Food-related gastrointestinal symptoms, nutrient intake and dietary interventions in patients with irritable bowel syndrome

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To Amanda, Jesper and Anders

"Life begins at the end of your comfort zone"

N. D. Walsch

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ABSTRACT

Food is a recurrent problem in irritable bowel syndrome (IBS) and it is common to exclude foods, which could lead to a reduced nutrient intake. Perceived food intolerance is very common in IBS, but if specific or more generalized food intolerance is the problem is unknown. Incompletely absorbed carbohydrates (fermentable oligo-, di-, mono-saccharides and polyols, FODMAPs) can trigger gastrointestinal (GI) symptoms, but if an enzyme (α-galactosidase), capable of digesting oligosaccharides, is able to relieve meal-related symptoms, or if a diet low in FODMAPs is more efficient in reducing symptoms than traditional dietary advice is not known.

Methods: Paper 1: The nutrient intake (from food diaries) in IBS patients was compared with a sex-and-age matched population from a Swedish national dietary survey. Paper 2: IBS patients completed questionnaires to assess self-reported food intolerance and the association with other clinical and demographic variables. Paper 3: In a randomized, double-blind, placebo-controlled, crossover trial; the effect of α-galactosidase on GI symptoms in IBS patients after carbohydrate-rich meals was investigated. Paper 4: In a randomized, single-blind, parallel group, four-week trial; the effect on IBS symptoms of a low FODMAPs diet was compared with traditional dietary advice in IBS.

Main results: The nutrient intake in IBS patients was similar to the Swedish general population. Eighty-four percent of IBS patients reported food-related GI symptoms, especially after intake of foods rich in incompletely absorbed carbohydrates and fat. Self-reported food intolerance was associated with more severe IBS symptoms and reduced quality of life. α-galactosidase was not superior to placebo in reducing GI symptoms after carbohydrate-rich meals in IBS patients. Fifty percent in the low FODMAPs group responded favorably to the dietary intervention (reduced GI symptoms), and 46 % were responders in the group who received traditional dietary advice.

Conclusions: Despite a high degree of self-reported food intolerance in IBS, the majority of these patients seem to have adequate nutrient intake. A low FODMAPs diet and traditional IBS dietary advice, but not α-galactosidase capsules, reduce symptom burden in patients with IBS.

Keywords: irritable bowel syndrome, gastrointestinal symptoms, diet

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Irritable bowel syndrome (IBS) är en vanlig funktionell mag-tarmsjukdom som kännetecknas av smärta och/eller obehag i magen i kombination med avföringsrubbning. Mat är ett återkommande och centralt problem för många patienter med IBS, som ofta uppger att de undviker ett eller flera livsmedel, vilket kan leda till minskat näringsintag. Upplevd födoämnesintolerans är mycket vanlig i patientgruppen men man vet inte om överkänslighet för något enskilt födoämne kan påvisas. Man har sett att inkomplett absorberbara kolhydrater, s.k. FODMAPs, kan orsaka IBS-symtom, men om ett enzym som kan underlätta upptaget av kolhydrater i tunntarmen kan lindra måltidsrelaterade symtom eller om en kost med lågt FODMAPs-innehåll medför färre symtom än traditionella kostråd är okänt.

Metod: För att bedöma hur IBS-patienter äter jämförde vi näringsintaget (kostdagböcker) från 187 IBS-patienter med en ålders- och könsmatchad kontrollgrupp (384 personer) från en nationell kostundersökning. För att sedan undersöka vilka livsmedel som IBS-patienter anser ge mag-tarmsymtom, fyllde 197 IBS-patienter i frågeformulär, där de specificerade mag-tarmsymtom efter intag av 56 olika livsmedel. Vi genomförde sedan två behandlingsstudier: Först undersökte vi om ett enzym (α-galaktosidas) kunde avhjälpa symtom som uppkom i samband med kolhydratrik mat hos 20 IBS-patienter. Efter det undersökte vi hos 75 IBS-patienter om en kost med lågt FODMAPs-innehåll är mer effektiv än traditionella kostråd vid IBS för att lindra mag-tarmsymtom.

Resultat: IBS-patienternas näringsintag skiljde sig inte nämnvärt från normalbefolkningen, trots att 84 procent av patienterna rapporterade mag-tarmsymtom efter intag av olika livsmedel och då framför allt efter livsmedel som innehåller fett och inkomplett absorberade kolhydrater. Mag-tarmsymtom efter intag av kolhydratrika måltider lindrades inte mer av α-galaktosidas jämfört med placebo. Femtio procent av testgruppen svarade positivt (minskade symtom) på låg-FODMAPs-kosten och 46 % svarade positivt i gruppen som fått traditionella kostråd.

Slutsatser: Patienter som har IBS äter ungefär som normalbefolkningen i Sverige och har som grupp ett adekvat näringsintag. De flesta IBS-patienter upplever att kost som innehåller mycket fett och inkomplett absorberbara kolhydrater orsakar symtom. Det verkar inte hjälpa IBS patienter att ta α-galaktosidas i samband med kolhydratrik måltid för att lindra mag-tarm-symtom. Emellertid verkar kostråd vara effektivt för att minska mag-tarmsymtom vid IBS och de kostråd vi testade bör i framtiden sannolikt kombineras i ytterligare studier av deras symtomlindrande egenskaper.

LIST OF PAPERS

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

I.   Böhn L, Störsrud S, Simrén M.

        Nutrient intake in patients with irritable bowel syndrome compared with the general population.

        Neurogastroenterol Motil. 2013;25:23–e1.

II.   Böhn L, Störsrud S, Törnblom H, Bengtsson U, Simrén M.

        Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life.

        Am J Gastroenterol. 2013;108(5): 634-641.

III.   Böhn L, Störsrud S, Törnblom H, Van Oudenhove L, Simrén M.

        A randomized double-blind placebo-controlled study: Effects of the enzyme alpha-Galactosidase on gastrointestinal symptoms in IBS patients.

        Submitted for publication.

IV.   Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnblom H, Simrén M.

        A randomized, controlled trial comparing a diet low in FODMAPs with traditional dietary advice in patients with IBS.

        Submitted for publication.

CONTENT

ABBREVIATIONS

BMI   Body Mass Index

BSF   Bristol Stool Form

FFQ   Food Frequency Questionnaire

FODMAPs   Fermentable Oligo-, Di-, Monosaccharides And Polyols

GI   Gastrointestinal

GOS   Galacto-oligosaccharides

HAD   Hospital Anxiety and Depression scale

IBS   Irritable Bowel Syndrome

IBS-C   IBS with constipation

IBS-D   IBS with diarrhea

IBSQOL   IBS Quality of Life

IBS-SSS   IBS-Severity Scoring System

MFI-20   Multidimensional Fatigue Inventory-20

PHQ-15   Patient Health Questionnaire-15

VSI   Visceral Sensitivity Index

1 BACKGROUND

1.1 Irritable bowel syndrome

Epidemiology

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder that affects persons world-wide, and a recent systematic review of eighty cross-sectional surveys found a global prevalence of 11.2 % in the adult population (with significant geographical differences ranging from 1.1 % to 45 %) (1). This makes IBS one of the most common GI disorders, and it is one of the leading causes for consultations in gastroenterology outpatient clinics, as well as in primary care (2). However, a large proportion of subjects with the disorder do not seek medical advice (2). IBS is more common in women than in men, with a female/male ratio of approximately 2 to 1 (3), and the peak prevalence is between the ages of 20 and 30 years (4).

Definition

IBS, which is the most common functional bowel disorder, is characterized by abdominal pain and/or discomfort related to abnormal bowel habit (diarrhea, constipation or mixed diarrhea and constipation), but with normal clinical routine investigations and tests (5). The etiology and pathophysiology are only partly understood (6) and available treatment options are limited (7). IBS has profound effects on quality of life (8) and is associated with substantial costs for the society (9). Unfortunately, there are no available objective biomarkers and the diagnostic criteria have changed somewhat over the years, which make prevalence figures from different time periods difficult to compare. The first diagnostic criteria developed for IBS was the Manning criteria from 1978, which included abdominal pain relieved by defecation, more frequent stools and/or looser stools with onset of pain, passage of mucus per rectum, feeling of incomplete emptying, and abdominal distension (10). Later, groups of multinational experts have refined the diagnostic criteria for IBS and other functional bowel disorders in the Rome I (11), II (12) and III (5) criteria, respectively. In Table 1 the most recent diagnostic criteria for IBS, the Rome III criteria, is shown. In order to make a confident diagnosis, a limited number of routine investigations are recommended, and normal results are expected. Moreover, in order to rule out more severe GI diagnoses as an explanation for the symptoms, it is considered essential to rule out "red flags" or alarm symptoms, such as symptom onset after 50 years of age, rectal bleeding, recurrent vomiting, fever, and family history of colon cancer. The presence of any of these necessitates a more thorough clinical

investigation before an IBS diagnosis can be made (2, 13). Based on the dominant stool form or consistency, IBS is also subtyped into IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U) (5).

Table 1. The Rome III Diagnostic Criteria*

Recurrent abdominal pain or discomfort** at least 3 days per month in the last 3 months associated with 2 or more of the following:	
1.	Improvement with defecation
2.	Onset associated with a change in frequency of stool
3.	Onset associated with a change in form (appearance) of stool

* Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
** "Discomfort" means an uncomfortable sensation not described as pain.

GI and extraintestinal symptoms

As stated above, the key symptoms in IBS are abdominal pain and abnormal bowel habit, but also other symptoms such as bloating, abdominal distension, flatulence, urgency, defecation straining, and feeling of incomplete bowel emptying are common (5, 14). The frequency and the intensity of GI symptoms vary substantially in IBS patients, and not everybody with symptoms seeks medical care for their symptoms. This may have different explanations, e.g. frequency or intensity of symptoms, coping abilities, cultural differences, and psychosocial factors (15). Besides, as the disorder is associated with symptoms such as flatulence, abdominal distension, diarrhea, constipation, and urgency to defecate, it is also associated with several taboos and embarrassing situations (16). Moreover, patients with IBS also often report symptoms related to other parts of the GI tract than the bowel (17), as well as multiple extraintestinal symptoms (18, 19). Backache, headache, lethargy, urinary symptoms, fibromyalgia, chronic fatigue syndrome, sleeping problems, and nausea are examples of comorbid symptoms/conditions that may co-exist with IBS (20, 21), and psychological co-morbidity is also commonly seen in IBS patients, especially in those who seek health care frequently (20, 22). The presence of multiple GI and extraintestinal symptoms in combination with typical IBS symptoms actually support a diagnosis of IBS (23).

Pathophysiology

The pathophysiology of IBS is incompletely understood, and there seem to be several important factors in IBS which could explain the origin and causes of symptoms, such as dysregulation of the brain-gut axis, genetic factors, psychosocial factors, early family environment, abnormal gut motility and sensitivity, impaired gut barrier function, low-grade inflammation and altered gut microbiota (24-28). Genetic factors may predispose to the development of IBS, but the exact role of genetic factors in IBS is so far not well known (29). One of the most widely studied pathophysiologic factors in IBS is visceral hypersensitivity, which is found in a substantial proportion of IBS patients, (30, 31) but whether this is due to abnormalities in the gut or in the brain, or at different sites in different individuals, is not known. The brain-gut axis is the constant communication between the central nervous system (CNS) and the enteric nervous system (ENS) of the gut. The brain influences the functions of the ENS and the gut affects the brain. The symptoms in IBS is currently believed to be caused by dysfunction in this communication (28, 32). Psychological co-morbidity and other psychosocial factors, coping abilities, daily hassles, and major life events can precede the onset of IBS and influence symptom exacerbation of IBS in susceptible persons (33). Early life trauma and abuse increase the risk of developing IBS, and socioeconomic status and social learning can influence the development and manifestation of illness behavior and symptoms in adults (34, 35). Moreover, IBS has traditionally been associated with altered GI motility, and in some patients increased frequency and irregular bowel contractions have been seen together with affected transit time through the GI tract, and in other patients an exaggerated motor response to meal ingestion has been reported (31, 36-38). Furthermore, other "new" pathophysiologic factors have been proposed, such as low-grade inflammation in the GI tract and immune activation, impaired epithelial barrier function, and altered microbiota composition and function in the colon, as well as in other parts of the GI tract (25). Taken together, the pathophysiology of IBS is complex and poorly understood and future studies need to determine the relative importance of the above mentioned factors, as well as how they interact and cause symptoms in patients with IBS.

