medication (mean IBS-SSS 166 [SD 82]) than those who had discontinued (260 [SD 101]; p=0·0002). There was no significant difference in mean IBS-SSS between those who received dietary advice as an addition (227 [SD 104]) versus those who did not get dietary advice (199 [84]; p=0·33).

Discussion

To the best of our knowledge, this study is the largest to evaluate the efficacy of restrictive dietary regimens versus optimised medical treatment in IBS. We found that all interventions reduced IBS symptom severity, with greater efficacy with dietary treatments than with optimised medical treatment. Similarly, all three interventions improved quality of life, anxiety and depression symptoms, and non-gastrointestinal somatic symptoms. Improvements in IBS symptom severity at 4 weeks largely persisted to 6-month follow-up in both dietary intervention groups, with no differences seen between the diets at follow-up.

Figure 2: **Symptom reduction assessed by the IBS-SSS**
Error bars represent SEM. $p_{interaction}$ is the p value for the interaction between group and time. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. IBS-SSS=Irritable Bowel Syndrome Severity Scoring System. LFTD=low FODMAP and traditional irritable bowel syndrome dietary advice. OMT=optimised medical treatment.

The efficacy of dietary intervention compared with pharmacological treatment targeting the predominant IBS symptom has not previously been studied. Furthermore, few direct comparisons exist between dietary treatment alternatives and pharmacological treatment.[9] In a systematic review and network meta-analysis, the low FODMAP diet was the most efficacious diet in IBS, with the traditional IBS diet (according to British Dietetic Association and NICE guidelines) being the second most efficacious.[13] Our study has shown that combining both dietary strategies is feasible and efficacious. Evidence supporting the efficacy of low-carbohydrate diets in IBS is scarce but a few studies on a starch-reduced and sucrose-reduced diet in IBS have shown promising results.[24,25] However, direct comparisons with our results are not easily made as study designs and dietary interventions differ. The magnitude of the efficacy of symptom-targeted medication in this study is in line with, and potentially better, than that reported in the literature.[23] However, our study has a shorter intervention period and different outcome definitions than other trials, making direct comparisons of responder rates difficult.

No notable differences generally occurred between the LFTD and low-carbohydrate diets regarding symptom improvement, adherence, patient satisfaction, or adverse events. This finding was surprising, as we hypothesised that the combination of the two established diets would outperform the low-carbohydrate diet. Both diets also showed positive long-term effects even though dietary intakes partly returned to baseline levels in both groups after 6 months. This finding indicates that small reductions in FODMAPs and carbohydrate intake might have beneficial effects. A reduction in FODMAP intake might partly have contributed to the long-term efficacy of the low-carbohydrate diet as the mean FODMAP intake was lower at 6-month follow-up than at baseline. The

probable mechanistic effect of a diet low in FODMAPs has previously been described,[26] with reduction of water retention and reduced gas production when osmotically active and fermentable carbohydrates are restricted, thereby reducing symptoms of IBS. In our study, this theory was supported by the higher success of this diet in reducing the proportion of loose stools rather than hard stools. The mechanism whereby low-carbohydrate diets can alleviate IBS symptoms has not been thoroughly characterised. An effect on gastrointestinal transit time has been proposed,[27] which might explain why the diet was particularly successful at reducing the proportion of hard stools in our study. Other potential mechanisms include carbohydrate malabsorption due to hypomorphic sucrase-isomaltase gene variants[14] or involvement of sugars in low-grade inflammation and increased gut permeability.[28] In a previous study, we found that concentrations of 2-hydroxybutyrate were increased among participants with IBS who responded to a dietary intervention,[29] indicating that ketone bodies might be associated with a positive treatment outcome in this patient group.

Symptom-targeted medical treatment, although potentially less efficacious than the dietary interventions, provided relief for a substantial proportion of participants. Participants who had continued with their prescribed pharmacological treatment reported a lower symptom severity at 6 months than participants who had discontinued their treatment, emphasising the need for personalised treatment approaches.

To aid the implementation of a restrictive diet, structured guidance with recipes and receiving support from dietitians with the FODMAP reintroduction were reported to be important in a qualitative assessment.[30] In clinical settings, the same practical support with recipes and reintroduction schedules should be used and seems feasible. However, the long-term goal of a restrictive dietary treatment should be for the patients to restrict enough to manage their symptoms during a flare, but otherwise aim to have the most versatile and unrestrictive diet possible. To ensure long-term safety and effectiveness, a patient treated with a restrictive diet should be provided with ongoing support from a dietitian.

A major strength of this study is the inclusion of a large number of participants with all IBS subtypes and a wide range of symptoms that were well characterised by use of validated questionnaires. Dropout rates were low during the intervention period. However, dropout rates increased during follow-up due to the COVID-19 pandemic as the hospital had to restrict visits that were solely for research purposes, and participants were less willing to visit the hospital. The COVID-19 pandemic hindered participants in both diet groups from attending follow-ups during 2020, accounting for a large share of dropouts. Other strengths of the study include the design of the pharmacological treatment strategy, which aligned with existing clinical guidelines, meaning that the treatments were coherent with clinical practice.[8,23] Furthermore, all foods used in the dietary interventions were provided to the participants, with recipes and instructions, to enable a controlled diet but still resemble real-life circumstances in which all foods need to be prepared at home.

This study also has limitations. First, participants were not masked to the foods included in the dietary interventions, but we did not reveal the specific nutrients of interest to reduce placebo effects. Second, the scoring system we developed to calculate deviations from the meal plan was not formally validated. Furthermore, there remains the possibility of a Hawthorne effect in all three groups that cannot be quantified as all groups received active treatments and, as we only recruited participants with moderate-to-severe IBS symptoms, symptom improvement might partly be explained by a regression to the mean effect. In real-life settings, patients with IBS are often given dietary advice as adjuvant treatment along with pharmacological treatment, but this combination was not studied during the intervention. Instead, participants in the optimised medical treatment group were offered dietary treatment after 4 weeks when official participation ended. As we only included follow-up questionnaires by regular mail at 6 months in the optimised medical treatment group, there were differential follow-ups in the three groups. Additionally, the intervention period of 4 weeks is shorter than some pharmacological treatment trials in IBS, which makes direct comparisons difficult. The decision on intervention length was based on practical and financial aspects with the home delivery of foods, as well as with the goal to resemble clinical practice in which initial follow-up of treatment effects is often performed after 4–6 weeks, followed by a decision to continue with the tested intervention or not. Finally, the study only included participants with moderate-to-severe IBS symptoms, thus limiting the generalisability to patients with mild symptoms.

To enhance our understanding and facilitate more personalised treatments for patients with IBS, we plan to report a qualitative assessment of patients' experiences on undertaking a restrictive dietary treatment. Additionally, we aim to investigate the effect of these interventions on gut microbiota composition, metabolites, and detailed nutrient intake. We aim to further assess adherence to the treatments relative to symptom management, analyse dietary changes at the food group level, and explore alterations in eating behaviours, such as meal frequency.

To conclude, a combined low FODMAP and traditional IBS diet and a fibre-optimised diet low in total carbohydrates and high in fat and protein were more successful than an optimised medical treatment strategy based on predominant IBS symptom at reducing symptom severity in people with IBS. All three interventions showed significant and clinically meaningful efficacy at improving gastrointestinal symptoms, non-gastrointestinal somatic symptoms, psychological symptoms, and quality of life. The sustained positive effects of dietary interventions suggest their potential to be considered as first-line treatments for IBS. However, it is essential to weigh various factors when making these clinical decisions, such as patients' preferences, cost-effectiveness, ease of implementation, compliance, and potential long-term adverse effects, including effects on nutritional status and the gut microbiota. Additionally, challenges related to dietary preferences, such as vegetarianism, might complicate the application of these treatments. There is still need for future research to identify predictive factors for treatment outcomes and enable personalised therapeutic strategies.

Contributors

MS, SS, HT, SN, and AJ designed the study. MS, SS, and HT received funding for the study. MS, SS, HT, SN, AJ, LB, ÅF, and CW carried out the study. SN, SS, and LB administered the project. SN and JPH analysed the data. SS and LB verified the data. SN drafted the manuscript. All authors provided a critical review and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. MS is the guarantor and affirms that the Article is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The corresponding author (SN) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

MS received unrestricted research grants from Glycom (DSM) and Genetic Analysis, served as a consultant or advisory board member for Danone Nutricia Research, Ironwood, Menarini, Biocodex, Glycom (DSM), Genetic Analysis, Arena, Tillotts, Takeda, Kyowa Kirin, BioGaia, AbbVie, Cinclus Pharma, and Pharmanovia, and as a speaker for Tillotts, Kyowa Kirin, Takeda, Biocodex, Sanofi, Janssen Immunology, Pfizer, Ferrer, BioGaia, and the Falk Foundation. HT served as consultant or advisory board member for Allergan, Cinclus Pharma, and VIPUN and as a speaker for Tillotts, Takeda, and Shire. AJ served as a consultant for VIPUN. All other authors declare no competing interests.

Data sharing

The data for this study are available to other researchers for scientific research purposes on request and after the proposed analysis plan has been approved. A data transfer agreement must be signed, which defines obligations that the data requester must adhere to regarding privacy and data handling. For data access, please contact the corresponding author.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Nybacka S, Törnblom H, Josefsson A et al. A low FODMAP diet plus traditional dietary advice versus a low-carbohydrate diet versus pharmacological treatment in irritable bowel syndrome (CARBIS): a single-centre, single-blind, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2024; published online April 18. https://doi.org/10.1016/S2468-1253(24)00045-1.