1.2 Food and GI physiology

Digestion and absorption

The main function of the GI tract is to digest the food we eat in order to facilitate absorption of nutrients that can be used in various processes in our body. The digestive process includes mechanical and chemical breakdown,

and absorption. This process starts before eating; just thinking of, tasting, smelling, chewing and swallowing food, stimulate production of gastric acid in the stomach. Then the food is chewed into smaller pieces in the mouth and is mixed with enzymes. The process continues in the stomach where the food is mixed with gastric acid and even more enzymes. Some digestion of carbohydrates and proteins takes place in the stomach; however, the final breakdown occurs in the small intestine.

When gastric acid enters the first part of the small intestine, i.e. the duodenum, the endocrine cells are triggered to neutralize the acidic intestinal content (chyme) in order to optimize the chemical effect from pancreatic digestive enzymes and bile, and also to protect the small intestine from the gastric acid. At the same time as the chyme is digested, it is transported through the GI tract in a suitable pace to make the nutrient absorption as effective as possible. The motility of the small intestine mixes and moves the content slowly forward towards the colon, until the majority of nutrients are absorbed. The intensity of the contractions is dependent on the parasympathetic and the sympathetic nervous system, the enteric nervous system and hormones. Under normal conditions, few unabsorbed nutrients are left when the chyme enters the colon. There are however a huge quantity of bacteria in the colon that can synthesize vitamin K, and break down cellulose and unabsorbed carbohydrates through fermentation. The amount of bacteria varies and for example increases when the consumption of dietary fibers is large, and treatment with antibiotics decreases the bacterial number. Bacterial metabolism produces gases such as carbon dioxide, methane and hydrogen (39).

Carbohydrates consist of starch, glycogen, cellulose, and different saccharides. Carbohydrates must be digested into monosaccharides in order to be absorbed and this is done by different enzymes secreted from the salivary glands, stomach, pancreas, and from epithelial cells in the small intestinal brush border. The monosaccharides glucose and galactose are effectively absorbed in the small intestine into the portal vein, but the capacity to absorb fructose, another monosaccharide, is limited and dependent on the concurrent absorption of glucose. Excess fructose and other non-digested carbohydrates are transported to the colon, where they are fermented into short chain fatty acids that generally are considered to be beneficial to health (40). Fructose and also sorbitol are incompletely absorbed in the normal small intestine, and simultaneous ingestion of glucose enhances fructose absorption and malabsorption occurs only when fructose is present in excess of glucose (41).

Proteins are digested by the enzyme pepsin to peptides in the stomach, and the major breakdown takes place in the small intestine by different proteases in the pancreatic juice. The end products are short-chain peptides and amino acids, and the epithelial cells absorb both smaller peptides and amino acids to the portal vein.

Lipids (fats) consist mainly of triglycerides. The digestion of lipids occurs exclusively in the small intestine due to the necessary addition of pancreatic lipase and bile. The end products after fat digestion are free fatty acids and mono-glycerides.

Absorption of water is very efficient in the intestine. When different substances are absorbed, water follows, through osmosis. The small intestine and the colon absorb approximately 99 % of the water.

Only a small part of the feces, from a normal diet, are undigested food, and feces consist mainly of waste products, rejected epithelial cells and colon bacteria.

1.3 Assessment of nutrient intake

Accurately measuring diet in free-living human subjects is difficult to accomplish with precision. The appropriate tool for dietary assessment will depend on the purpose for which it is needed. Different methods have been developed for the purpose of assessing dietary intake. These range from simple food lists, household survey methods, food frequency questionnaires to detailed individual weighed records collected over a period of several days. Each method has its merits, practical difficulties and associated errors that needs to be considered (42). The purpose for which the dietary assessment is needed will decide the appropriate method. The purpose may be to measure nutrients, foods or eating habits on individual levels or in a larger group of subjects. In Table 2 an overview of the most common self-report dietary assessment methods are presented. When validating dietary assessment methods, i.e. biomarker-based validation, underreporting is most often observed. Recall methods are limited by memory. Record methods are biased by the fact that the subjects are likely to change their intake and both methods are potentially affected by over-reporting of healthy foods or what the subject is "expected to eat".

Table 2. Overview of common self-report dietary assessment methods.

Method	Description	Strengths	Weakness
Weighed food record (commonly 3-7 days; 7 days is "gold standard")	The subject weighing every item of food and drink prior to consumption in a specially designed booklet.	Widely used methods Precision of portion sizes	High respondent burden Misreporting Changing intake behavior Day-to-day variations Coding requires expertise
Estimated food record	The subjects register every item of food and drink prior to consumption in a specially designed booklet. The portion size is estimated or household measures are used.	Widely used method Lower respondent burden than weighed food diaries	Relatively high respondent burden Estimation of portion size Misreporting Day-to-day variations Coding requires expertise
24-h recall	A trained interviewer asks the respondent to remember in detail all the food and drink they consumed during the previous 24 hours.	Low respondent burden Can be administered by telephone	Requires a trained interviewer Relies on memory Estimation of portion size Single day vs day-to-day variation Coding requires expertise
Diet history	A trained interviewer asks the respondent to describe customary food and/or nutrient intakes over a relatively long period e.g. 6 months or longer.	Low respondent burden Can be administered by telephone	Cannot be self-completed Relies on memory Estimation of portion size Coding requires expertise
Food Frequency Questionnaire	Consists of a list of foods and a selection of options relating to the frequency of consumption (i.e. times a day/daily/weekly/monthly)	Low respondent burden Can be self-completed Can be optically scanned	Estimation of portion size Possible over-reporting of "healthy" foods

Traditionally, the diet-record method has been considered to be the most accurate method to assess food intake. However, the validity depends on the subjects' willingness to cooperate. The number of consecutive days of recording often influences the compliance, the recording can interfere with normal eating behavior, and the subjects may alter their intake due to self-consciousness, being ashamed or convenience (43). The estimated method to

assess nutrient intake is widely used, with a lower burden on respondents than the weighed food diaries. The weakness of this method is however difficulties when the investigator converts these estimates into weights that can then be used to calculate food and nutrient intake, and it is of course more time consuming for the investigator.

Alternative methods have other limitations, for instance underreporting due to limits of memory (diet history, 24-h recall method). Food-frequency questionnaires (FFQs) are designed to collect dietary information from large numbers of individuals. Depending on the length of the food list, and if portion size is not included in the questionnaire, it is not possible to measure the complete nutrient intake from these questionnaires. Validation of these self-reported dietary intake approaches, through methods with biomarkers, has unfortunately shown underreporting and systematic and random errors (44). However, only a few biomarkers (e.g. energy and protein) qualify as valid reference instruments to reflect dietary components (44). When performing studies to assess nutrient intake in a population, one has to take above-mentioned limitations into account and weigh these against the purpose of the investigation.

1.4 Food and IBS

Food and diet concerns patients with IBS (45), and they frequently report association between food ingestion and onset or worsening of GI symptoms (46, 47). The majority of IBS patients report adverse reactions to one or more foods and consider that their symptoms are aggravated by food intake. Several studies have investigated this and have come up with more or less the same findings, i.e. approximately two thirds of IBS patients report an association between food intake and worsening of their symptoms (46-49). In one study, female sex and anxiety seemed to predict a higher degree of food-related symptoms in IBS patients (46), which is in line with the finding that female IBS patients report more changes in their dietary habits because of GI problems than men with IBS (47).

Many IBS patients believe that food allergy or specific food intolerances can explain their symptoms (47). Food allergy is an immune response that occurs reproducibly on exposure to a specific food and can result in different symptom manifestations, including anaphylactic shock, which is a very severe condition. Food allergy is found in about 2-10 % of the general population (50), but there is no evidence to date that has suggested an increased frequency of food allergy in IBS compared to the general

population (51-53), even though there may be a subgroup within the IBS population where a link to genuine allergy mechanisms may be involved in symptom generation (54). However, perceived food intolerance, on the other hand, which is very common in the general population (55), is even more common in IBS, as 20-65 % of IBS patients attribute their symptoms to these non-toxic and non-immune-mediated adverse reactions to food (46, 47, 56, 57), but the underlying mechanisms are not well understood. Psychological factors are common in patients with symptoms compatible with IBS who attribute their symptoms to food intolerance (46, 58), but still only explains a small proportion of the variance in symptom severity in patients with self-reported food intolerance (59), so this does not seem be the major explanatory factor for food intolerance in IBS.

Typical symptom generating foods in patients with IBS are foods rich in fat (60) and carbohydrates (61-64), as well as cabbage, onion, beans, milk, wheat, coffee, peas/beans, hot spices, deep-fried food, pizza and cream (46, 47, 65). The current opinion is that a more general food sensitivity is a plausible explanation to some of these reactions, and the potential underlying mechanisms are discussed below. The perceived food intolerance may lead to avoidance of different foods in IBS, and sometimes patients risk nutrient deficiency. Several studies report that people with IBS often avoid different food items as a way of coping with the disease, which possibly could lead to a lower intake of essential nutrients (2, 46, 47, 66, 67). However, patients with IBS seem to have a body mass index (BMI) comparable to the general population (46), and few studies have addressed nutrient intake in IBS and assessed the nutritional adequacy of their diet (68). Moreover, differences in the presence and severity of subjective food intolerance between subgroups of IBS patients are not well covered in the literature.

When comparing individuals with IBS with subjects without IBS, there is weak evidence suggesting increased incidence of lactose malabsorption in IBS patients, when using a hydrogen breath test (69-72). The importance of lactose intolerance in IBS is therefore questionable, but in some studies lactose intolerance has been reported to be of relevance for patients with IBS, and a positive effect on symptoms after lactose restriction has been demonstrated (69, 71, 73). However, there are also other studies with limited or no effect of lactose restriction in IBS patients (70), so the clinical relevance of lactose intolerance is still controversial.

Failure to completely absorb fructose in the small intestine, i.e. fructose malabsorption, is common in the general population, and is usually not linked to symptoms (74). However, in IBS patients it has been proposed that the

presence of fructose malabsorption may be of relevance for symptom generation, even though it is probably not more common with fructose malabsorption in IBS patients than in the general population (62, 75), but also this is controversial, as opposing studies exist (76).

1.5   Effects of food on GI function in IBS

1.5.1   Fat

Fat is an important mediator of postprandial GI motor and sensory effects (77) and a potent stimulating factor of the colonic response to a meal (78). It is well known that especially large meals and meals with a high fat content are potent stimulators of the gastrocolonic response in general (79, 80), and in IBS patients in particular (81). Moreover, also in the upper part of GI tract, fat has profound effects on GI physiology, including effects on various GI peptides, with both GI and non-GI effects (82), which may also be involved in symptom generation after intake of fatty foods in IBS patients.

Abdominal pain after a meal is a common feature in IBS patients. One potential explanation behind this is the fact that the colonic hypersensitivity, seen in many IBS patients, is exaggerated after delivery of fat into the proximal small intestine. This has been studied by measuring the sensitivity to balloon distensions in the sigmoid colon before and after administration of lipids into the duodenum. A larger proportion of patients reported pain at the different pressure steps during the balloon distension after versus before duodenal lipids, and this was different from the findings in healthy controls, supporting an exaggerated sensory component of the gastrocolonic response in IBS patients (60, 83). It is tempting to speculate that this mechanism is involved in postprandial symptoms in IBS.

Another potential mechanism behind worsening of symptoms in IBS patients after meal intake is the effect of nutrients on gas transit and tolerance. Bloating and abdominal distension are prominent symptoms in patients with IBS and other functional GI symptoms, and it has been demonstrated that IBS patients with abdominal bloating have disturbed gas transit in the GI tract and tend to accumulate gas in the GI tract and also have a reduced tolerance to gas in the GI tract (84). This is modulated by nutrients, and especially the effect from lipids on gas transit and tolerance is enhanced in patients with IBS (85).

Taken together, lipids may worsen symptoms in IBS through different mechanisms, and probably the relative importance of these may differ between individuals.

1.5.2 Carbohydrates

As stated above, many patients with IBS report symptoms after intake of food items rich in different carbohydrates, and this may be related to incomplete absorption of different carbohydrates in the small intestine leading to negative effects in the colon in sensitive individuals. Traditionally, IBS patients have been encouraged to increase intake of dietary fibers (86), but many IBS patients state that their symptoms are worsened by increased fiber intake (87). Dietary fibers are non-starch polysaccharides that are mainly found in plant cell walls, and includes insoluble fibers (e.g. lignin, celluloses, and some hemicelluloses), and soluble fibers (e.g. β-glucan from oats and barley, pectin and gums in psyllium) and these have well established positive effects on health in general (88). In functional GI disorders, the positive effect of dietary fibers on stool form/consistency has been used therapeutically (89) but there is still conflicting data whether increasing or decreasing intake of dietary fibers is beneficial in subjects with IBS (87, 90, 91).

Many of the food items that are rich in dietary fibers, such as cereals, wholemeal bread, vegetables and fruits, also contain large amounts of incompletely absorbed short-chain carbohydrates which may cause GI symptoms in individuals with IBS through fermentation and osmotic effects in the colon when ingested (61). In fact, in the last years several lines of evidence have emerged showing that intake of food rich in these incompletely absorbed short-chain carbohydrates, collectively called FODMAPs - Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols - can be responsible for symptoms in large groups of patients with IBS (92). In line with this, recent evidence has suggested that reducing the FODMAPs content is efficient in reducing symptoms in IBS and other GI conditions (64, 93-97). In the FODMAPs concept the following groups of carbohydrates are included:

- *Oligosaccharides:* The human GI tract lack enzymes that are able to hydrolyze certain oligosaccharides, such fructans and galacto-oligosaccharides (GOS), thus absorption of these are not possible (98). Foods that contain large amounts of

oligosaccharides are peach, artichoke, wheat, rye, onion, legumes, chickpeas, lentils.

- *Disaccharides:* The dietary disaccharides, sucrose, lactose, maltose, isomaltose and trehalose are hydrolyzed by enzymes (disaccharidases) expressed by small intestinal epithelial cells. The absorption of lactose relies on the activity of the enzyme lactase in the epithelial brush border. Of the disaccharides this is the only enzyme that is commonly deficient, as lactase deficiency is the common state in the main part of the world, leading to unabsorbed lactose passing into the colon. However it varies greatly in different ethnic groups, with the frequency of maintained lactase production being larger in northern Europeans than in Asian and African ethnic groups (99, 100). Typical foods containing lactose are milk, yoghurt, and ice-cream.

- *Monosaccharides:* The absorption of dietary mono-saccharides varies. Glucose and galactose are effectively absorbed in the small intestine. However, the absorption of fructose is more variable, and is dependent on the concurrent presence of glucose (101). When fructose is present in excess of glucose, malabsorption occurs, as co-ingestion of glucose enhances fructose absorption (41). Some fruits and vegetables contain large amounts of "free" fructose, for example apple, cherries, watermelon, asparagus, artichokes, and honey, and ingestion of large amounts of such food items may therefore lead to substantial amounts of fructose passing unabsorbed to the colon.

- *Polyols:* The ability to absorb polyols (sorbitol, mannitol, maltitol and xylitol) varies between individuals and across different polyols, and the absorption is generally slow and passive. Polyols are present in foods such as apple, apricot, cauliflower, and in all sugar substitutes that end with –ol (e.g. sorbitol, maltitol, xylitol).

The mechanisms through which FODMAPs may cause symptoms in susceptible individuals are through osmosis and fermentation. Short-chain carbohydrates are osmotically active and if they are incompletely digested or absorbed, or if the absorption process is slow, this will increase the water volume in the small intestine. They can also be fermented in the colon, leading to production of different gases. These two actions will lead to luminal distension that may aggravate symptoms in subjects with IBS (92, 102, 103). The increased luminal water may in addition to distension also

lead to looser stools. Moreover, besides gases, the colon bacteria also produce osmotically active short-chain fatty acids with effects on sodium and water absorption, as well as on motility. However, not all subjects that ingest large amounts of FODMAPs report symptoms (76) and the presence of visceral hypersensitivity or other factors may be an additional prerequisite to have symptoms after FODMAPs ingestion (92, 93).

Based on these findings, a diet with low FODMAPs content has been tested in IBS with promising results, i.e. marked improvement of GI symptoms results in the majority of patients (94-96). The low FODMAPs diet implies a carbohydrate restricted diet, and the potential problem is that it is quite intrusive and difficult to follow, and the long-term effects are still not known, with potential negative effects on gut microbiota composition (97, 104).

1.5.3 Other factors

Gluten has recently been put forward as an important dietary factor to consider in patients with IBS, even in the absence of celiac disease (105). The mechanism behind the potential negative effects of gluten in IBS is still debated, but effects on intestinal permeability (106), a FODMAPs effect (107) or immune mechanisms (108) are plausible. Other dietary factors that may affect GI function negatively in IBS patients include alcohol and caffeine (46, 47).

Recently, alterations in gut microbiota composition and function have been put forward as an important factor in functional bowel disorders (27).The GI microbiota is the microbe population living in our intestine. It contains tens of trillions of microorganisms, including at least 1000 different species of known bacteria. Microbiota can, in total, weigh up to 2 kg. One third of our GI microbiota is common to most people, while two thirds are individually unique (109). Diet profoundly affects gut microbiota and many of the effects of the diet on gut function can be modified by the gut microbiota composition and function (110). Therefore, manipulation of gut microbiota through dietary changes has been put forward as one promising treatment option for IBS in the future. Moreover, part of the variance in response to different dietary manipulations may be due to differences in gut microbiota composition.

1.6   IBS and dietary advice

Diet and lifestyle changes are important management strategies in IBS. However, few randomized controlled trials exist on dietary treatment of IBS patients. Instead, the current recommendations are primarily based on studies assessing physiological function in relation to dietary components (57, 111). In 2012, the British Dietary Association published evidence-based guidelines for the dietary management of IBS in adults (112), even though these were mainly based on non-randomized trials. A comprehensive literature search was conducted and relevant studies from 1985 to 2009 were identified and critically appraised. Three lines of dietary management were identified where the first line includes clinical and dietary assessment and advice about healthy eating and lifestyle management, including physical activity and also some general advice on lactose and non-starch polysaccharides. In the second line there were more advanced dietary interventions to reduce IBS symptoms, which include non-starch polysaccharides, FODMAP and also recommendations about probiotics. The third line included elimination diets. In the conclusion the authors raised the need for adequately powered randomized controlled trials on different dietetic strategies in the future. Some of the currently used approaches to dietary advice in IBS are briefly discussed below.

1.6.1   Carbohydrates

Dietary fibers

An increase of dietary fibers has been widely advocated as a first-line treatment in IBS, based on the effect on stool form and consistency, but with contradictory results. This advice was based on positive initial results of a diet with high wheat-fiber content on IBS symptoms (86). However, several studies failed to confirm these positive results (113, 114), and a survey of IBS patients later found that 55 % of the patients even reported a deterioration by bran, whereas only 10 % found it helpful (87). These disappointing results of an increased fiber intake in IBS patients may be related to an abnormal colonic fermentation (115). Today the advice regarding increasing fiber intake is mainly proposed to patients with constipation as their main complaint, and to use soluble fibers, particularly ispaghula or psyllium, instead of the insoluble fiber wheat bran (116). Soluble fibers, which is prevalent in several fruits, such as apricots, figs and prunes, have a greater water-holding capacity than insoluble fibers and a

more pronounced effect on fecal bulking, which is probably beneficial for IBS patients.

Lactose

A majority of patients with lactose intolerance can consume a considerable amount of lactose before having symptoms (117), and the use of enzymatic treatment (lactase supplements) seems to be of limited value (118). Therefore, perceived lactose intolerance could be relevant only for a subgroup of IBS patients. In these patients a lactose reduced diet might have a positive effect on some of the symptoms, especially diarrhea and gas/bloating, but the general impression is that the importance of lactose intolerance in IBS have been overestimated during the past.

FODMAPs

Up to 96 % of individuals with IBS state that abdominal bloating occurs (119), and is the most bothersome symptom in a large proportion of the patients (120). Abdominal bloating increases in severity during the day, when eating and then settles overnight (119, 120). There is good evidence that intake of fermentable carbohydrates, FODMAPs, could increase the severity of bloating, but also loose stools in IBS subjects (121, 122). Avoidance of FODMAPs is therefore recommended in order to reduce symptom severity of bloating and other GI symptoms observed, and this recommendation is based on controlled clinical trials (123). However, available treatment trials have either used a standard or habitual diet as comparator, without the aim to improve symptoms with this comparative diet (96, 97), or used a non-randomized, non-blinded study design (64). This dietary regime requires specialist dietetic knowledge for successful compliance and detailed information on which food to avoid. The first 2-8 weeks the diet is proposed to be as strict as possible in order to achieve symptom relief, and thereafter a planned and systematic re-introduction of foods high in fermentable carbohydrates is recommended (64). In order to have an adequate dietary regime in the long run, it is considered essential to reintroduce foods containing FODMAPs to identify the carbohydrates that are tolerable on an individual basis and those that trigger symptoms. The reintroduction should include one FODMAP at a time during three days. If no symptoms occur with e.g. honey (fructose), a challenge with the next FODMAP during three days can be pursued. The method demands perseverance and careful planning together with a dedicated and well-informed supervisor, and so far no clinical trials demonstrating that this approach with reintroduction is effective and how this should be done exist. All clinical trials assessing the effect of low FODMAPs diet in IBS are 2-4 weeks. Moreover, FODMAPs, as well as resistant starch, are suggested to have positive physiological effects on

colonic health, which may lower disease risk just like prebiotics (124). Recent studies have shown that low FODMAPs diets have led to alterations in colonic luminal microenvironment (104, 125), which potentially may have negative health effects long-term, but this needs to be addressed in prospective follow-up studies. Therefore, health implications and functional significance of reduced intake of fermentable carbohydrates might lead to caution about reducing the intake of FODMAPs in the long term and the restriction of such carbohydrates only to the level of adequate symptom control is recommended.

One interesting approach that would reduce the need to follow a strict carbohydrate restricted diet in order to improve symptoms would be to administer an enzyme that could digest poorly digested carbohydrates, and thereby facilitate absorption in the small intestine. This approach is currently used for lactase deficiency, where lactase can be administered (100). α-galactosidase is an enzyme with amylase-like activity, which has been reported to be effective in reducing gas production and relieving gas-related symptoms after meals rich in incompletely absorbed carbohydrates (126-128). The enzyme is derived from the mold Aspergillus niger and can break down fructans and GOS in the small intestine before they are metabolized by colonic bacteria. By this mechanism α-galactosidase has the potential to facilitate the intestinal absorption and to minimize the bacterial gas production of these carbohydrates. This enzyme has been tested in healthy subjects and in children with IBS, with a reported reduction in GI symptoms, particularly gas-related complaints, when ingested in conjunction with meals (126-129). However, it is not yet established if α-galactosidase is efficient in alleviating GI symptoms in adult patients suffering from IBS.

1.6.2 Probiotics

The gut microflora can be an important part in the pathophysiology of IBS and a modulation of this environment may improve symptoms (130). There is emerging but conflicting evidence for the use of probiotics in IBS (131). Even though the overall effect is modest and probiotics are unlikely to be beneficial for all IBS patients, it seems as some probiotics are favorable in improving symptoms. However, the preferred probiotic strains, products, and regimen of use are not clear (132, 133).

1.6.3 Food elimination diets

Most patients with IBS have made alterations in their diets, which in some cases may be extreme. Food elimination diets have been used to identify food intolerance or allergy in individuals with IBS. However there are no standard diet describing which foods should be excluded, and this diet should only be tried when single food avoidance has not improved symptoms and when multiple food intolerance are suspected (111). Food elimination diets are time consuming for the patient and for the practitioner, as it usually take 3-4 months to complete, including re-introduction phase. The elimination diet requires a high degree of motivation and compliance (65, 134). Potentially offending foods can only be identified after elimination and subsequent reintroduction. A detailed review is required after completion of the elimination diet and food reintroduction phase to assess the nutritional adequacy of the diet. However, existing studies with elimination studies in IBS show conflicting results (65, 111, 135-138), and in current recommendations and narrative reviews on dietary advice in IBS, extensive elimination diets are not recommended (4, 57).

There is one study that have used a food elimination diet based on IgG antibodies to various foods in IBS patients with good results (134), but no study has reproduced these findings, and another study found no association between IgG to various foods and symptoms (139), so this approach is still controversial.

1.6.4 Other common dietary approaches

Other common dietary advice often includes reducing the intake of coffee and fat, despite the fact that randomized controlled studies supporting this are lacking (57). This is instead based on studies assessing physiological function in relation to these dietary components (78, 140), and to a lesser degree upon research examining the role of dietary components in the therapeutic management of IBS patients. Moreover, eating small, frequent meals, rather than large, infrequent meals are often recommended, which is also based on GI physiologic effects of larger versus smaller meals (79, 80). Another approach that is gaining popularity is to reduce the gluten content in the food, but as stated above, the evidence supporting this dietary approach in patients without celiac disease is controversial (108).