Supplementary material

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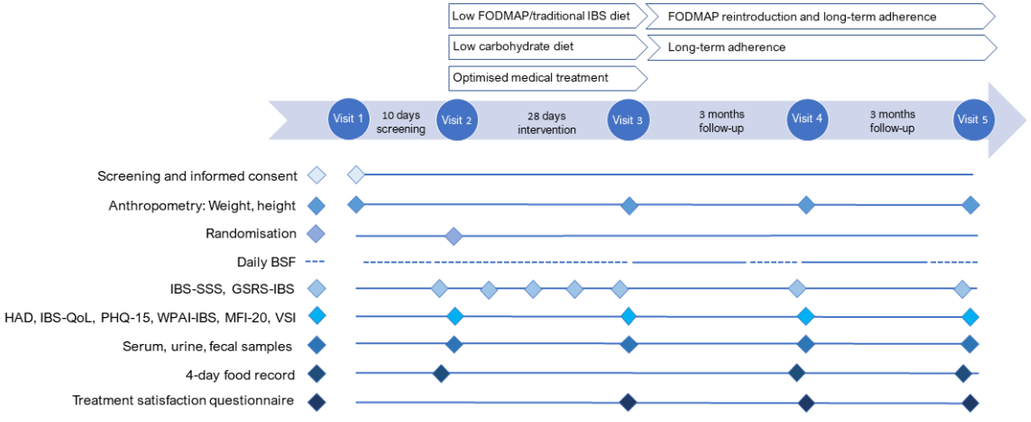
Supplementary material

Supplementary Table 1. Inclusion and exclusion criteria for participation in the CARIBS study.

Inclusion criteria	Exclusion criteria
Adult women and men (≥18 years)	Any other GI or other disease that could explain or influence symptoms or GI function
Moderate to severe IBS symptom severity (IBS-SSS ≥175)	Already been treated with any of the dietary interventions included in the study or having tested all pharmacological treatments of relevance for the symptom profile
Residing in the Gothenburg region	Food allergy
	Food hypersensitivity other than lactose intolerance
	Already being on a restrictive diet
	Any other serious disease or illness
	Body mass index 18 kg/m^2 - 35 kg/m^2[§]
	Pregnant or breastfeeding females
	Inability to communicate in Swedish

IBS-SSS=irritable bowel syndrome severity scoring system.
[§]The rationale for excluding participants with a BMI >35 was not to risk worsening metabolic status and blood lipid profiles in obese individuals who are already at risk of having impaired blood lipid levels, wore they be randomised to the LCD group.



Supplementary Figure 1. Overview of the visits and procedures of the CARIBS randomised controlled trial.

Blood samples

During visit 2, fasting blood samples were taken and sent to the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg, Sweden, for analysis of transglutaminase, immunoglobulin A antibodies, total immunoglobulin A levels, hemoglobin, white cell count, platelets, sodium, potassium, creatinine, calcium, C-reactive protein, thyroid-stimulating hormone, free thyroxine, aspartate aminotransferase, alanine aminotransferase, albumin, glucose, hemoglobin A_{1c}, and blood lipids (cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides). At end of intervention, and at follow-up visits month 3 and 6, glucose, hemoglobin A_{1c}, and blood lipid levels were analysed from fasting blood samples in order to assess potential metabolic effects of the intervention diets.

Questionnaires

The IBS severity scoring system (IBS-SSS)[1] evaluates the severity of IBS symptoms (score range 0 to 500) and was completed at day -1, day 7, day 14, day 21, day 28, and 3 and 6 months after completion of the intervention. The IBS-SSS assess the severity of IBS symptoms in five domains: pain severity and frequency, bloating severity, bowel habit dissatisfaction and life interference (0 to 100 points each).

The Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS)[2] was completed to assess IBS-specific gastrointestinal symptoms, including a total score as well as domain scores for the severity of abdominal pain, bloating, satiety, diarrhoea, and constipation, with higher scores meaning more severe symptoms. The GSRS-IBS was completed at day -1, day 7, day 14, day 21, day 28, and 3 and 6 months after completion of the intervention.

The Bristol stool form scale (BSF)[3] was used as the basis for a stool diary that was completed during 10 days of screening, during the 28 days of the intervention, and during seven days before the 3- and 6-months follow-up visits. In this diary, stools and stool consistency were recorded. Hard stools are defined as 1-2, normal stools as 3-5, and loose stools as 6-7 on the BSF scale.

The disease-specific Irritable Bowel Syndrome Quality of Life Questionnaire (IBS-QoL) was used to assess quality of life[4]. The summed total score ranges from 0 to 100, where a low score implies poor quality of life. The form was completed on days 0 and 29, and 3 and 6 months after completion of the intervention.

The Hospital Anxiety and Depression (HAD)[5] scale was used to determine the severity of anxiety and depression. The scale consists of subscales for anxiety (7 items) and depression (7 items), which provides a score between 0 and 21 points on each sub-scale. The higher the score, the more pronounced the symptoms. HAD was completed at days 0 and 29, and 3 and 6 months after the intervention.

To screen for somatisation and non-GI somatic symptom severity, the Patient Health Questionnaire (PHQ-15)[6] was used. Excluding the three gastrointestinal symptoms in the questionnaire yields a measure of non-GI somatic symptom severity, that is, the PHQ-12.[7] Higher scores indicate more severe non-GI somatic symptoms. PHQ-15 was completed at days 0 and 29, and 3 and 6 months after the intervention.

The Visceral Sensitivity Index (VSI)[8] measures GI-specific anxiety, that is, anxiety originating from fear of GI symptoms, which is related to the unpredictable symptom pattern commonly found in IBS. The form was completed on days 0 and 29, and 3 and 6 months after completion of the intervention.

The Multidimensional Fatigue Inventory-20 (MFI-20)[9] measures general fatigue, physical fatigue, decreased activity, reduced motivation, and mental fatigue. This was completed on days 0 and 29, and 3 and 6 months after completion of the intervention.

The Work Productivity and Activity Impairment Questionnaire–IBS (WPAI-IBS)[10] measures whether IBS symptoms affect the ability to work and perform everyday activities with four different variables: absenteeism, presenteeism, overall work impairment, and activity impairment. WPAI-IBS was completed on days 0 and 29, and 3 and 6 months after completion of the intervention.

Dietary assessments

Dietary intakes were assessed using an estimated food record during 4 consecutive days, meaning that random weekdays and weekend days were included. Participants were instructed to record all foods and drinks consumed as detailed as possible e.g., stating brand names, fat content, and cooking method. The amounts of foods consumed were estimated using household utensils or standard measures, i.e., slices, cups, etc. Energy and nutrient intakes were calculated using the software DIETIST XP 3·1 (kostdata.se) which has a Swedish FODMAP database add-on.[11]

Adherence to the diet

All deviations from the meal plan during the intervention was recorded in a diary. Each deviation, e.g., eating high-FODMAP foods or less than 5 meals/day in the LFTD, or eating carbohydrate-rich foods in LCD, was added into a diet deviation score. Each meal that was skipped generated a 0·5 score, and each meal that did not adhere with the diet regime was scored 1. A score of "0" indicated complete adherence and scores were summed up for each week. At follow-up visits, participants were asked if they had continued with the diet with options "*yes, completely*", *yes, partially*", "*no, only to some extent*", or "*no, not at all*".

Treatment satisfaction questionnaire

Participants allocated to dietary treatment filled in a short questionnaire assessing seven potentially positive and seven potentially negative aspects of the diet, at end of intervention and at follow-up visits.

Supplementary material

Supplementary Table 2. Energy and nutrient content in the dietary treatment groups in the CARIBS intervention study.

	Low FODMAP/traditional IBS diet	Low carbohydrate diet	Low carbohydrate lactose free
Dietary variables			
Energy, kJ	9659 (736)	9740 (786)	9740 (786)
Protein, g	99 (15)	132 (19)	132 (19)
Fat, g	88 (19)	175 (22)	175 (22)
Carbohydrates, g	264 (23)	50 (9)	50 (9)
Dietary fibre, g	29·3 (4·6)	23·9 (5·6)	23·9 (5·6)
Vitamin C, mg	206 (87)	158 (84)	158 (84)
Iron, mg	12·6 (2·3)	13·0 (2·9)	13·0 (2·9)
Calcium, mg	773 (194)	946 (328)	946 (328)
Retinol equivalents	956 (455)	1047 (355)	1047 (355)
Vitamin D, µg	9·8 (5)	6·8 (6·5)	6·8 (6·5)
Vitamin E, mg	20·8 (5·1)	29·3 (6·3)	29·3 (6·3)
Thiamine, mg	2 (0·5)	1·5 (0·6)	1·5 (0·6)
Riboflavine, mg	1·6 (0·2)	1·7 (0·5)	1·7 (0·5)
Niacine, mg	26·5 (8·4)	25·6 (12·4)	25·6 (12·4)
Vitamin B6, mg	2·6 (0·6)	2·2 (0·6)	2·2 (0·6)
Vitamin B12, µg	4·9 (2·2)	7·4 (4·2)	7·4 (4·2)
Magnesium, mg	432 (57)	436 (117)	436 (117)
Potassium, mg	3525 (459)	3272 (428)	3272 (428)
Zink, mg	12·4 (4·2)	16·3 (5·7)	16·3 (5·7)
Saturated fat, g	28 (9·4)	65·5 (11·5)	65·5 (11·5)
Monounsaturated fat, g	31·8 (9·2)	67·2 (14·1)	67·2 (14·1)
Polyunsaturated fat, g	21·6 (4·8)	25·1 (6·9)	25·1 (6·9)
Folate, µg	461 (88)	476 (81)	476 (81)
Selenium, µg	64 (20)	190 (158)	190 (158)
Lactose, g	0·2 (0·2)	6·1 (3·8)	0·8 (0·9)
Fructan, g	1·7 (0·3)	3·3 (1·1)	3·3 (1·1)
Excess fructose, g	0·4 (0·3)	2·0 (2·3)	2·0 (2·3)
Polyol, g	0·4 (0·3)	6·1 (5·4)	6·1 (5·4)
Galacto-oligosaccharide, g	0·3 (0·1)	1·2 (2·4)	1·2 (2·4)
Total FODMAP, g	3·4 (0·9)	18·9 (7·1)	13·4 (6·7)

Data are mean (SD). FODMAP=fermentable oligo-, di-, monosaccharides and polyols. IBS=irritable bowel syndrome.

Supplementary material

Supplementary Table 3. Foods included in the dietary treatment groups in the CARIBS intervention study.