2 AIMS

The overall aim of this thesis was to acquire a better understanding of the nutrient intake in IBS patients and impact of food on IBS symptoms, in order to improve dietary advice given to patients suffering from this condition.

Paper I

To determine the nutrient intake in IBS patients in comparison with the general population, as well as evaluating if their nutrient intake meet nutrition recommendations.

Paper II

To determine which food groups and specific food items IBS patients report to cause GI symptoms, and to investigate the association with GI, extraintestinal and psychological symptoms, as well as with quality of life.

Paper III

To assess if the enzyme α-galactosidase is superior to placebo in reducing GI symptoms and intestinal gas production after ingestion of carbohydrate-rich meals in adult patients with IBS.

Paper IV

To compare the effects on IBS symptoms between a low FODMAPs diet and traditional dietary advice in patients with IBS.

3 PATIENTS AND METHODS

3.1 Patients

Papers I-II. We included patients with IBS according to the Rome III (5) criteria, who participated in treatment trials and in a study assessing the relative importance of different pathophysiological factors in IBS at the gastroenterology outpatient clinic at Sahlgrenska University Hospital. The patients completed questionnaires as part of the baseline evaluation in these trials. We excluded patients with other severe diseases that were likely to have an impact on nutrient intake and GI symptoms.

Paper III. IBS patients that previously had taken part in studies at the gastroenterology outpatient clinic at Sahlgrenska University Hospital were invited take part in this study. They were already diagnosed with IBS according to the Rome III criteria (5), and had specific complaints of frequent bloating, abdominal distension and/or flatulence determined by the Rome III Modular questionnaire (141) and the distension/bloating sub-score of the IBS Severity Scoring System (IBS-SSS) questionnaire (142).

Paper IV. We recruited IBS patients meeting the Rome III criteria (5) from the gastroenterology outpatient clinics at Sahlgrenska University hospital in Gothenburg, Karolinska University Hospital and Sabbatsbergs Hospital in Stockholm. In Gothenburg the patients were also recruited through advertisement in the local newspaper. We excluded patients with other severe diseases that were likely to have an impact on symptom generation, and also patients that already followed a diet excessively restricting certain nutrients.

3.2 Questionnaires

All patients completed questionnaires at different stages of the studies as specified below.

GI symptoms
In Papers I-IV the patients completed the IBS-SSS (Figure 1). This questionnaire assesses the severity of IBS symptoms during the previous ten days. The score ranges from 0 to 500. By using "cut-off values" the patients were divided into three groups; < 175 mild IBS; 175 – 300 moderate IBS; and > 300 severe IBS (142).

Figure 1. Schematic figure demonstrating the included items in IBS-SSS.
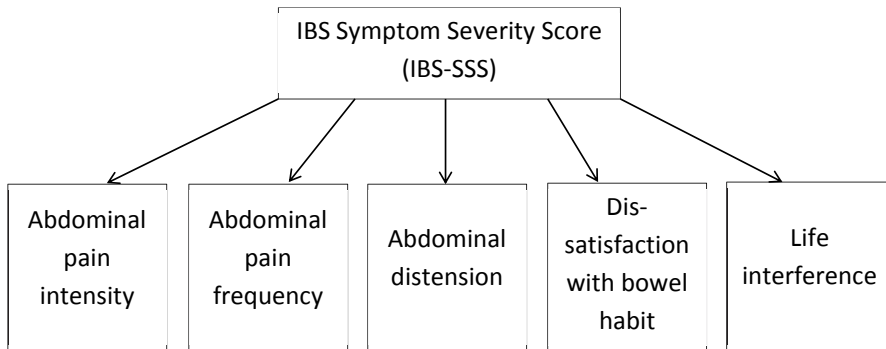
Moreover, in Paper III, a modified version of the IBS-SSS was completed in the morning, the day after each test day, in order to specifically assess the effects of the study medication. The modified questionnaire version included only the current experience of severity of abdominal pain, abdominal distension and dissatisfaction with bowel habits.

In Paper IV the patients recorded all bowel movements in a stool diary, based on BSF, the Bristol Stool Form scale (5), every day during the screening period, as well as during the intervention period. The stool frequency was recorded as number of stools per day and the BSF scale was used to assess the mean stool consistency. Information from the stool diaries were used to subtype IBS patients according to Rome III, (5), and to assess changes in stool frequency or consistency during the intervention period compared to baseline. This form had also been used in Paper I-II to subtype patients.

Meal−related GI symptoms

In Paper III, the severity of eight GI symptoms were rated (scores from 0 to 20) in a symptom-questionnaire; gas, bloating, abdominal discomfort, abdominal distension, nausea, stomach rumbling, urgency to have a bowel movement and abdominal pain. This questionnaire was completed each half-hour during test days (143).

Psychological and extraintestinal symptoms

In Papers I and II patients completed the Hospital Anxiety and Depression (HAD) scale to assess severity of general anxiety and depression, respectively (144). For the analyses in Paper I we used the HAD scale cut-off scores to define patients with and without clinically significant anxiety and depression (score ≥ 11).

In Papers II and IV, the Visceral Sensitivity Index (VSI) was used to measure GI symptom-specific anxiety (22, 145). Higher scores on both of these scales assessing general and GI-specific anxiety, and depression, indicate more severe symptoms.

In Paper IV, the Multidimensional Fatigue Inventory-20 (MFI-20) (146) was used to assess the severity of general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. A higher score indicates more severe fatigue.

Quality of Life

The Irritable Bowel Syndrome Quality of Life Questionnaire (IBSQOL) was used in Paper II to measure effects of IBS symptoms on quality of life, divided into nine dimensions (147). A low score implies poor quality of life.

Self-reported food intolerance

The patients in Paper II completed a questionnaire assessing the occurrence of symptoms from intake of 56 different food items or food groups, without any severity grading. This questionnaire is frequently used clinically at the department of allergology at Sahlgrenska university hospital as an assessment tool of food intolerance. The included food items or food groups were chosen to include relevant foods implicated in food allergy and intolerance (53, 148-150). The foods were grouped according to different potential underlying mechanisms/content responsible for symptom generation, such as foods containing incompletely absorbed carbohydrates, fat, biogenic amines, lectins, preservatives or having a potential to release histamine or to cross-react with airborne allergens (Figure 2). Only food items reported to cause GI symptoms were included in the analyses (Paper II). The results were used to assess the proportion of subjects reporting GI symptoms as well as the number of food items reported to cause GI symptoms in each individual as a measure of the degree of self-reported food intolerance.

Figure 2. Foods in the self-reported questionnaire responsible for symptom generation.
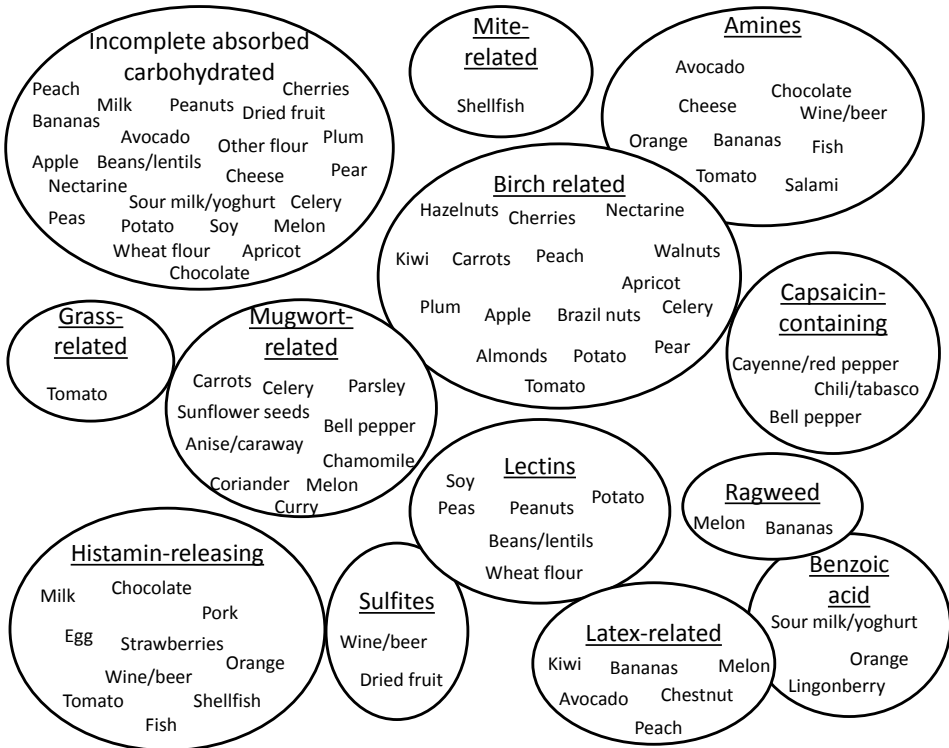
3.3 Dietary intake

Food records in IBS patients

Papers I and IV. The IBS subjects were given thorough instructions from a dietitian in order to accurately complete a food record. The dietary intake data was obtained for four days; 3 consecutive weekdays and one connected weekend day (Paper I) or Wednesday-Saturday (Paper IV). Patients were instructed to consume their usual diet, to enter time of the food intake, the specific food item, and to enter the amount in the food diary as accurately as possible (in grams or household measures). All food items and beverages were entered in the software Dietist.XP version 3.1 (Kostdata.se, Stockholm, Sweden), which converts food items into nutrients and energy amounts.

Composite foods were split into ingredients. From the 4-days food records, average daily intakes were calculated.

In Paper IV, a new Swedish database was used in addition to Dietist.XP, to assess the content of lactose, fructose, galacto-oligosaccharides, fructans and polyols (Liljebo et al. Manuscript in preparation).

Food records in the control group

Paper I. To assess the nutritional intake of the general population we used data from a national dietary survey, "Riksmaten", conducted in 1997-1998, where the participants had completed a pre-coded food diary with pre-printed alternatives for food items, and meal components. They had access to a portion-guide with food photographs to estimate amounts of food, together with amounts in household measures, pieces, etc. Analysis of the data from the food registration of the national dietary survey was performed using the software MATs, version 4.03 (Rudans Lättdata, Västerås, Sweden), which covers around 1700 foods and 48 nutrients.

3.4   Breath test

Paper III. The breath test is a non-invasive test that can detect hydrogen and methane gas produced by bacterial fermentation of unabsorbed carbohydrates that is excreted in the breath. Hydrogen is derived only from bacterial metabolism in the intestine, and methane is produced through consumption of hydrogen by methane-producing bacteria, methanogens (151, 152).

Samples of expired air were collected each half-hour during test days to assess the concentrations of hydrogen and methane in parts per million (ppm). All breath samples were end-expiratory and collected in a system used for the sampling and storing of alveolar air (GaSampler System, QuinTron Instrument Company, Milwaukee, WI, USA). Analysis was immediately done by use of a gas chromatograph (QuinTron Breath Tracker, QuinTron Instrument Company, Milwaukee, WI, USA).

3.5 Dietary interventions & assessment of treatment effect

Paper III. The participants arrived in the morning the test day and completed questionnaires. The patients were randomized to receive three capsules containing the digestive enzyme α-galactosidase (Nogasin®, Oy Verman, Kerava, Finland) or a corresponding placebo with identical capsule design before start of three study specific meals at both of the study days. Each capsule with the active enzyme had a total content of 400 galactosidic units (GaUI) where 1 GaUI equals the amount of enzyme that releases 1 μmol of galactose from the substrate in 1 min. The dose of the enzyme given at each meal during the active treatment day by consequence was 1200 GaUI. They were served a carbohydrate-rich breakfast and lunch together with enzyme or placebo (Table 3, Figures 3 and 4). Symptom registration (the meal-related GI symptoms questionnaire, see above) and breath samples were collected every half hour for 7.5 hour in all participants. In the evening at home the patients were instructed to eat a prefabricated dinner meal. Two weeks later the procedure was repeated, however, the content of the capsules was the opposite from the first visit. The patients completed the IBS-SSS questionnaire before breakfast each test day and also the modified IBS-SSS the morning after test day (before breakfast).

Table 3. The composition of the test meals.

Time	Food	Nutrients
Breakfast 8.00	Rye porridge, jam, lactose free- milk Wholemeal bread, margarine, cheese, bell pepper Apple juice	736 kcal 15.2 g protein 18.0 g fat 108.3 g carbohydrates
Lunch 11.30	Chicken and bean casserole (contents; beans, chickpeas, onion, garlic, tomato, chili, mushrooms, rape oil, black pepper, salt, stock cube, thyme) White bread (wheat), margarine, cheese Apple juice	697 kcal 52.0 g protein 19.1 g fat 73.0 g carbohydrates
Supper	Fish au gratin (prefabricated) Apple juice	780 kcal 50.1 g protein 22.5 g fat 90.1 g carbohydrates

Figure 3. Rye porridge breakfast.

Figure 4. Bean- and chicken casserole lunch. White bread (wheat), margarine, cheese and apple juice are missing in the picture.

Paper IV. Patients with IBS were randomized to receive dietary advice from a dietitian about one of two different diets: a low FODMAPs diet or traditional IBS dietary advice and to follow these diets for four weeks (Tables 4 and 5). The subjects were provided with both verbal and written instructions in the form of a pamphlet with detailed information of which foods to avoid and of alternative food items that could be ingested instead. The patients were blinded to the identity of the dietary advice (called "diet A" and diet B", respectively). Symptom severity was assessed using the IBS-SSS and patients completed a 4-days food diary during screening and during the last week of the intervention period. A responder to the intervention was defined as a patient who demonstrated a reduction of the total score of the questionnaire IBS-SSS ≥ 50 at the end of the treatment period (day 29) compared with baseline (day 0).

Table 4. A selection of instructions from the low-FODMAP diet ("Diet A").

Food to avoid	Suitable foods
High in fructans and/or GOS	
Cereal grains (wheat, rye, barley)	Rice, potato, oats, polenta, quinoa, buckwheat
Bread and pasta (white, wholemeal)	Wheat free or gluten-free bread and pasta
Beans and pulses	Green beans
Garlic and onions	Spring onion (green part), herbs
Nuts and seeds; cashew, pistachios	Peanuts, pecans, walnuts, sunflower seeds
High in polyols	
Apple*, pear*, nectarine, plum, prune	Banana, orange, kiwi, honeydew melon
Cauliflower, mushroom, sweet corn	Carrot, parsnip, cucumber, spinach, lettuce
Sugar-free products with sorbitol, xylitol, mannitol	Sugar, glucose syrup, dextrose
High in fructose	
Mango, apple*, pear*, watermelon, honey	Pineapple, strawberries, blueberry
High in lactose	
Milk, yoghurt, ice cream	Lactose free milk, yoghurt, ice cream
Food to limit	
Coffee, alcohol, carbonated drinks	Non-caffeinated drinks, water, non-fizzy drinks

*Some food items contain more than one type of FODMAP, i.e. apples and pears are rich in fructose as well as polyols.

Table 5. A summary of the traditional IBS diet ("Diet B").

Dietary advice
- Eat regular meals   - Do not skip meals or eat late at night   - Take your time when eating, chew your food well   - Limit fatty foods, spicy foods, onions, legumes, coffee and alcohol   - Avoid carbonated drinks, chewing gum and sugar-free products   - If constipated: increase the amount of dietary fibers as well as fluids.   - If diarrhea: limit intake of dietary fibers, berries are often better than fruits, cooked vegetables better than raw   - Continue eating probiotics, however, do not start eating probiotics during the study period

3.6 Research design

Papers I-II were retrospective studies which partially are based on the same study population (Table 6).

- In Paper I we assessed the nutrient intake of IBS patients in order to investigate if they had a different intake compared to the general population. We also investigated if the intake differed between subgroups of IBS patients based on IBS severity, presence of absence of depression or anxiety, and the IBS subtype based on the predominant bowel habit.

- In Paper II we evaluated the IBS patients' self-reported symptoms from different food items and food groups. In relation to these reported food-related GI symptoms we investigated how levels of anxiety and depression, severity of IBS and somatic symptoms and quality of life influenced the perceived food intolerance, measured as the number of food items reported to cause GI symptoms.

Papers III-IV were prospective studies (Table 6).

- In Paper III we performed a randomized, double-blind, placebo-controlled, cross-over study to assess if α-galactosidase alleviates symptoms after intake of carbohydrate-rich meals. The patients were served two

meals at site and one meal was ingested at home, together with capsules containing α-galactosidase or placebo.

- In Paper IV we performed a randomized, controlled, parallel, single-blind intervention trial where the participants were randomized to eat according to the low FODMAPs diet or to the traditional IBS dietary advice during four weeks. They completed several questionnaires during the screening period as well as during the intervention period to assess the effects of the dietary regimens on GI symptoms.

Table 6. Design and methods for the included studies.

	Paper I	Paper II	Paper III	Paper IV
Focus	Food intake in IBS patients in comparison to general population	Self-reported GI symptoms related to food intake	Impact from enzyme supplementation on food related GI symptoms	Effect of dietary advice on GI symptoms
Design	Retrospective Gender-age-matched Comparative Case-control Observational	Retrospective Cross-sectional Observational	Prospective Randomized Double-blind Crossover Placebo-controlled Interventional	Prospective Randomized Single-blind Parallel Controlled Multi-center Interventional
Data collection	Cases were retrieved from two previous studies and one ongoing. Controls were retrieved from a national dietary survey.	Participants in IBS studies aiming to explore pathophysiological factors in IBS.	IBS patients with specific gas-related symptoms were recruited from previously performed studies.	Subjects with IBS diagnosis were recruited from 3 Swedish gastroenterology units and through advertisement in local newspaper.
Questionnaires	IBS-SSS HAD Food Diary	Self-reported food intolerance HAD VSI IBS-SSS PHQ-15 IBSQOL	IBS-SSS Modified IBS-SSS Meal-related GI symptoms questionnaire.	IBS-SSS BSF HAD VSI MFI-20 PHQ-15 Food Diary

3.7 Statistics

Papers I-IV. Descriptive data were presented as proportions for categorical variables and as mean values ± SD for the continuous ones, except for figures in Paper II, where box-and-whisker plots without extreme values and outliers were used.

Papers I-II, IV. Differences in continuous variables between patients with IBS and the general population and between the two IBS severity groups were made using independent-samples Student's t-tests. The comparisons among the different IBS groups were performed using ANOVA and if group differences were detected, post hoc testing using Bonferroni correction was done. For correlation analyses between questionnaires in Paper II, Pearson's product – moment correlation coefficient was used.

Paper III. Data were analyzed using linear mixed models implemented using the mixed procedure in SAS 9.4 software (SAS Institute, Cary, NC, USA). To test the response to the first two meals, the first 16 time points (up to 450 minutes) were used. For the analysis, the first time point (0 minutes) served as the pre-meal baseline time point (reference category). Different models were estimated for each symptom as well as hydrogen and methane as the dependent variables. Drug and time were entered as categorical within-subject independent variables. Main effects as well as the drug*time interaction effect were included in the model. The Kronecker product of an unstructured (drug) and first-order autoregressive (time) variance-covariance matrix was used to model the data as this provided the best fit based on the minimization of Akaike's Information Criterion (AIC). To test our hypothesis of a differential symptom or breath test hydrogen response to the meal for active drug versus placebo, the drug*time interaction effect was followed by a planned contrast comparing the difference between the average of all post-meal time points and the pre-meal baseline time point between active drug and placebo. Since this study was testing a hypothesis where the potential treatment effect was uncertain, no formal power calculation was done.

Paper IV. The primary endpoint in this trial was the change in IBS-SSS at the end of the treatment period relative to baseline, and the proportion of responders to the dietary intervention based on the recommended cut-off of a reduction (=improvement) in IBS-SSS ≥ 50. To plan our sample size, we performed a power calculation based on the ability to detect a difference between the two diets in reduction of IBS-SSS of at least 50 with 80 % power at α=0.05, assuming a SD of 70, and this indicated that we would need at least 31 patients in each group. In order to have at least 62 evaluable patients, we planned to randomize at least 70 patients.

As secondary endpoints we analyzed the effect of the dietary interventions on the individual items of IBS-SSS, as well as on bowel habits measured by stool diaries. Moreover, the adherence to the dietary advice was assessed by comparing dietary intake at baseline with the last week of the intervention period within and between the treatment groups. Potential baseline predictors for being a responder (IBS-SSS reduction ≥50 at the end of the intervention period) were also evaluated by comparing baseline variables, i.e. questionnaire data, demographics, IBS characteristics and dietary intake between responders and non-responders in the treatment groups. Categorical variables were compared with chi-square test, whereas continuous variables were compared with independent -samples and paired -samples t-tests, after the normality of the distribution had been demonstrated with Kolmogorov-Smirnoff statistic, and with histograms of the data. All patients who were randomized and who received dietary instructions were included in the responder comparisons, where drop-outs were considered to be non-responders (intention to treat analysis), whereas for comparisons of questionnaire data at the end of the intervention period vs. baseline, only patients who completed the intervention are included (per protocol analysis).

In all studies two tailed P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS statistical package, version 19.0 (SPSS Inc., Chicago, IL, USA), in all papers, except for Paper III.

4 MAIN RESULTS

4.1 Patients

Table 7 shows the baseline characteristics of the included participants in
Papers I-IV.

Table 7. Characteristics of the included participants in each paper.

	Paper 1		Paper II	Paper III	Paper IV	
	IBS patients n=187	Controls n=374	IBS patients n=197	IBS patients n=20	Low FODMAPs diet n=38	Traditional IBS diet n=37
Females, n	139	278	142	19	30	31
Mean age, years	40	40	35	49	44	41
Age range, years	19-70	19-70	18 – 72	22-75	18-69	18-68
Predominant bowel habit						
IBS-C, n	55	-	46	-	9	13
IBS-D, n	62	-	86	-	10	8
IBS-nonCnonD, n	70*	-	65	-	19	16
IBS-SSS						
Mild-moderate, n	94	-	79	3	15	18
Severe, n	92	-	117	17	23	19
HAD						
Anxiety, mean ± SD	6.4 ± 4.4	-	8.4 ± 4.5	8.0 ± 4.5	8.2 ± 4.5	7.0 ± 4.3
Depression, mean ± SD	3.6 ± 3.6	-	5.1 ± 3.6	5.0 ± 3.8	5.1 ± 3.8	3.8 ± 2.9
VSI, mean ± SD	-	-	47.0 ± 15.8	41.9 ± 16.3	40.6 ± 12.6	41.8 ± 16.7
PHQ-15						
No/mild, n	-	-	56	5	10	12
Moderate, n	-	-	76	9	18	13
Severe, n	-	-	64	6	9	12

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-nonCnonD, IBS non constipation non diarrhea;
IBS-SSS, IBS-Severity Scoring System; HAD, Hospital Anxiety and Depression scale; VSI, Visceral Sensitivity
Index (GI-specific anxiety); PHQ-15, Patient Health Questionnaire-15 (Somatic Symptom Severity).
* Subgrouping based on the predominant bowel habit missing in five patients in Paper I.

4.2 Paper I. Nutrient intake in IBS

In this study we included 187 subjects with IBS according to the Rome III criteria and 374 age- and gender matched controls from a national dietary survey (153).

The IBS patients reported higher intake of protein and dietary fibers than controls, but otherwise no significant differences in intake of energy and macronutrients were noted. The distribution of energy between protein, fat and alcohol were consistent with the Nordic Nutrient Recommendations 2004 (NNR 2004) (154), but not for the carbohydrate and the dietary fiber intake, which were lower than recommended in both IBS patients and in controls (Table 8). No differences in energy intake or intake of macronutrients were seen between subgroups of IBS patients, based on IBS symptom severity, presence or absence of anxiety or depression, or the predominant bowel habit.

Table 8. Intake of energy and macronutrients in subjects in Paper I, comparison made between IBS patients and an age-and gender-matched group from the general population (controls).