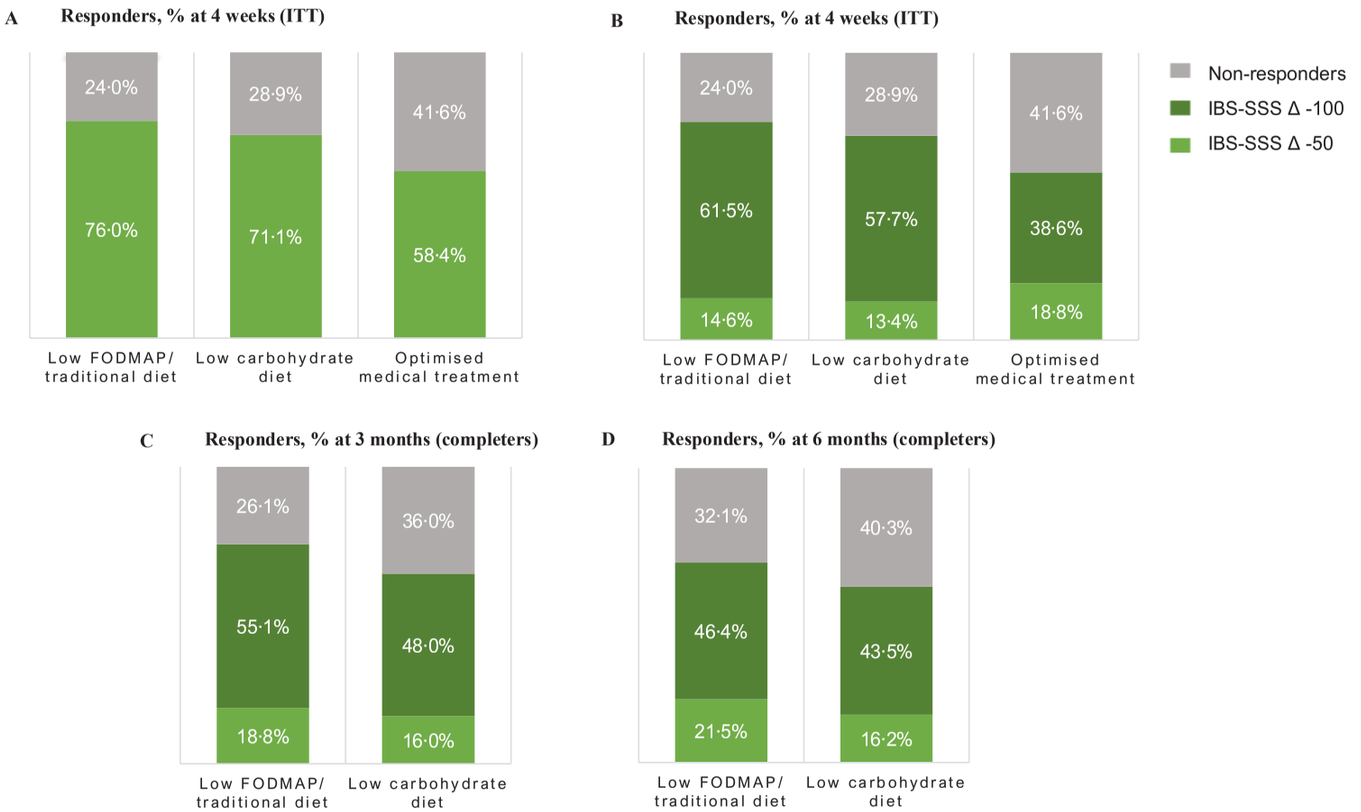
	Low FODMAP/traditional IBS diet	Low carbohydrate diet	Low carbohydrate lactose free
Breakfast options	Gluten-free and wheat-free bread with margarine, ham/turkey/bell peppers/cucumber	Protein bread (low in carbohydrates with fibres derived from a mix of pea- and soybeans, flaxseed, whole grain rye, wheat bran and sesame seeds) with butter, ham/cheese/bell peppers/ avocado/peanut butter	Protein bread (low in carbohydrates with fibres derived from a mix of pea- and soybeans, flaxseed, whole grain rye, wheat bran and sesame seeds) with lactose-free butter, ham/cheese/bell peppers/ avocado/peanut butter
	Lactose-free yoghurt with oat muesli and raspberries	Omelette with cheese/tomatoes/onion/ham	Omelette with cheese/tomatoes/onion/ham
	Banana pancakes with cottage cheese and strawberries/blueberries, syrup	High-fat yoghurt (10% fat) with nuts (almonds/hazelnuts/cashews/macadamia) blueberries/raspberries and shredded coconut	High-fat yoghurt (10% fat, lactose-free) with nuts (almonds/hazelnuts/cashews/macadamia) blueberries/raspberries and shredded coconut
	Oatmeal with almond milk, banana/blueberry jam, boiled egg	Scrambled eggs with bacon/tomatoes/arugula	Scrambled eggs with bacon/tomatoes/arugula
		Boiled eggs	Boiled eggs
Lunch/dinner (main ingredients)	Bean sprouts	Avocado	Avocado
	Bell peppers	Broccoli	Broccoli
	Carrot	Cabbage	Cabbage
	Chives	Cauliflower	Cauliflower
	Cucumber	Celeriac	Celeriac
	Eggplant	Fennel	Fennel
	Fennel	Garlic	Garlic
	Ginger	Green beans	Green beans
	Green beans	Mushrooms	Mushrooms
	Lettuce	Onions (yellow and red)	Onions (yellow and red)
	Parsnip	Squash	Squash
	Spinach	Tomatoes	Tomatoes
	Squash	Salad caprese	Salad caprese
	Tomatoes	Greek salad	Greek salad
	Fresh herbs	Salad with shrimps	Salad with shrimps
	Potatoes	Falafel	Falafel
	Gluten- and wheat-free pasta	Shirataki noodles (low carb noodles)	Shirataki noodles (low carb noodles)
	Rice	Hazelnuts	Hazelnuts
	Rice noodles	Fresh herbs	Fresh herbs
	Quinoa	Cheese	Cheese
	Cheese	Feta cheese	Feta cheese, lactose-free
	Feta cheese	Cream (15-40% fat)	Cream (15-40% fat, lactose-free)
	Lactose free cream (15% fat)	Coconut milk	Coconut milk
	Coconut milk	Soybeans	Soybeans
	Sour cream	Eggs	Eggs
	Eggs	Bacon	Bacon
	Quorn	Pork	Pork
	Pork	Beef	Beef
	Beef	Chicken	Chicken
	Chicken	Salmon	Salmon
	Salmon	Cod	Cod
	Cod	Chicken soup	Chicken soup
	Chicken soup	Fish soup	Fish soup
	Fish soup		
	Corn tortillas		
Snacks	Banana	Roasted soybeans	Roasted soybeans
	Orange	Kiwi	Kiwi
	Grapes	Peanuts	Peanuts
	Kiwi	Quark	Quark
	Sesame seed cookies	Protein pudding	Protein pudding
	Lactose free quark	Cottage cheese (4% fat) with blueberries and pumpkin seeds	Cottage cheese (4% fat, lactose-free) with blueberries and pumpkin seeds
	Gluten-free and wheat-free bread with margarine, ham/turkey/bell peppers /peanut butter/cream cheese/marmalade	High-fat yoghurt (10% fat) with nuts (almonds/hazelnuts/ cashews/macadamias) and flaxseeds/berries/shredded coconut	High-fat yoghurt (10% fat, lactose free) with nuts (almonds/hazelnuts/ cashews/macadamias) and flaxseeds/berries/shredded coconut

	Lactose-free cottage cheese with raspberries/blueberries and pumpkin seeds	Almond cake made with almond pulp, orange zest, agave syrup, and dark chocolate (90% cocoa)	Almond cake made with almond pulp, orange zest, agave syrup, and dark chocolate (90% cocoa)
	Chia seed pudding (chia seeds and almond milk)	Peanut and dark chocolate cookies	Peanut and dark chocolate cookies
	Lactose-free yoghurt with oat muesli	Chocolate panna cotta	Chocolate panna cotta, lactose-free
	Raspberry sorbet	Coconut and dark chocolate cookies	Coconut and dark chocolate cookies
	Pineapple pie	Dark chocolate, sugar free and sweetened with polyols	Dark chocolate, sugar free and sweetened with polyols
	Gluten- and wheat-free lemon and poppyseed cake		
	Gluten- and wheat-free carrot cake		

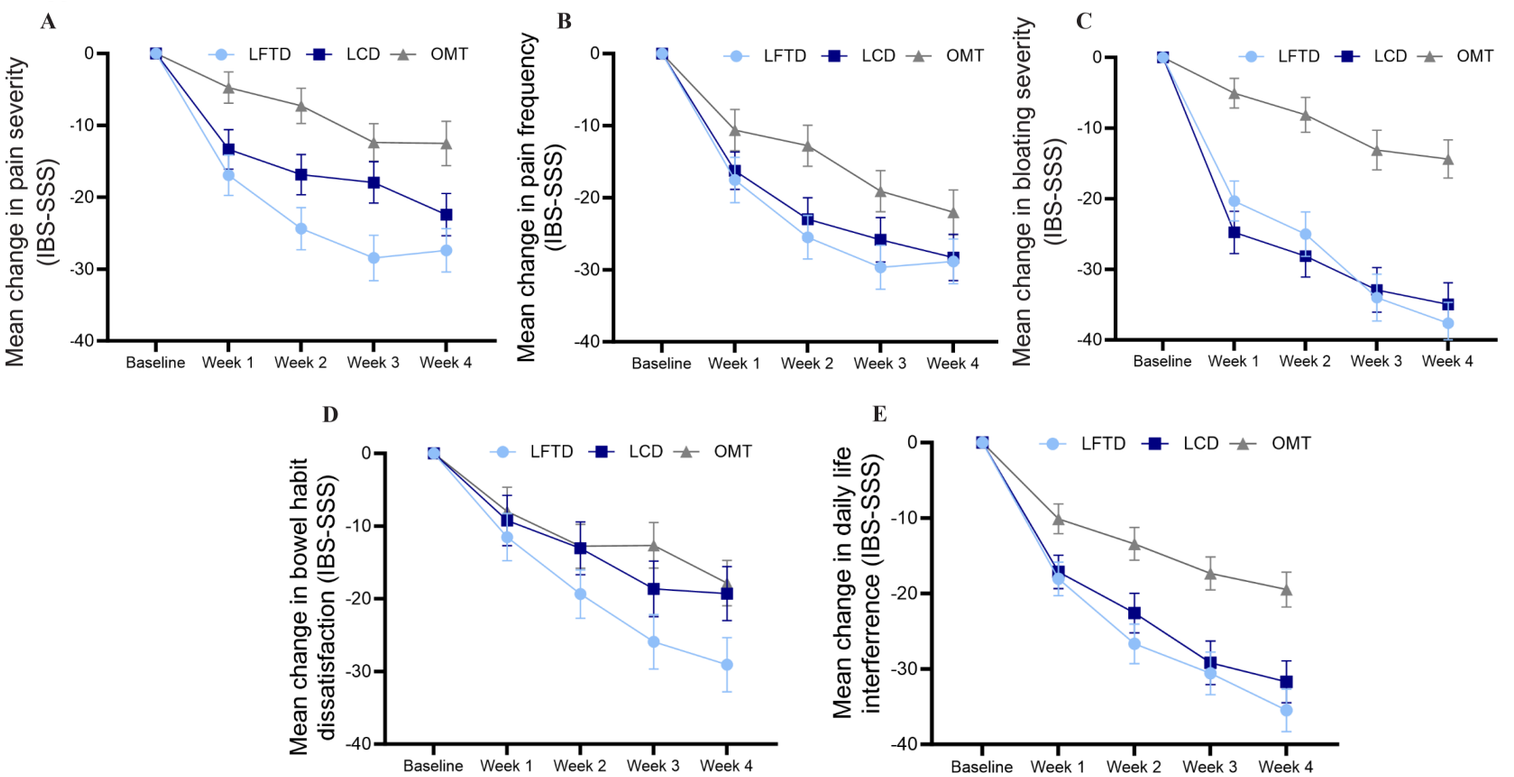
Supplementary Table 4. Pharmacological treatment options based on predominant symptom and with the starting dose used. The sequence of treatment choices for constipation and diarrhoea is given by line numbers.