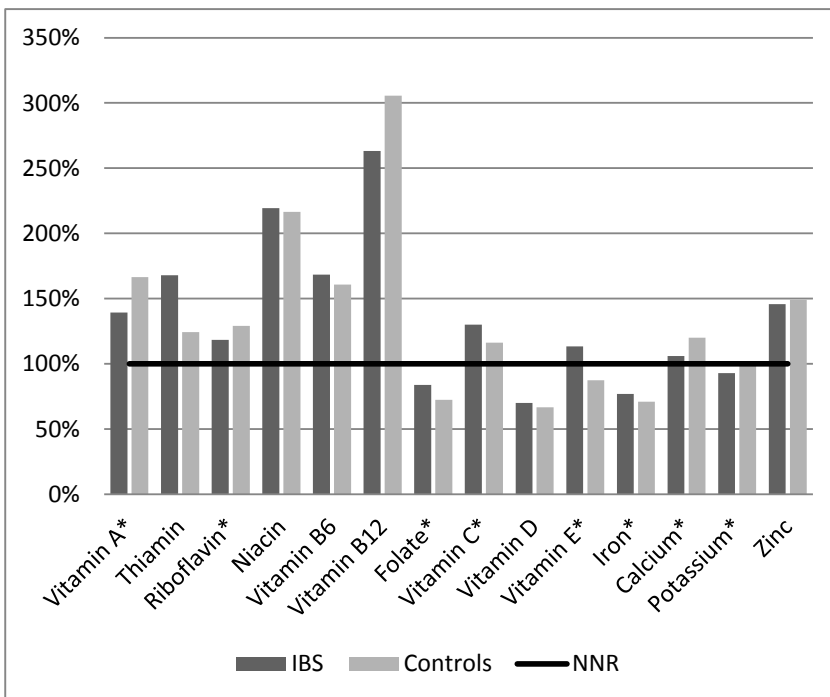| Paper I				
Energy and macronutrients	Recommended intake according to NNR 2004	IBS patients (n=187)	Controls (n=374)	p-value
Energy (kcal ± SD)	-	2037 ± 541	1973 ± 513	0.17
Protein (E% ± SD)	10-20	17 ± 3	16 ± 2	0.007
Fat (E% ± SD)	25-35	35 ± 7	34 ± 5	0.17
Carbohydrates (E % ± SD)	50-60	47 ± 8	47 ± 5	0.64
Dietary fibers (g/MJ* ± SD)	3	2.2 ± 0.7	2.0 ± 0.6	<0.001
Alcohol (E% ± SD)	<5	2.6 ± 3.2	3.1 ± 3.5	0.10

The recommended intake (RI) is shown for women in the ages 31-60 years (as 74 % of the subjects were females and the mean age for the studied population was 40 years of age).
*1 MJ ≈240 kcal

When comparing the intake of vitamins and minerals between IBS patients and controls, the IBS patients reported lower intake of vitamin A, riboflavin, calcium, and potassium, and a higher intake of folate, vitamin C, vitamin E, and iron than the age- and gender-matched controls from the national survey.

The mean intake of vitamins and minerals in IBS patients and control subjects were above the average requirements according to NNR 2004. However, when compared to the recommended intake (RI) according to NNR 2004, *both* patients and controls reported intake of folate, vitamin D, and iron that were below the recommendations, whereas controls only had an intake below RI for vitamin E and the IBS population had a lower intake than RI for potassium (Figure 5). No differences in micronutrient intakes between subgroups of IBS patients, based on IBS symptom severity, presence or absence of anxiety or depression, or the predominant bowel habit were seen.

Figure 5. Nutrient intake in IBS patients vs. the controls, in comparison with recommended intake according to NNR 2004.
* p<0.05 IBS vs. controls.

4.3 Paper II. Food-related GI symptoms in IBS

We included 197 IBS patients (Rome III) in this study. In all, 84 % of the patients reported at least one food item to cause GI symptoms. The proportion of subjects that reported GI symptoms related to the different food groups are displayed in Table 9. On average, patients reported GI symptoms from 7.8 ± 8.3 (range 0-54) food items.

Table 9. Food groups/constituents and related food items in Paper II and the proportion of patients reporting GI symptoms related to the different food groups.

Food groups	Foods reported to cause GI symptoms	% patients reporting GI symptoms
Incompletely absorbed carbohydrates	Peach, cherries, plum, potato, pear, apple, apricot, nectarine, soy, peas, beans/lentils, peanuts, wheat flour, other flour (most commonly rye), milk, sour milk/yoghurt, cheese, chocolate, celery, melon, bananas, avocado, or dried fruit	70 %
Histamine-releasing	Egg, fish, tomato, shellfish, strawberries, orange, wine/beer	68 %
Biogenic amines	Cheese, fish, salami, tomato, chocolate, orange, wine/beer, bananas, avocado	58 %
Benzoic acid and sulfites	Sour milk/yoghurt, tomato, orange, lingonberry, wine/beer, dried fruit	56 %
Fried and fatty foods	No food items were defined	52 %
Lectin-containing	Potato, soy, peas, beans/lentils, peanuts, wheat flour	49 %
Capsaicin-containing	Cayenne/red pepper, chili/tabasco, bell pepper	42 %

Patients that reported a higher number of food items causing GI symptoms, (as an indirect measure of more severe self-reported food intolerance) had more severe IBS symptoms (IBS-SSS; p=0.004) and more severe somatic symptoms in general (PHQ-15; p=0.03). However, there were no correlations between self-reported food intolerance (number of food items reported to cause GI symptoms) and anxiety, depression, GI-specific anxiety, body mass index or age. Women tended to report more food items responsible for their GI symptoms than men (p=0.06). IBS subtype based on the predominant bowel habit was not associated with number of food items causing symptoms. Lower quality of life in the IBSQOL domains sleep, energy, diet, social functioning, and physical status were significantly associated with a higher number of food items reported to cause GI symptoms.

4.4 Paper III. Symptoms after carbohydrate–rich meals in IBS: The effect of enzyme supplementation

Twenty IBS patients (Rome III; 19 females) with bloating as a predominant symptom started and completed this randomized, double-blind, placebo-controlled cross-over study where the effect of α-galactosidase (Nogasin®) on GI symptoms after intake of carbohydrate-rich meals was assessed (Figure 6).

Figure 6. Flow chart demonstrating the number of patients in the different phases of the study.
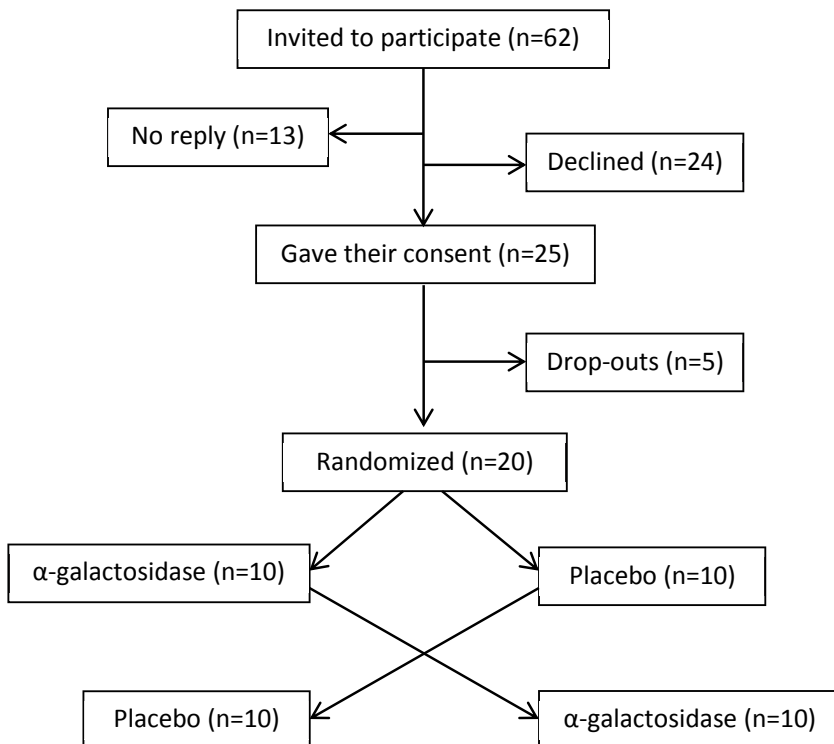
The patients reported increasing severity of meal-related GI symptoms after the test meals, and significant effects of time were found for symptom ratings of gas, bloating, discomfort, distension, urgency to have a defecation, and abdominal pain (Figure 7 and 8). However, symptom ratings were not different between the test days when α-galactosidase (Figure 7) or placebo (Figure 8) was ingested before the meals.

Furthermore, no significant differences were found between α-galactosidase or placebo for any of the GI symptoms assessed the day after the test days.

A significant effect of time was found for both hydrogen ($F=6.2$, $p<0.0001$) and methane ($F=1.7$, $p=0.044$) concentrations in breath tests from baseline, but these changes in hydrogen and methane concentrations did not differ between α-galactosidase or placebo (Figure 9).

Figure 7. GI symptoms (mean values) during the test day with α-galactosidase. The arrows represent the time points for intake of the carbohydrate-rich meals.
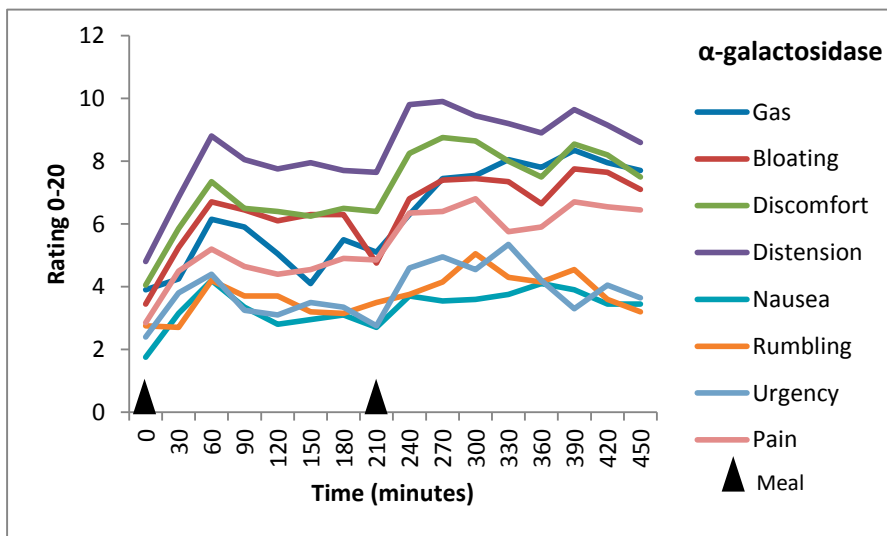
Figure 8. GI symptoms (mean values) during the test day with placebo. The arrows represent the time points for intake of the carbohydrate-rich meals.
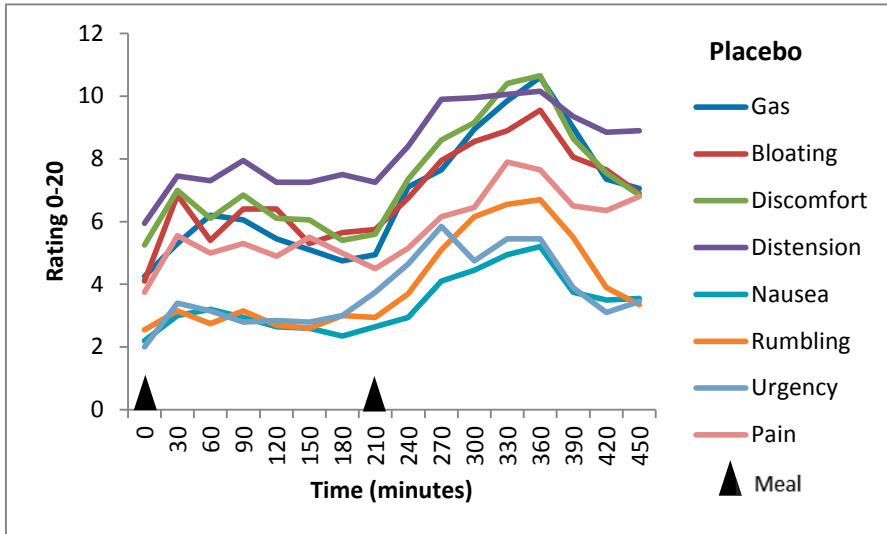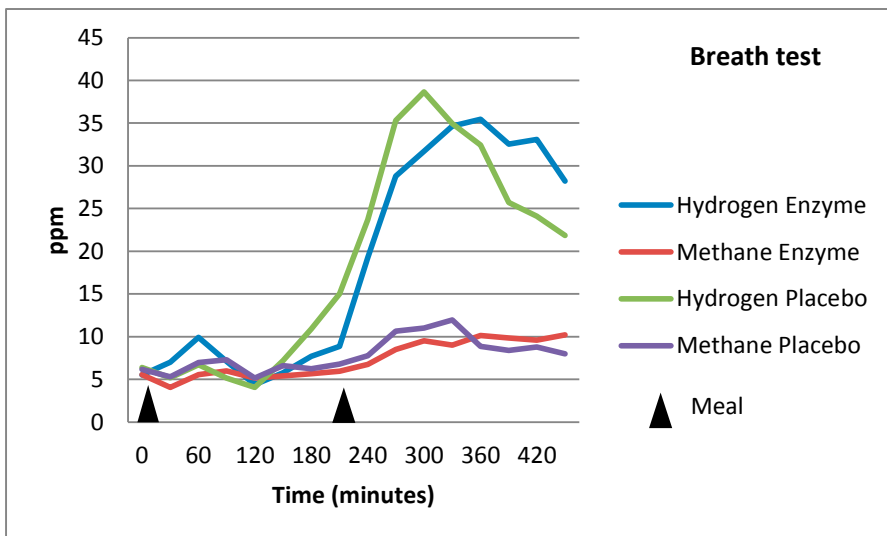

Figure 9. Hydrogen and methane in expired air (mean values) during test days with intake of α-galactosidase (enzyme) or placebo, respectively.

4.5 Paper IV. Low FODMAPs diet vs. traditional dietary advice in IBS

In this randomized, controlled, single-blind, parallel group study we screened 84 patients with IBS according to Rome III criteria. Seventy-five patients were randomized to follow one of the two diets, and 67 patients completed the dietary intervention (Figure 10).

Figure 10. Flow chart demonstrating the number of patients in the different phases of the study.
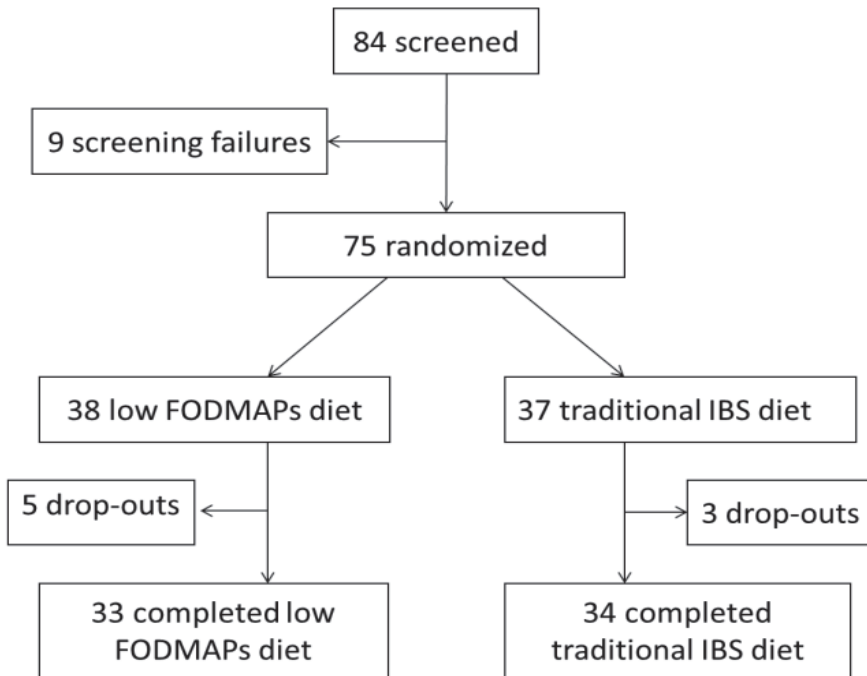
The IBS symptom severity was reduced in both dietary intervention groups at the end of the study period compared to baseline, without any differences between the groups (p=0.72) (Figure 11). In line with this, the responder rate (IBS-SSS reduction ≥50 at the end of the treatment relative to baseline) was similar in both groups (Figure 12). When assessing the effect of the

interventions on the individual items of the IBS-SSS score, all items were improved in both groups at day 29 relative to baseline, and this reached statistical significance for some of the items (Figures 13 and 14).

Figure 11. Comparison between baseline and at week 4 for severity scores (IBS-SSS) in the low FODMAPs diet group and the traditional IBS diet group.
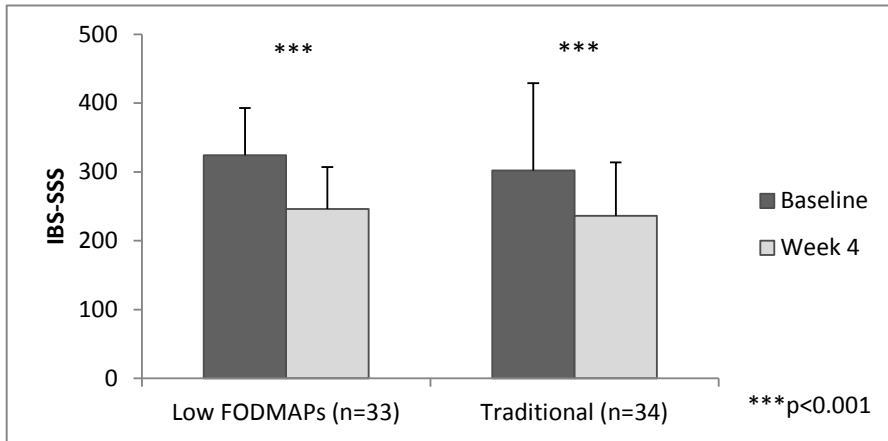
Figure 12. Responder rate at the end of treatment compared to baseline according to IBS-SSS reduction.
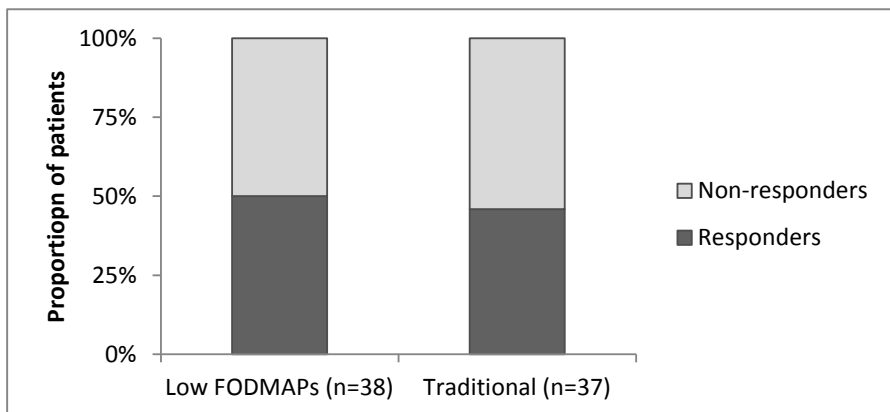
Figure 13. Ratings of the individual items of the IBS-SSS score in low FODMAPs diet.
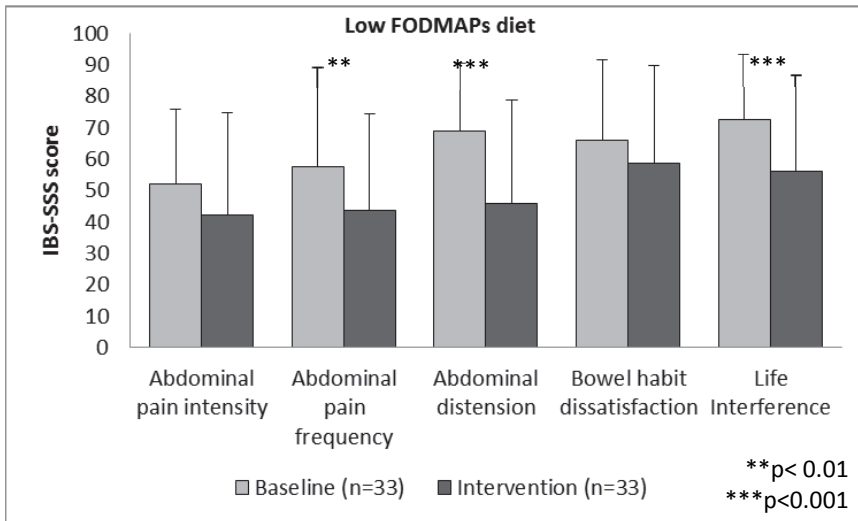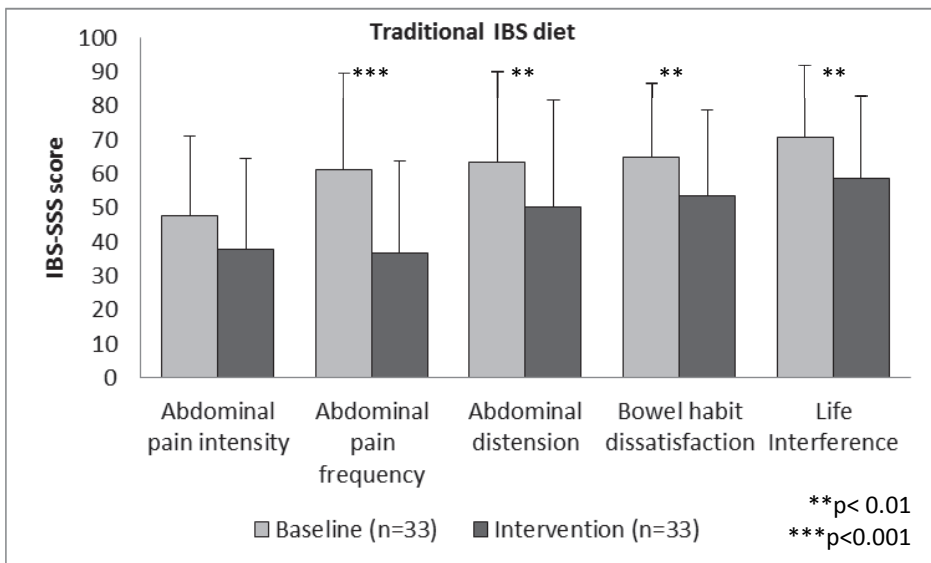

Figure 14. Ratings of the individual items of the IBS-SSS score in the traditional IBS diet.

When comparing responders and non-responders in the two treatment groups, lower intake of FODMAPs at baseline (p=0.01), being older (p=0.05) and female (p=0.02) were associated with a positive response to the low FODMAPs group, whereas having non-constipated IBS (p=0.02) was associated with a positive response to the traditional IBS diet.

At baseline both groups in Paper IV had similar intake of nutrients, including the intake of FODMAPs. However, during the last week of the intervention period, clear changes in the dietary intake were noted, both within the groups and between the groups. Most notably, the low FODMAPs group reduced their intake of FODMAPs, which was not the case in the traditional IBS diet group, indicating good adherence to the dietary advice. Unexpectedly, both groups substantially reduced their energy intake during the dietary intervention. We therefore compared the participants' intake at the end of the intervention period to the Nordic Nutrition Recommendation 2012. Both groups reached the recommendations except for energy intake and intake of carbohydrates and dietary fibers which were low in both diet groups. The intake of carbohydrates and dietary fibers were significantly lower in the low FODMAPs group (Table 10).

Table 10. Intake of energy and macronutrients during the dietary interventions in relation to recent Nordic Nutrition Recommendations (NNR 2012).

Energy and macronutrients	Recommendations according NNR 2012	Low FODMAPs diet during intervention (n=33)	Traditional IBS diet during intervention (n=33)	p-value between diets
Energy (MJ)	2250[1]	1658	1889	0.03
Protein (E%)	10-20	18	16	0.67
Fat (E%)	25-40	37	37	0.11
Carbohydrates (E%)	45-60	38	41	0.007
Dietary fibers (g/MJ)	3	2.2	2.6	0.003
Alcohol (E%)	<5	4	3	0.005

[1] Required energy= calculated the mean resting energy expenditure (155) based on age, sex and weight and multiplied with the average Physical Activity Level in the Nordic countries (PAL=1.6)
*1 MJ ≈240 kcal

5 DISCUSSION

In the present thesis we have demonstrated that food is a central issue in the management of patients with IBS. In line with previous studies, we demonstrated that food-related GI symptoms in patients with IBS are very common; in fact the vast majority reported at least one food item that they consider to cause GI symptoms. Despite this, patients suffering from IBS do not seem to have a greater risk than the general population to develop nutrient deficiency and as a group they have a sufficient general nutrient intake. IBS patients often experience GI symptoms in relation to food intake and this self-reported food intolerance was demonstrated to be associated with more severe symptoms in general and with reduced quality of life. Many different food items from various food groups were reported to influence symptom generation in IBS patients, such as fatty/fried foods, histamine releasing foods, foods containing preservatives, foods rich in biogenic amines, and especially food rich in incompletely absorbed carbohydrates. Unfortunately, a simple approach to use a capsule with an enzyme, α-galactosidase, that can digest carbohydrates and thereby facilitate their uptake and reduce fermentation of non-digestible carbohydrates, do not seem to alleviate symptoms related to food-intake with high amounts of incompletely absorbed carbohydrates. However, in the last paper in this thesis we demonstrated that providing IBS patients with dietary advice seem to be a good way to reduce GI symptoms, but that the recently developed low FODMAPs diet do not seem to be superior to traditional IBS dietary advice.