Constipation	Diarrhoea	Abdominal pain
1. Bulking agent (Sterculia) 4 g q.d.	1. Loperamide 2 mg b.i.d.	*Chronic/frequent pain:* Amitriptyline 25 mg q.h.s.
2. Osmotic laxative (Macrogol) 13·125 g q.d.	2. Cholestyramine 4 g q.d.	*Episodic pain:* Hyoscyamine 0·2 mg prn.
3. Linaclotide 290 µg q.d.	3. Ondansetron 4 mg q.d.	*Pain with diarrhoea:* Amitriptyline 25 mg q.h.s
		Pain with constipation: Linaclotide 290 µg q.d.

Abbreviations: q.d, once a day; b.i.d, twice a day; q.h.s, before bed; prn, as needed



Supplementary Figure 2. Proportions of participants defined as responders to treatment according to a) a decrease in IBS severity scoring system (IBS-SSS) of ≥50 at four weeks based on a modified intention to treat, (ITT) population, b) a decrease in IBS-SSS of ≥50 and ≥100 at four weeks (ITT) c) a decrease in IBS-SSS of ≥50 and ≥100 at three months (completers), and d) a decrease in IBS-SSS of ≥50 and ≥100 at six months (completers).



Supplementary Figure 3. Mean changes in the different domains of the IBS severity scoring system, i.e., a) pain severity, b) pain frequency, c) bloating severity, d) bowel habit dissatisfaction, and e) daily life interference, showed significant reductions relative to baseline (all p<0·001, within groups) in the low FODMAP/traditional IBS diet (LFTD), low carbohydrate diet (LCD) and in the optimised medical treatment (OMT). At week 4, between group comparisons (ANOVA) showed significant differences in all individual domains except for bowel habit dissatisfaction (p=0·062). Error bars represent standard error of the mean.

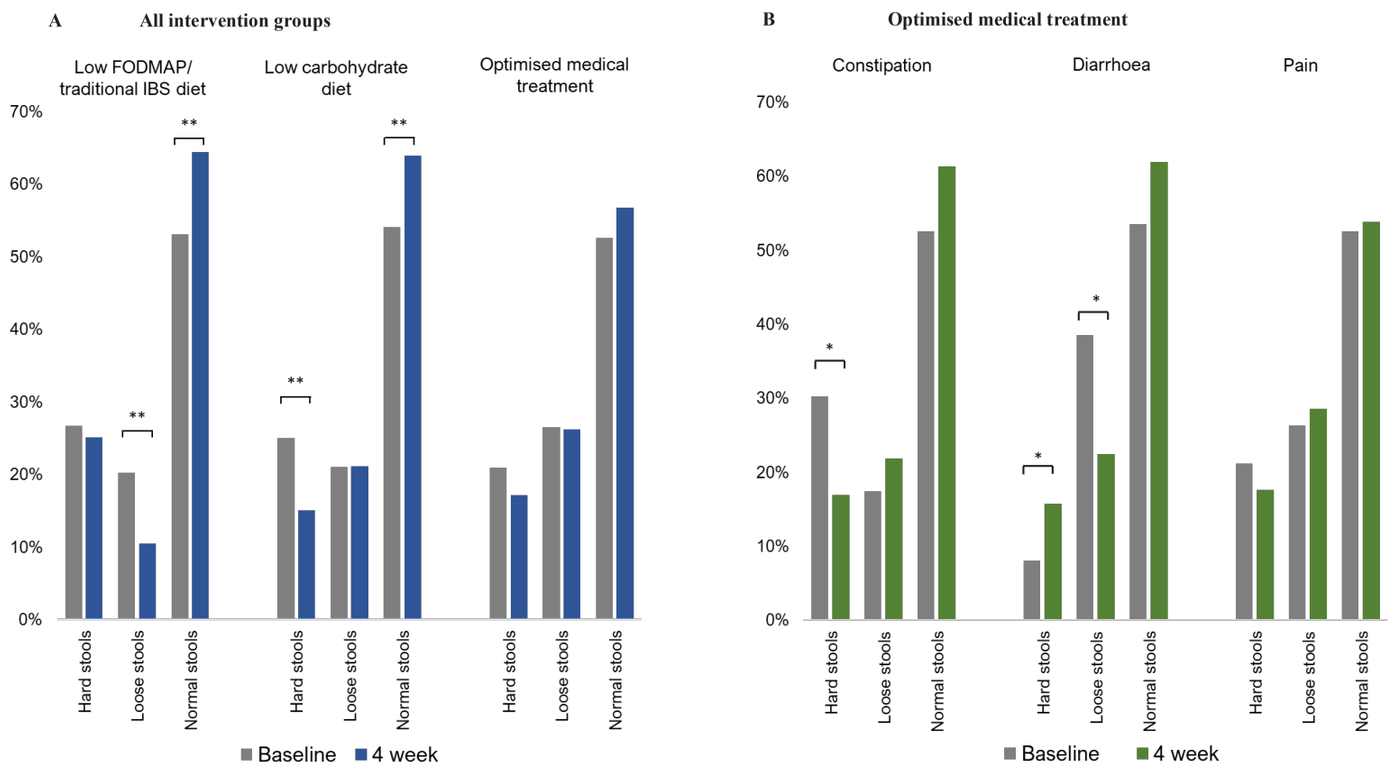
Supplementary material

Supplementary Table 5. Responders to treatment after the four-week intervention stratified by subtype of IBS.

	Low FODMAP/traditional IBS diet			Low carbohydrate diet			Optimised medical treatment		
	Responders (n=73)	Non-responders (n=23)	p-value	Responders (n=69)	Non-responders (n=28)	p-value	Responders (n=59)	Non-responders (n=42)	p-value
IBS subtype Rome IV			0·089			0·48			0·91
Constipation	32 (78·0%)	9 (22·0%)		32 (74·4%)	11 (25·6%)		17 (56·7%)	13 (43·3%)	
Diarrhoea	25 (78·1%)	7 (21·9%)		25 (69·4%)	11 (30·6%)		28 (58·3%)	20 (41·7%)	
Mixed	16 (76·2%)	5 (23·8%)		6 (54·5%)	5 (45·5%)		9 (56·3%)	7 (43·8%)	
Unclassified	-	2 (100%)		6 (85·7%)	1 (14·3%)		5 (71·4%)	2 (28·6%)	

Data are n (%). FODMAP=fermentable oligo-, di-, monosaccharides and polyols.

Supplementary material



Supplementary Figure 4. Changes in stool consistency among completers to the four-week intervention. a) At group level, the proportion of loose stools was reduced while normal stools were increased in the low FODMAP/traditional IBS diet, whereas the proportion of hard stools was reduced, and normal stools were increased in the low carbohydrate diet. b) In the optimised medical treatment group, the proportion of hard stools decreased in the group treated for constipation, and hard stools increased while loose stools decreased in patients treated for diarrhoea. *p<0·05, **p<0·001.

Supplementary material

Supplementary Table 6. The treatment satisfaction questionnaire after the 4-week intervention assessing positive and negative aspects of a low FODMAP/traditional IBS diet and a low carbohydrate diet.

	Low FODMAP/traditional IBS diet (n=91)	Low carbohydrate diet (n=92)	P-value
Statements			
The diet has improved my IBS symptoms	71 (78·0%)	66 (71·7%)	0·37
The diet has improved my overall health	56 (61·5%)	47 (51·1%)	0·12
The food tasted good	81 (89·0%)	79 (85·9%)	0·59
The recipes were simple	82 (90·1%)	87 (94·6%)	0·37
The food is affordable	46 (50·5%)	44 (47·8%)	0·77
The rest of my family can eat the same food	41 (45·1%)	54 (58·7%)	0·072
It is easy to find options while eating out	8 (8·8%)	25 (27·2%)	0·001
The diet worsened my IBS symptoms	4 (4·4%)	8 (8·7%)	0·24
The diet worsened my overall health	3 (3·3%)	7 (7·6%)	0·20
The food did not taste good	0 (0%)	5 (5·4%)	0·024
The recipes were difficult	3 (3·3%)	3 (3·3%)	0·31
The food is too expensive	2 (2·2%)	1 (1·1%)	0·77
I am not used to cook my own food	18 (19·8%)	18 (19·6%)	0·97
It is difficult to find options while eating out	34 (37·4%)	21 (22·8%)	0·012

Data are n (%) who agreed with the statement. FODMAP=fermentable oligo-, di-, monosaccharides and polyols. IBS= irritable bowel syndrome.

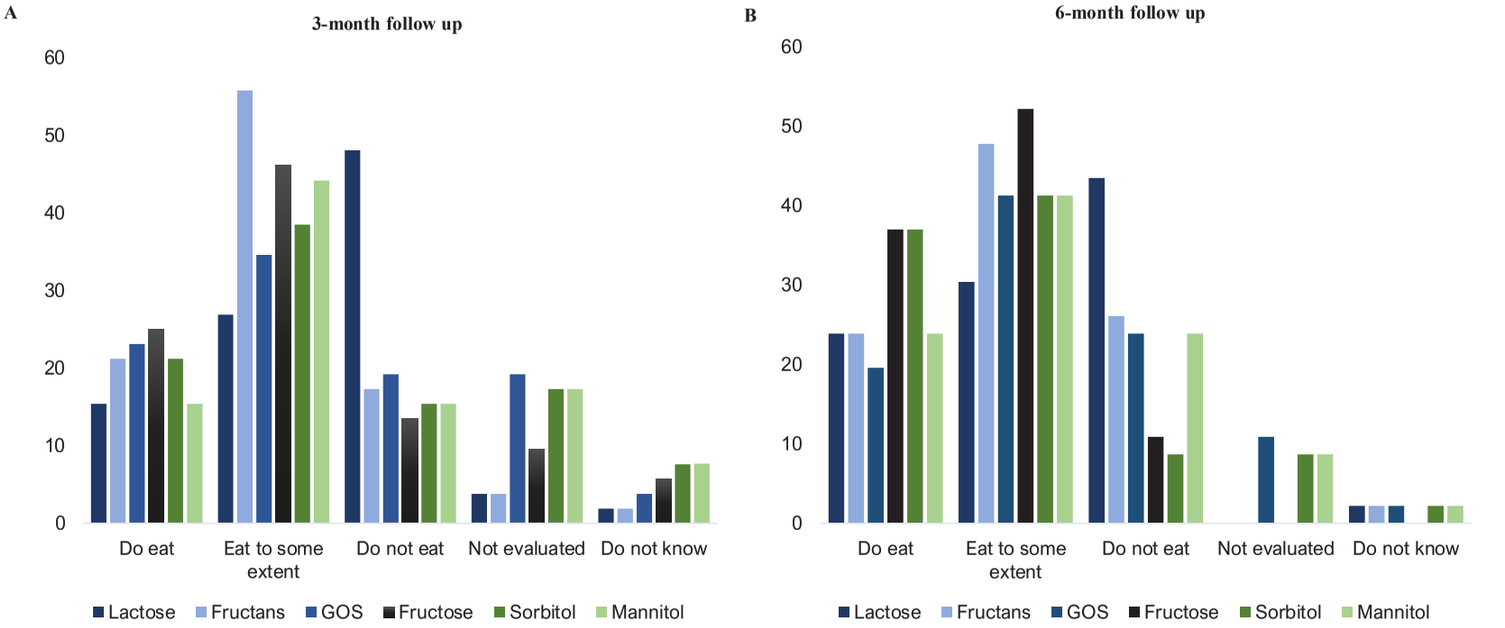
Supplementary material

Supplementary Table 7. Blood lipids and sugars from baseline to 6 months follow-up.

	Low FODMAP/traditional IBS diet				Low carbohydrate diet				Optimised medical treatment	
	0 (n=96)	W4 (n=91)	M3 (n=69)	M6 (n=56)	0 (n=97)	W4 (n=92)	M3 (n=75)	M6 (n=62)	0 (n=101)	W4 (n=91)
Fasting blood cholesterols and sugars										
Cholesterol, mmol/L	4·9 (1·0)	4·6 (0·9)***	4·6 (1·0)***	4·8 (1·0)*	4·9 (1·1)	5·2 (1·1)*	5·0 (1·1)	5·1 (0·9)	5·0 (1·0)	5·0 (0·9)
HDL cholesterol, mmol/L	1·7 (0·5)	1·5 (0·4)***	1·7 (0·5)*	1·7 (0·5)	1·7 (0·5)	1·7 (0·5)	1·7 (0·5)	1·7 (0·5)	1·7 (0·4)	1·7 (0·4)
LDL cholesterol, mmol/L	3·1 (0·9)	3·0 (0·9)*	2·9 (0·9)*	3·0 (0·9)	3·1 (1·0)	3·4 (1·0)**	3·2 (1·0)	3·3 (0·9)	3·2 (0·9)	3·2 (0·9)
Triglycerides, mmol/L	1·0 (0·8)	0·9 (0·5)**	1·0 (0·8)	1·0 (0·7)	1·0 (0·7)	0·9 (0·5)*	1·0 (0·7)	1·1 (0·7)	1·1 (0·6)	1·1 (0·5)
P-glucose, mmol/L	5·2 (0·5)	5·2 (0·6)	5·3 (0·5)	5·2 (0·6)	5·3 (0·7)	5·2 (0·5)	5·2 (0·5)	5·3 (0·5)	5·2 (0·4)	5·2 (0·5)
Hba1c, %	5·1 (0·3)	5·0 (0·3)	5·1 (0·3)	5·0 (0·3)	5·1 (0·3)	5·0 (0·3)*	5·1 (0·3)	5·1 (0·3)	5·0 (0·3)	5·0 (0·3)
Hba1c, mmol/mol	31·8 (3·1)	31·7 (2·9)	31·8 (3·3)	31·4 (2·8)	31·7 (3·1)	31·5 (3·0)*	31·8 (3·1)	32·2 (2·9)	31·3 (3·0)	31·4 (3·0)

Data are mean (SD). FODMAP=fermentable oligo-, di-, monosaccharides and polyols. HDL=high density lipoproteins. LDL=low density lipoproteins. M=month. W=week.*P-values <0·05 **P-values <0·001, ***P-values <0·0001 paired samples t-test relative to baseline.

Supplementary material



Supplementary Figure 5. Reintroduction of fermentable oligo-, di-, monosaccharides and polyols at the three- and six-month follow-up visit revealed that fewest participants had reintroduced lactose, while excess fructose and sorbitol were the FODMAP groups that most had reintroduced. Data on n=53 participants at month 3 (16 missing values), and n=46 at month six (10 missing values).

Supplementary material

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Paper II

Patients' experiences of dietary changes during a structured dietary intervention for irritable bowel syndrome.

Cecilia Weznaver[1], Sanna Nybacka[1], Magnus Simren[1, 2], Hans Törnblom[1], Sofie Jakobsson[3#], Stine Störsrud[1#]

1. Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

2. Center for Functional GI and Motility Disorders, University of North Carolina-Chapel Hill, Chapel Hill, NC, United States

3. Institute of Health and care Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

 # These authors contributed equally.

Abstract

Introduction: Diet plays an important role in management of gastrointestinal (GI) symptoms in patients with irritable bowel syndrome (IBS). Restrictive diets have gained popularity as treatment for IBS, but no studies have examined the patients' experiences of implementing such diets. Thus, this study aimed to explore the experience of patients with IBS undergoing a structured dietary intervention.

Methods: Using inductive content analysis, semi-structured interviews were conducted in 19 patients with IBS, recruited from a randomized controlled trial evaluating two different restrictive diets for 4 weeks: a diet low in total carbohydrates; and a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) combined with traditional IBS dietary advice.

Result: Three main themes developed from the qualitative analysis and together they describe the dietary intervention as supportive, dietary changes as challenging and contributing to reflection. Patients found the dietary support effective in both initiating and adhering to their dietary changes. Despite the support, the implementation of the diet was perceived as challenging when it interfered with other important aspects of their lives. However, going through the dietary change process, the patients began to reflect on their eating behaviors, which enabled individual dietary adjustments. The adjustments that patients maintained were not only due to alleviation of GI symptoms, but also based on personal preferences.

Conclusions: Patients with IBS undergoing restrictive diets seem to benefit from structured support. However, considering the individual patient's life situation and personal preferences, individualized dietary options should be encouraged to achieve long-term dietary changes.

KEYWORDS

irritable bowel syndrome, dietary intervention, structured dietary changes, nutrition, experiences, qualitative research.

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI) characterized by chronic or recurrent abdominal pain and altered bowel habits without evidence of organic disease (1). In a recent global epidemiology study, 4.1 % of the adult population was affected with IBS, with a predominance of women and the majority diagnosed are under 50 years (2). The pathophysiology of IBS is multifactorial and not yet fully understood. Contributing pathophysiologic mechanisms such as variations in gut neuromuscular function, immune activity, mucosal barrier integrity and a disordered gut-brain interaction are current explanatory models (3). Patients with IBS present with differences in symptom patterns, severity, and the simultaneous presence of non-gastrointestinal somatic and psychological symptoms (2, 4). Having IBS is associated with a reduced quality of life, and increased healthcare use (5, 6), and no clear association with socioeconomic status has been found (2, 4).

Dietary factors are of importance in IBS and can both trigger and alleviate symptoms (7-10). The identification of dietary items that trigger symptoms is often experienced as a frustrating process of trial and error (11). When dietary support from healthcare does not correspond to the patients' needs, there is a risk that non-reliable dietary information is sought from alternative sources (12, 13). Added to this, even if dietary advice given by general practitioners and gastroenterologists are perceived as trustworthy, it can be too simplistic without meeting individual needs of practical advice for real life situations (14). Dietary treatments have been shown to alleviate gastrointestinal (GI) symptoms in patients with IBS (15-17), and European guidelines for dietary management in IBS has been developed and known as traditional IBS dietary advice by the British Dietetic Association (BDA) together with The National Institute for Health and Care Excellence (NICE) (18, 19).

During recent years, much of the focus has been on restrictive diets, and in particular the low fermentable oligo-, di- and monosaccharides, and polyols (FODMAP) diet that reduce the intake of poorly digested carbohydrates (20-26). After an initial restriction phase, a systematic and gradual reintroduction of FODMAP is considered to be an important part of identifying an individual tolerance to FODMAP for a balanced symptom-relieving long-term diet (15, 27-31). Anecdotally, other restrictive diets, such as a low carbohydrate, high fat and protein diet (referred to as low carbohydrate diet, LCD), has been reported to reduce GI symptoms of individuals when trying to lose weight or control blood sugar levels with this diet (32). LCD was shown effective in a study including a small number of patients with diarrhea predominant IBS (IBS-D) (33) and in a study with IBS of all subtypes (34). Even if the LCD has shown positive effects on factors associated with the metabolic syndrome (35), there is an increased risk of dyslipidemia (36). This implies that both the low FODMAP diet (LFD) and the LCD need guidance and adequate follow-up by a trained dietitian (37) to avoid malnutrition and other potential adverse health effects (18, 19, 31, 38-40). Dietetic counselling to self-manage has been shown to be of importance to reach optimal dietary efficacy (41-43). In addition, other dietary options have also been proposed, such as a less restrictive option than the LFD to avoid adverse effects, like the FODMAP-gentle diet (44).