5.1 Subjects

When performing clinical research in general, it is important to have representative patient samples, or at least to be aware of which part of a certain disease population that you are studying. This is of relevance for the interpretation of the data and for the generalizability of results, and later for the potential implementation in clinical practice. In IBS studies performed at a specialized university-based clinic, selection bias is an obvious risk, as the majority of IBS patients are managed in primary care. Moreover, food and nutrition studies also *per se* carry a risk of selection bias, as patients who are more interested in food may be more willing to participate in such studies.

In Papers I and II IBS patients were retrieved from treatment studies (156, 157) and a pathophysiology study (31, 38) at the gastroenterology unit at Sahlgrenska University Hospital, where questionnaires used in these studies as part of the baseline assessment, were evaluated in the current papers.

These studies were multifactorial and had not food intake as a major focus which reduces the number of participants with special interest of food and therefore hopefully capture a mixed IBS population, even though the study was performed in a secondary/tertiary care setting. Moreover, at our dedicated unit with a special interest in functional GI disorders we accept all referrals for IBS, including self-referrals, which in previous publications on IBS have attracted a comparably representative IBS population with active problems (22, 30, 158). Therefore, for the purpose of these studies, i.e. to study food-related GI symptoms and nutrient intake in patients with current IBS symptoms, we believe that our recruitment approach was valid, and that we reached a fairly representative IBS population with active symptoms.

In Paper III, our aim was to reach an IBS population with symptoms related to incompletely absorbed carbohydrates. Bloating, abdominal distension and other gas-related symptoms are prominent symptoms in relation to these food constituents (121, 122). Therefore, patients were recruited based on reports of gas-related symptoms in previous studies at our unit. However, several patients were reluctant to undergo the study mainly due to the two full day visits at the hospital, which meant that the patients had to take time off from work and also to eat foods regarded as being symptom triggers, which may have introduced a negative selection bias, and potentially excluded patients with prominent gas-related symptoms due to incompletely absorbed carbohydrates.

In Paper IV, the participants were recruited from the gastroenterology outpatient clinics at three hospitals, and through advertisement in a local newspaper. During the recruitment phase several of the participants expressed their interest in food and their conviction of its importance in symptom generation in IBS, which was good for the commitment, required for the intervention, but may have introduced a selection bias. However, dietary interventions are only possible in patients with an interest in changing their diet, which therefore has to be the target group in such studies.

Taken together, our study populations seem to be relevant for the research questions in the present thesis, even though we cannot generalize all findings to all subjects with IBS in the community.

5.2 Dietary assessment

As mentioned in the background, different ways of assessing nutrient intake are available, and all of these have potential problems (43). A food diary was used in Paper I and Paper IV. Underreporting of energy intake is common in dietary assessments which also imply underreporting of most nutrients (159-163). Nutrient intake data are not absolute values as they are based on reported food consumption, which have a considerable error margin (164). In order to find out whether the intake of a particular nutrient is adequate, biochemical measurements and thorough individual dietary assessments are necessary (164), which were not done in the current papers. In our studies we used food diaries that are not affected by systematic errors to the same degree as e.g. FFQ. A food diary has the advantage to capture detailed information about food intake for a short period of time. On the other hand, reactivity bias can be a problem as patients may change their eating behavior or their habitual food choices as a consequence of the recording in real time (43). A possible way to reduce this bias may be to limit the number of days to register food intake. In our study we used four days, which we consider to be a reasonable compromise between capturing day-to-day variability in food intake, and putting too much burden on the subject.

In our studies, comparisons with nutrient intake was done with either 'average requirements' (AR) in Paper I, and in the thesis a comparison was made for data in Paper IV with 'recommended intake' (RI). The term AR is used to define the intake of a nutrient that represents the *average* requirements for a defined group of individuals. RI of certain nutrients is used in planning diets for groups (164) and includes a *safety margin* of two standard deviations or more, i.e. the amount of nutrient that can meet the known requirement among *practically all* healthy individuals.

5.3 Dietary intake

In Paper I we investigated if the nutrient intake in patients with IBS differed from the general population in Sweden. The overall intake was similar, which was somewhat surprising to us, as it is well known based on clinical experience that patients often complain of the adverse effects of various food items on GI symptoms, and many patients exclude different food items from their diet (165). One possible explanation for these seemingly discrepant findings can be that IBS patients shift their intake from foods considered to cause symptoms to a larger intake of less offending food items. This will

yield a limited variety of food items in the diet, but without necessarily affecting nutrient composition or energy intake. Our finding with normal nutrient intake in IBS patients as a group is in line with some (68, 166-168), but not all (169, 170) previous studies on this topic. Different methods of assessment of nutrient intake, different study populations, as well as regional differences may explain the discrepancy between studies.

In order to minimize investigator bias, the analyses of the food diaries in Papers I and IV were done after all data were collected, with only the patients' study number printed on the diary in order to minimize impact from personal opinions or preconceptions of the included patients.

In Paper IV we used the food diaries to detect (expected) nutritional alterations due to the dietary advice, i.e. partly as a "quality control". The low FODMAPs group significantly lowered their intake of FODMAPs as intended, which was the case in both responders and non-responders to this intervention. On the other hand, the patients who followed the traditional IBS dietary advice did not reduce their intake of FODMAPs. An unwanted finding in this study was the considerable decrease in energy intake in both the low FODMAPs group and in the traditional IBS diet group during the intervention period. This decrease implicate that patients eliminate food items from their diet but do not replace them appropriately with adequate amounts of alternative foods, which in the long run may lead to involuntary weight loss and development of nutrient deficiency. This unexpected and unwanted finding highlights the importance of monitoring nutrient intake when dietary advice is given to patients.

5.4 Self–reported food–related GI symptoms

More than 80 % of patients in Paper II reported GI symptoms related to food intake, which is even higher than in previous studies (46-48). This may partly be due to the fact that we included a larger number of food items in our questionnaire than in some of the previous studies – reporting only one of these as being related to GI symptoms was enough to include the patient in the group with self-reported food intolerance. However, regardless of what the correct proportion of patients reporting an association between food and symptoms is, it can be concluded that food-related GI symptoms are very common in IBS. Moreover, our study also demonstrated that self-reported

food intolerance was associated with a certain clinical phenotype within the IBS population with more severe symptoms and reduced quality of life.

Foods do not only consist of energy and nutrients but also different food constituents with possible effects on symptoms. In Paper II we explored potential associations between some of these constituents and the reported symptoms from foods containing these. Fatty/fried food are one food group that was reported to be associated with GI symptoms in this study, as 52 % reported GI symptoms from this food group. Fat intake enhances the gastrocolonic response and increase visceral sensitivity in IBS patients (171, 172), but also increase gas retention (85), so different mechanisms may explain this association. Incompletely absorbed carbohydrates (or FODMAPs) were also frequently reported to be associated with GI symptoms, which makes it logical to advice patients to reduce dietary intake of FODMAPS. There were also some new associations proposed in our study, which should be considered more as hypothesis generating proposals, such as the associations between GI symptoms and foods rich in biogenic amines, foods containing preservatives, capsaicin- and lectin-containing foods, and foods considered to be histamine-releasing.

Almost all foods included in our questionnaire contributed to some self-reported GI symptoms, and of course it is making it too easy to say that these constituents are the sole explanation of symptom generation. It is most likely a combination of many different aspects of food that causes symptoms; energy content, volume of meal, content of fat, incompletely absorbed carbohydrates, dietary fibers, histamine-releasing properties of foods, contents of lectins, biogenic amines, capsaicin, and preservatives etc. All of these have probable individual effects on the GI tract and food rarely only consist of one single item, but is a combination of several food items in connection with mental state, coping strategies, childhood, heritage, what you ate yesterday and so forth. The biopsychosocial model proposed to be of relevance for IBS (173) in general, can probably also be applied to the effects of food on GI symptom generation in IBS.

5.5   Effect of α–galactosidase on GI symptoms

An appealing method to reduce symptoms would be to take a pill together with offending foods in order to eliminate food-related symptoms such as bloating, abdominal distension and flatulence. Unfortunately, we could not find evidence for an effective alleviation of GI symptoms with capsules containing the enzyme α-galactosidase administered in combination with meals rich in incompletely absorbed carbohydrates. This is at odds with some

previous trials (126-129), but these were not performed in adults with IBS. Moreover, our study design only made it possible to study the effect of the enzyme during one day. A cumulative effect may be possible if the enzyme is ingested daily for several days, but this remains to be proven. Moreover, the enzyme has effect only on incompletely absorbed carbohydrates, and more specifically certain oligosaccharides. Negative effects from other food constituents are not affected by this enzyme.

5.6   Dietary advice in IBS

In Paper IV we demonstrated that dietary advice lead to reduced IBS symptoms over four weeks. However, we could not demonstrate that the very popular and frequently advocated low FODMAPs diet was better than traditional IBS dietary advice. This may seem to be at odds with recent evidence from clinical trials (64, 96, 97, 123), but previous studies have not had an active comparator, or have used a non-randomized trial design. Therefore, our trial is the first study comparing a low FODMAPs diet with an active comparator in a randomized, single-blinded design. Our interpretation of the study results is that there probably are elements in both diets that are beneficial, and we propose that future studies try to combine elements from both diets in dietary advice to IBS patients.

Moreover, recent evidence suggests that there may be adverse effects of a low FODMAPs diet on the gut microbiota composition (97, 104). Therefore strict use of this diet should probably only be used short term to eliminate current symptoms and only exceptionally as a continuous long term dietary change (104). Besides, it is imperative that this elimination is under supervision from a dietitian (or another person with good knowledge about FODMAPs). Currently, a strict FODMAPs exclusion diet should not last more than 2-8 weeks, based on the potential adverse effects on microbiota composition in the colon, and as no long-term studies are available. A gradual reintroduction of FODMAPs is advocated, but how this should be done and the effectiveness of such an approach has not yet been studied (93, 123). Further, a low FODMAPs diet should be completely avoided in asymptomatic persons. FODMAPs stimulate the growth of the beneficial bifidobacteria (97) and are also substrate for bacteria to promote production of short-chain fatty acids. These fatty acids have positive effect on the immune system and are the most important source of energy to the colonic epithelial cells and may be protective for cancer development in the colon (174) .

For future dietary intervention trials in IBS, we consider that it is important to individually assess the nutrient intake, as it is common that IBS sufferers alter their food intake to control symptom intensity and frequency (66). It could be useful to determine the IBS patients' total energy intake, if they have large intake of certain possibly offending foods such as fatty foods, coffee, spices, or incompletely absorbed carbohydrates (in e.g. onion, beans, and apples), and of course to assess the intake of micronutrients and look for a potential risk of developing deficiencies. It is necessary to establish a partnership between the patient and the practitioner to come up with individual solutions to avoid irregular eating habits, unfavorable cooking methods and symptom generating choices of food items. It is imperative to listen to the patients' narratives about their experiences and perceived symptoms to different foods to adequately be able to optimize treatment routines. An individualized dietary treatment approach for IBS should be tested in prospective trials.

6 CONCLUSION

The present thesis has shown that in spite of food-related GI symptoms being reported by the majority of IBS patients, as a group they generally have an adequate nutrient intake. Moreover, the self-reported food intolerance that was seen in 84 % of our IBS patients was associated with more severe symptoms in general, which makes dietary adjustments an attractive therapeutic approach. However, as the food items reported to cause GI symptoms differ between individuals it seems essential to assess nutrient intake on an individual basis, and to investigate which food items the patient consider to cause symptoms in order to optimize personalized dietary advice. We investigated different approaches to influence negative effects of dietary constituents, and we did not find any evidence in support of a clinically beneficial effect of the enzyme α-galactosidase in IBS, but dietary advice seem to be an efficient tool to reduce symptoms. Specifically, both the traditional IBS dietary advice and the recent development of a low FODMAPs diet reduced symptom severity, and future studies should investigate if elements from these diets can be combined in dietary advice to patients with IBS.

7 FUTURE PERSPECTIVES

Future studies should focus on developing more accurate ways to record food intake that are simple and applicable both for the patients as well as for investigators. It would also be preferable to study eating behavior in IBS in greater detail, i.e. where, how, when and why?

Identify patients with IBS with poor nutrient intake, and investigate the symptom patterns and response to dietary interventions in this group of patients.

The effects of food constituents on GI symptoms in IBS need to be examined further through challenge tests in prospective studies.

Future studies should aim at further improving strategies for providing dietary advice to patients with IBS, potentially combining elements from different strategies and ideally customize dietary advice for different patient populations.

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