Previous qualitative research studies concerning patients' experience of living with IBS show large interindividual differences and that it is influenced by factors such as gender identity and life situation (45, 46). Improvement in symptoms was associated with receiving more supportive and educational person-centered care (47). Since most of the present knowledge in IBS is based on quantitative research, there is a need for more qualitative studies to enhance our management of the patients. Although the use of dietary treatments to alleviate symptoms in IBS is widespread, there is a knowledge gap regarding the execution of dietary treatments. One randomized controlled trial (48) has addressed the patients' perspectives when eating restrictive dietitian-guided diets as a treatment for IBS, but in general the patients' perspective has rarely been included in published studies.

In this study, we aimed to qualitatively explore the experiences of dietary changes in patients with IBS. The patients had undergone a structured dietary intervention that included restrictive low-carbohydrate diets (LFD and LCD respectively) to alleviate GI symptoms. Gaining insight into patients' dietary experiences in modifying their diet is essential for increased understanding within a complex treatment domain that affects patients' daily and social lives. A further understanding is likely to provide valuable information and may help advance strategies to support optimization of future dietary management in IBS.

MATERIALS AND METHODS

Study design and population

The patients included in this study were recruited from two dietary intervention groups in a randomized controlled trial (RCT), comparing the effect on IBS symptoms of three different treatments given for 4 weeks; a LCD, a LFD combined with traditional IBS dietary advice (low FODMAP traditional diet; LFTD), (19) and optimized medical treatment. Participants undergoing dietary intervention were allowed to maintain already prescribed medications at an unchanged dosage, provided that the treatment had commenced at least six weeks prior to randomization. The study was performed at an outpatient clinic specialized at GI disorders at Sahlgrenska University Hospital, Gothenburg, Sweden. All patients had been diagnosed with IBS using the ROME IV criteria (1), and reported at least moderate symptom severity according to the validated symptom severity questionnaire, IBS severity scoring system (IBS-SSS); i.e., IBS-SSS ≥175 (49) and were able to communicate in the Swedish language. The study protocol has previously been published (50). When included in the RCT, the participants were also invited to take part in this qualitative study (Figure 1). A purposive selection strategy was used to achieve a variety regarding sex and age reflecting the general IBS population according to current research. In addition, the sample also represented both dietary interventions equally, subtypes of IBS, and different duration of IBS symptoms. (Table 1). The recruited participants all agreed to a one-to-one and audio-recorded interview led by a dietitian. All interviews were given a patient code to ensure confidentiality. The patients were informed that participation was voluntary and that they could terminate their participation at any time.

Table 1. *Baseline participant characteristics and sociodemographic variables of 19 patients with irritable bowel syndrome (IBS) participating in the semi-structured interviews.*

Characteristics and sociographic	**N***	
Patient characteristics		
Age, years, median (range)	40	(20-68)
Women, N (%)	14	(74)
BMI, kg/m^2, median (range)	23.4	(18.8-31.1)
Duration of IBS, years, median (range)	20	(1-45)
IBS-subtype, Rome IV		
IBS-C	6	
IBS-D	6	
IBS-M	7	
Intervention diet		
LCD	9	
LFTD	10	
Marital status		
Married/cohabiting - no children at home	6	
Married/cohabiting - children at home	7	
Single living	3	
Living with parents	2	
Living in collective housing	1	
Occupational status		
Full time/student	17	
Unemployed/retirement pension	2	
Educational level		
Elementary school	2	
High school	7	
University	10	

The structured dietary interventions

The RCT included a 10-day screening period, followed by a 4-week dietary intervention and a 6-month follow-up period that totally included five study visits for the participants. After screening and randomization, the 4-week dietary intervention started at visit 2. (Figure 1). Detailed dietary information and instructions with recipes, daily menus containing breakfast, lunch, dinner, and snacks and a list of food options allowed during the intervention was provided. The patients were

instructed to maintain a weight and energy balance and report any deviations from the meal plan. Free grocery bags with all ingredients needed to prepare the food were delivered home to the participants each week. A mandatory telephone or e-mail follow-up was done after two weeks, and the participants were instructed that they could send additional questions and address any problems by emails or phone to the study coordinators during the trial. The controlled 4-week dietary intervention ended at visit 3, where the concept of their diet was introduced, and continuation during the 6-month follow-up period discussed depending on patients' perceived outcomes and preferred future options (Figure 1). For those randomized to the LFTD were also a standardized reintroduction of groups of FODMAPs presented and recommended both orally and written according to a standard and structured procedure (31) at visit 3. The reintroduction aimed for the participant to identify which individual FODMAP groups, and in what amount, that would trigger IBS symptoms in order to expand the diet with the personally remaining well-tolerated FODMAP. After visit 3, the delivery of grocery bags ended but all participants were encouraged to continue with their allocated diet plan. (50)

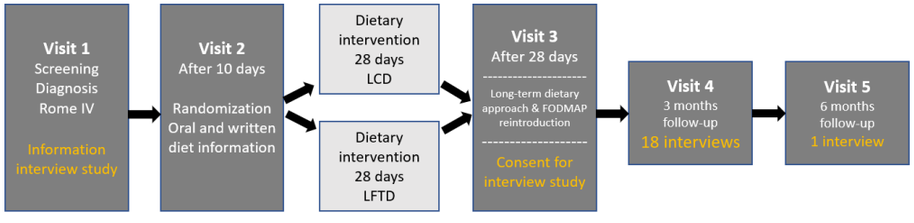

Figure 1*. Flow-chart showing the visits where the 19 interviews were performed in relation to the visits in the randomized controlled trial (RCT). The semi-structured interviews focused on the patients' experience of dietary change when undergoing a structured dietary intervention to alleviate GI symptoms in patients with irritable bowel syndrome (IBS). LCD, low in total carbohydrates diet; LFTD, low FODMAP diet combined with traditional IBS dietary advice.*

Data collection

The semi-structured interviews were conducted at the follow-up visits 4 and 5, i.e., 3 and 6 months after the end of the intervention (Figure 1) in an outpatient clinic room that was furnished for a more private and relaxed conversation likely to encourage dialogue. All interviews were performed by one of the authors (CW) in Swedish between 2018 and 2020. The interview guide used was developed to be able to explore the patients' experience of dietary changes during restrictive dietary intervention with the goal of alleviating GI symptoms. The four designed questions aim to capture experiences during and after the dietary intervention. To adhere to the inductive approach, interview questions were open-ended and with subsequent probes to invite the participants to exemplify and freely elaborate (see Supporting information, Table S1). The questions were tested in one pilot interview and as no difficulties were experienced no changes were made and the interview was included in the analysis. The interviewer repeated and summarized the interviews to provide an

opportunity for the respondent to clarify what had been said. Field notes were taken, and the latent content was also considered through noted silence, sighs, and laughter. The interviews lasted between 24 and 72 min and were audio taped. The recordings were transcribed verbatim by a medical secretary and one of the authors (CW).

Data analysis

Inductive content analysis (CA) with the approach of Elo et al (51) was applied to analyse the diet-related experiences that were told during the semi-structured interviews. A six-step analysis process was used for analysing the text from specific to the general aspects and thereafter combined to general statements for concluding the insights that emerged. Audio recordings and written materials were repeatedly re-assessed during the analysis. The initial reading and understanding were important for achieving an overall understanding. Reoccurring content in the text and contradiction were noted. Highlighting relevant meaning units from the texts started the process of open coding. When the meaning units were condensed, the first abstraction from the original data started and thereafter data were extracted into subcategories. Preliminary subcategories were compared, grouped, and re-grouped to deepen the understanding of similarities and differences in the patients' experiences, which finally led to categories. The categories were ordered in themes that descriptively covered all data. To achieve reliability the members of the research team were actively involved in all steps of the analysis by listening to the interviews, monitoring and discussing the content of the interviews and labelling and modifying categories and themes until consensus was agreed upon. All the members had different experiences in terms of dietary interventions, research methods and professions that contributed to an open mind set during the discussions. (Figure 2)

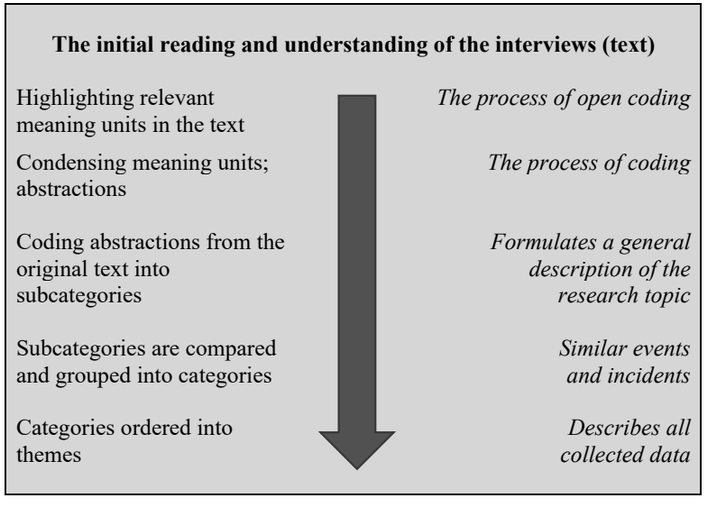

Figure 2. *The content analysis (CA) process follows the recommendation of Elo et al (44). A six-step analysis process was used for analysing the text from specific to the general aspects.*

RESULTS

Study population

Twenty-two participants agreed to participate in the study. Two interviews were postponed due to several rebooking of visits, and one participant did not show up for the interview. A variation in the selection was reached before rescheduling interviews for these individuals and therefore these three interviews were not performed. Participant characteristics and sociodemographic variables of the remaining 19 interviewed participants included in the present study are found in Table 1.

Qualitative analysis

By inductive CA, three themes were identified which describe the experiences of implementing the required dietary changes: “Supportive, educational and motivating”, “Multidimensional challenges”, and “Reflective and developing”. Nine categories were obtained which together with the participants’ quotes clarify the themes in a more detailed way (Table 2).

Table 2. *Themes and categories of the patients´ experiences of dietary changes during structured dietary interventions to alleviate GI symptoms in IBS. The results were obtained by inductive content analysis of semi-structured interviews with 19 patients. Quotations from each theme and category are followed by a bracket referring to a specific respondent and intervention diet. The quotations are translated by the first author (CW).*

Themes	Categoriers	Quotations
SUPPORTIVE EDUCATIONAL AND MOTIVATING	Structured dietary support	*“You* [*the study staff*] *are interested and do everything to make it work* [*the intervention diet*]*. It feels great not to fight this all by myself.”* (p18, LFTD)
		”… much like going to an AA [*alcoholics anonymous*] *meeting, you need someone, like a peer support or whatever it is called. That someone asks: - How is this turning out? Is it going well?”* (p7, LCD)
	Support from others	*”But many* [*work colleagues*] *were very understanding /…/ And many had the same problem! They thought it was interesting and wanted to look at the book* [*intervention menus*] *and to understand.”* (p5, LFTD)
	Learning by eating	*“But I didn´t think that diet was so significant. But now with this* [*experiences from the*

		intervention diet]*! /…/ But now, I realize that for me it´s important to have these fixed mealtimes. "* (p7, LCD)
		"If I want to try something new [foods], I will do as I did with this [reintroducing FODMAP]; I test a little and then a little bit more and a little bit more." (P2, LFTD)
	Personal gains and collective benefit	*"You feel chosen being included* [*in research*] */… / I think that it can be an advantage, that you may see it in a bigger perspective than just for yourself."* (p8, LFTD)
		"Well, I have the dream that my stomach will be all fine!" (p19, LFTD)
MULTIDIMENSIONAL CHALLENGES	Limits in time and energy	*"It is required that you are reasonably alert and active, both physically and mentally, in order to have the energy to get through it* [*coping with the intervention diet*]*."* (p14, LCD)
		" I had the ambition to make changes but I didn´t have the time." (p19, LFTD)
		"So, it was a relatively big step going from cooking a few times a week and cooking simpler things, to cooking more, and more structurally. Pretty much every day! It was a big… effort!" (p11, LCD)
	Struggles within social contexts	*"It also feels like you provoke some people when you say no* [*to food*]*, and then you feel that an explanation is required, why you say no. Because those people have still made an effort, bought a cake for someone's birthday. And then you say no."* (p4, LCD)
		"It's my boyfriend who thinks I'm very awkward [*with food*]*. Therefore, it felt very nice*

		that I got this [*intervention diet*]*. But he still thought it was hard."/… /"It's tough to feel that it´s a big conflict at home because I have special things* [*issues*] *with food."* (p5, LFTD)
	Dominant dietary preferences	*"… And too much fat! It feels weird to eat such fatty foods* [*the intervention diet*]*. For a long time… or forever!"/… /"I try to eat… choose foods that are good for health"* (p6, LCD)
		" It is probably my old habit, that you should eat a certain number of potatoes and a certain amount of vegetables, and a small part of meat. And now there was more meat in relation to the other [*the intervention diet*]*. And it feels wrong. It doesn't feel like this matches my idea of how to eat."* (P17, LCD)
REFLECTIVE AND DEVELOPING	Self-awareness	*"I´ve been rethinking - not binge eating just because it's good for the moment, and then there's a price to pay afterwards."* (p13, LFTD)
		"I discovered that I didn´t eat as varied as I always thought." (p19, LFTD)
		"But somehow, it´s only because of this [*the intervention diet*] *that I have understood that you can actually feel better…"* (p8, LFTD)
	Individual adjustments and developments	*"But towards the end* [*of the dietary intervention*]*, from thinking that this was nice… I felt towards the end, that now I understand the concept, now I want to make my own schedule, so that I can do what I really feel good about in terms of fiber, what works and what is easy."* (p5, LFTD)
		"I was inspired by the intervention food, as you can vary it in many ways... I have developed the recipes further myself!" (p18, LFTD)

Supportive, educational, and motivating

Structured dietary support

Receiving structured dietary support (recipes, daily menus, list of food options, home delivery of groceries and follow-up meetings) from trained dietitians regarding what, how and when to eat to alleviate GI symptoms was found to be very helpful. The participants generally found the food to be tasty and the recipes and daily menus easy to follow. However, more recipes were requested to ease long-term adherence to dietary changes after the 4-week intervention. Free home delivery of groceries was experienced by most participants as convenient and facilitating during the implementation of the diet, but with some practical problems arising when, for example, participants needed to change the day of food delivery. Some participants experienced less facilitation from the home delivery of foods, especially when they still had to purchase food for the rest of their family. It was appreciated with the continuous support through e-mails and phone calls, and the follow-up meetings after the intervention period were perceived as supportive for continued adherence to the dietary changes. Participants expressed that they had not been able to initiate or implement these dietary changes themselves. They felt grateful that they were not left alone to make the dietary changes, which was something they had experienced previously from healthcare. In addition, the participants also stated that the dietary support received made them feel seen, understood, and treated with respect.

Support from others

Some participants highlighted the importance of solid support and commitment from their relatives at home or people in their social contexts during the dietary intervention. These participants experienced support at home concerning the dietary changes as highly facilitating and, for some, even as crucial to continue with the diet. With a supportive partner the dietary changes became a fun adventure that increased their togetherness. Participating in the dietary intervention was said to affect eating behavior at work and when this was noticed by colleagues and led to an interest and support it was perceived as empowering. When colleagues shared similar problems themselves, the participants felt included, and less odd and alone with suffering from GI problems.

Learning by eating

The participants expressed that the dietary intervention period gave them new dietary learnings regarding the impact of their food choices on their GI symptoms, especially regarding the effects of carbohydrates. The dietary instructions made sense first after adapting them. This way, the participants revealed foods that triggered GI symptoms and identified better alternatives. Specifically, fixed mealtimes and smaller portion sizes were experienced as positive. Trying new foods and learning new ways to cook entailed new dietary learnings. Even those who did not experience much alleviation of their GI symptoms from the intervention diet, identified new learnings, such as eating a more varied diet as well as economic advantages when making lunch boxes instead of eating out. Adhering to the diet during the intervention period was taken seriously, which facilitated obtaining new knowledge and experiences. The participants expressed that the new knowledge led to an urge for more knowledge.

The FODMAP reintroduction was experienced as a learning by eating process. After the dietary intervention period, the participants in the LFTD group were introduced to the reintroduction and generally perceived the concept and the information as positive and easy to understand. Participants who completed the reintroduction expressed gaining dietary knowledge about their individual food tolerance and acquiring a useful tool for mitigating future GI symptoms with their food intake. However, the reintroduction of FODMAP and how to incorporate it into everyday life was experienced as a challenge for most participants. Even the most motivated participants had difficulties in finding a good timing for the reintroduction of FODMAP, fearing a possible setback that could interfere with other plans in everyday life. Also, motivation was lost when the efforts of reintroduction did not give a rapid or positive response.

Personal gains and collective benefit

Participants found motivation to perform the restrictive intervention diet by participating in finding a cause and a treatment for IBS, and with an effort to avoid or reduce medication. The patients' hope for now receiving more help from health care than they had previously received contributed to expectations. The participants presented a wide range of expectations from having less symptoms to being completely asymptomatic. Being part of a research project gave motivation to continue with the intervention diet even when it was perceived as difficult to adhere to. Patients expressed gratitude for participating in the study and wanted to support the researchers. If their contribution to research could help others, the effort to perform the dietary changes felt more meaningful. Participants expressed that other people took them and their GI symptoms more seriously since they participated in research.

Multidimensional challenges

Limits in time and energy

A frequently mentioned challenge was the limitations of everyday time and mental and bodily energy to focus on the requested dietary changes because of a full-time job, family life and hobbies. Furthermore, the GI symptoms were sometimes described as draining and causing fatigue, which made it even more difficult to have the energy for the necessary dietary changes. When the everyday cooking, required in the intervention diets, was not part of their regular routine, it was perceived and declared as especially time and energy consuming. Those who normally prepared foods also had to spend more time cooking than desired because they were not used to the new recipes. For those with family members who had other dietary needs to consider, preparing their own study meals as part of the intervention diet led to unwanted and tiring extra meal preparation time.

Struggles within social contexts

Social contexts and relationships with others were felt to affect the possibilities to implement the dietary changes. The participants consistently had to adapt to people around them and make compromises to make the restrictive intervention diet fit into everyday life. Not eating everything or refusing food during the intervention period was sometimes perceived as being socially

provocative. It was stated that adhering to the intervention diet was often easiest to perform in their home environment where they could adapt their food in their own manner. However, having an unsupportive partner who continued to cook usual food dishes without considering the patients' needs while following the intervention diet, contributed to arguments and frustration. Eating in specific social situations, such as during family vacations, was experienced as particularly difficult during the intervention. At work, several participants felt that they differed in a negative way from colleagues in terms of dietary aspects and could receive derogatory comments about their choice of food during this time.

Dominant dietary preferences

The participants experienced their previously acquired dietary habits as dominant and hard to change. Participants perceived it challenging to follow the intervention diets when these were conflicting with their dietary preferences. However, to have unfamiliar foods "prescribed" from the intervention study helped some break dominating eating habits. Entrenched habits, such as buying ready-made fast food, affected willingness to follow changes that required cooking. A recurring comment in the narratives was an entrenched desire for eating more healthily overall. The participants' preferences for a healthy diet were mostly expressed to be in line with the general nutrition recommendations (52), and in line with this several of the participants expressed a fear of gaining weight or wanted to lose weight. Both these dietary preferences were often declared to be more significant and dominant than an alleviation of IBS symptoms. Since the LCD contained a high fat content, the participants often associated this diet with dyslipidemia and unwanted weight gain, and this could be a reason not to continue with the diet after the intervention.

Reflective and developing

Self-awareness around food

Participants experienced increased self-awareness related to their eating behaviors when managing the challenges of the required dietary changes. Participants gained insights about having certain patterns that they had developed during different situations related to food intake, for example, wrongly referring to food allergies when declining food. Strategies became obvious, such as avoiding all social situations that included eating. Participants who experienced a great alleviation of IBS-related symptoms from the dietary changes became aware of how much it had affected them before and how much energy they now regained. By implementing the dietary changes, the participants became aware of the effort required to continuously plan daily food intake beforehand to maintain their new dietary habits, which was noticed, for example, when the home deliveries of the groceries and provided recipes ended. However, not achieving the expected symptom alleviation from the performed dietary changes also led to the awareness that the IBS symptoms are multifactorial, and that food is just one of several factors that can affect GI symptoms. Reflections on the impact of stress, anxiety, family life and the importance of regular exercise were mentioned as relevant regarding symptom management.

Individual adjustments and developments

Most participants felt that their interventions diets were too strict, and four weeks was enough to endure and therefore unrealistic to continue long-term with the diet. Dietary changes that were maintained were those that alleviated the symptoms, but also those that were easy to integrate into everyday life. The participants stated that the dietary changes primarily had to fit with everyday life and not the other way around. Participants in the LFTD group who completed the FODMAP reintroduction phase experienced a sense of liberation when they were able to reintroduce their most desired FODMAP-containing foods. Nevertheless, when the process of reintroducing FODMAP after the 4-week intervention was experienced to be challenging, some participants instead opted to adjust their dietary intake in their own manner that suited their individual preferences. Dietary changes that were maintained were e.g., to adhere to the intervention breakfast as a good and effective way to start the day or to continue eating small and frequent meals. Simplifying the recipes from the intervention, reducing portion sizes, or eating only one prepared meal a day were common adjustments. The most frequent recipes retained from the intervention were those perceived as tasty and healthy for the whole family. Meanwhile, some participants integrated the intervention diet completely in daily life, read more about diet and created new recipes to develop the concept further. Dietary changes involving an increased fat and meat intake were less likely to be maintained due to health and environmental concerns. According to the participants' own summaries, a reduced intake of total carbohydrates, increased intake of vegetables and a more varied diet were part of the maintained dietary changes.

DISCUSSION

This study aimed to qualitatively explore participants` experiences of undergoing a structured dietary intervention in order to alleviate GI symptoms in patients diagnosed with IBS. Our study marks the beginning of the exploration on aspects of restricted dietary changes from these patients' point of view. As the patients with IBS received structured dietary treatment, they experienced it as: 1) supportive, educational, and motivating which contributed to both initiating and adhering to the dietary changes. However, the implementation of the dietary changes was also experienced as 2) multidimensionally challenging in many ways, often depending on the patients' lifestyle and individual needs. In addition, 3) reflective and developing processes emerged by undergoing the dietary changes. The patients began to reflect on their eating behaviors, and they experienced a new self-awareness around food during and after the intervention period. The new insights helped them to individually adjust and develop ways to manage their diet to alleviate GI symptoms based on their lifestyle and personal preferences.

The first theme was related to the participants' perceived benefit of support in various forms to achieve dietary changes. Previous studies have shown that patients with IBS often feel unsupported and left without sufficient dietary information from the healthcare system in general (12, 14). This was confirmed by our participants and reinforces our findings about the positive dietary effects when they felt supported during the intervention, and not abandoned as experienced previously. The participants emphasized that receiving professional support from dietitians and structured dietary tools such as receiving recipes and home delivered groceries strongly contributed

to the initiation of, and adherence to, the diets. Therefore, we can conclude that supporting the patient to initiate dietary changes becomes one of the most crucial points for dietary change. Our findings also showed that support provided, such as structured follow-up visits and calls, ultimately provided sustainable dietary changes and should always be considered in the dietary treatment plan. Reintroduction of FODMAP requires practical implementation to evaluate the individual effect and tolerance levels (38-40, 53), and our participants confirm that the reintroduction phase is a challenging process. This study therefore highlights the importance of systematic support from experienced dietitians during the reintroduction phase of FODMAP (18, 19, 38) and furthermore, our result emphasizes the importance of supporting the initiation of FODMAP reintroduction as this was experienced as being particularly difficult.

Our study also reveals that not only the support from healthcare professionals, but also that encouraging support from e.g., relatives and colleagues provided confidence and comfort and had an important impact on adherence to the diet. Nevertheless, family dynamics and social contexts have previously been shown to bring many challenges and sometimes negative impact on food and related aspects in patients with IBS (12, 14, 47, 54). This corroborates with our results, as many participants felt that the implementation of the dietary changes could be negatively affected by people around them. If this is the case, we suggest encouraging the patients to invite partners and/or family members to the dietary consultation to increase understanding of the disease and dietary treatment.

Secondly, the participants experienced various challenges during and after the dietary intervention. This part provides us with further understanding and knowledge of the multidimensional struggle to alleviate IBS symptoms with dietary treatments. We encountered that dietary changes competed with other aspects of everyday life, such as time and mental and bodily energy. A previous study described symptoms in IBS to be draining and causing fatigue (55), which is in line with our findings. For those participants who experienced IBS-related fatigue, the lack of energy was an obstacle to perform the requested dietary changes. To make it easier for patients who mention fatigue as a dominant problem, it may be worth recommending a less restrictive diet (44) for an optimal outcome. In addition, several participants expressed the need for more simplified cooking tasks and less time preparing food. To facilitate dietary changes, it would be beneficial if less time-consuming food options were made available for the patients, such as simpler recipes, IBS-friendly ready-made options and IBS-adjusted grocery bags.

Another challenge that interfered with the necessary dietary changes was the dominant dietary preferences of the participants. For some participants, their dietary preferences were of greater importance than alleviation of GI symptoms. Patients' food expectations and preconceived ideas about food can interfere with the effectiveness of a dietary treatment in IBS and have been described in previous research (43). For example, all participants stated that it was important to eat a healthy diet. When the intervention diets, the high-fat LCD in particular, did not match the participants' preconceived views of a healthy diet, it became both confusing and unsustainable to follow these diets. Likewise, although the median BMI range of the participants indicates a normal weight, a general desire for weight loss was expressed by most of the participants. This contributed to some of the dietary changes ultimately not being justifiable for them despite achieving an alleviation of their GI symptoms. Overall, the participants experienced challenges reflect the fact

that living with IBS is complex and multifactorial (2, 4) and affects patients in various ways (45, 46).

The third theme concerns the participants' discovered need for reflection on their diet and eating behavior to be able to change and develop this further. Several participants expressed that four weeks with a restrictive dietary intervention was difficult to endure, but when it ended, they still wanted to continue with some of the dietary changes but to do so in a personalized manner. This corresponds well with the structured recommendations on how to reintroduce FODMAP which also encourages personal selections of FODMAP considered to be most relevant to the patient (31). A common insight was that dietary changes were neither initiated nor maintained without effort and commitment, which in the end made the participants become more involved in their food choices. The required dietary changes increased the participants' self-awareness both related to their diet, GI symptoms and to their situation of life and relevant practical perspectives.

The participants showed great flexibility and imagination to find personal solutions to continue with their dietary changes. Many participants concluded that the dietary changes they maintained after the intervention period were those that they perceived as being healthier, those that for them contributed to a more varied food selection, and those that saved time. This shows us that the patient's individually adjusted dietary changes gradually became tailored to both alleviate the GI symptoms and being consistent with the person's lifestyle and dominant dietary preferences.

Thus, restrictive diets such as LFD and LCD appear to initially benefit from structured dietary support including the reintroduction of FODMAP, to enable the patient to learn and evaluate treatment efficacy. To maintain desirable dietary changes long-term, a contributing factor should be to adjust them to the patient's individual life situation and overall perspective. However, how to implement long-term sustainable dietary changes when living with IBS requires more research, but individualized dietary adjustments that encourage a varied diet should be supported.

Strengths and limitations

Some potential limitations must be addressed. First, we were only able to include Swedish speaking patients and that might limit the external validity of the results. The degree of education was high among our patients and may not be representative of an average population. Also, the patients had moderate or severe IBS symptoms at recruitment, which might limit the generalizability of our results to people with milder symptoms. While the provision of free grocery bags in the study enhances adherence, it must be acknowledged that this may not be feasible in clinical practice and our findings may not be entirely replicable in real-world scenarios. However, providing recipes and shopping lists of groceries may to some extent provide similar support as were received by the study participants.

Strengths of the study are that it is pioneering, and paving the way in research, for giving the patient with IBS views on how dietary treatments are perceived. The qualitative approach of inductive CA is a systematic way of analysing and describing unexplored research fields (51, 56) and therefore suitable for our purpose. Furthermore, the present study includes a high number of interviews, and a purposive selection that included a variety of patients characteristics regarding

sex, age, BMI, duration of IBS, IBS subtypes, sociodemographic factors, and that both intervention diets were represented.

CONCLUSION

Participation in the dietary intervention study with structured dietary support, follow-ups and reintroduction of FODMAP was perceived as a helpful starting point for dietary changes and contributed to adherence. Despite challenges, the participants' process of implementing the dietary changes initiated reflections enabling for individual dietary adjustments. The dietary changes that participants maintained were not primarily related to the most effective changes for symptom alleviation, but changes that were not too challenging to maintain in the patients' current life situation and consistent with the personal view of overall health. Accordingly, initiation of restrictive diets such as LFD and LCD appear to benefit from structured dietary support. However, how to implement long-term sustainable dietary changes when living with IBS requires more research, but individual dietary adjustments of restrictive diets to achieve a varied diet should be encouraged when living with IBS.

TRANSPARENCY DECLARATION

The authors affirm that this manuscript is an honest and transparent account of the study being reported and no important aspects of the study have been omitted.

ETHICAL STATEMENT

This study was approved by **[**removed for blind peer review**]** and conducted according to the Declaration of Helsinki. All participants gave written and oral informed consent before any data collection was initiated.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ETHICAL STATEMENT

This study was approved by the Regional Ethical Review Board of the University of Gothenburg (T1079-17). 2016-04-21and 2018-01-02 and conducted according to the Declaration of Helsinki. All participants gave written and oral informed consent before any data collection was initiated.

AUTHOR CONTRIBUTIONS

SS, SJ, CW conceptualized this study. CW did the data collection. CW carried out the analysis with support from SJ and SS to provide a consensus on the interpretation. CW drafted the manuscript. All authors critically reviewed and approved the manuscript.

Corresponding author: RD Cecilia Weznaver, PhD-student, Advanced Accredited Practicing Dietitian. University of Gothenburg, Institute of Medicine, Sahlgrenska Academy. Sahlgrenska University hospital, Section of Gastroenterology and Hepatology, Dietitian Clinical Nutrition, S-405 30, Gothenburg, Sweden cecilia.weznaver@gu.se

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