FACULTY OF MEDICINE AND HEALTH SCIENCES

The long-term effect and adherence of a low FODMAP diet in patients with IBS.

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ABSTRACT

Background and aim of study: Short-term trials with low FODMAP diet (LFD) have shown promising results in the symptomatic management of Irritable bowel syndrome (IBS). The LFD is an intensive diet consisting of three phases. In the first phase, all food that contains fermentable oligosaccharides, disaccharides, monosaccharides and/or polyols (FODMAPs) are eliminated in the diet. This restriction phase is followed by a reintroduction phase and stabilisation phase. Data on long-term effects of the diet on IBS and long-term adherence are lacking. This study aims to investigate the adherence and satisfaction with the diet and the long-term quality of life and symptom control in patients with IBS referred to a dietician in a tertiary care centre.

Methods: All patients, diagnosed with IBS by a gastroenterologist and referred between January 2014 and March 2016 for dietary advice and education concerning the LFD by an experienced dietician in the UZ Gent, are invited to participate in the study. Informed consent is acquired from all study participants, or their legal guardians, before participating in the study. The questionnaires are sent by email or regular mail and include the IBS-QOL questionnaire developed by Drossman et al. and a self-made questionnaire examining long-term adherence and satisfaction to the LFD, difficulties in application of the diet, disease course and IBS symptoms. Electronic data files of the participants are consulted following informed consent. Gender, age, IBS-subtype, number of dietary consultations and presence of abdominal bloating and flatulence at the moment of referring of the patient to the dietician for LFD are included in the data file. Statistical analysis is done using SPSS statistics 24 (SPSS Inc. Chicago IL, USA). The study was approved by the Ethical Committee of the UZ Gent (Belgian Registration numbers B670201629101 and B670201629104).

Results: Of the 234 eligible patients, 90 filled in the questionnaires (38,5%). The median time span between the first dietary consultation and the day of completing the questionnaires is 99,5 weeks or nearly 2 years (min 49 w, max 168 w). 80 % report still following a diet in which certain FODMAP-rich food types are avoided. Only 15.3 % never deviate from the diet. One of the main reasons for not following the diet strictly is the lack of symptoms (50%). 55.6% of the participants deviate from the LFD when they are on holidays and when they eat in a restaurant. Eating with other people and feeling social pressure as well as eating at a friends' or family's place are also possible reasons to deviate (52.1% and 50%, respectively). 62.2 % indicate difficulties in applying the diet in real life. However, 88.9 % is satisfied that

they follow or have followed the diet. The mean quality of life of the study participants is 72.3 scored on 100. The IBS-QOL does not significantly differ between patients following the diet very strictly, and patients deviating often from the diet (p=0.669). The predominant disease course in the participants of this study is mild IBS with indolent course (43.0%). Abdominal distention is rated the most severe IBS symptom (mean score=5.5) by the participants, followed by flatulence (mean score=5.0) and abdominal pain (mean score=4.5). Patients who are still following the LFD, experience significantly less severe abdominal pain than patients who stopped following the diet or patients who have never started the LFD (p=0.044).

Conclusion: The long-term IBS related quality of life seems to be similar to or even slightly better than the results found in short term studies. The long-term adherence and satisfaction to a low FODMAP diet is high in patients with IBS responding a questionnaire. Nevertheless, patients indicate that it is difficult to follow the LFD in the daily routine. Practical issues, social factors and the absence of symptoms were indicated as the main reasons for a drop in adherence.

ABSTRACT (DUTCH)

Inleiding en doel van de studie: Korte-termijn studies met het laag FODMAP dieet (LFD) tonen veelbelovende resultaten wat betreft het gebruik van het laag FODMAP dieet in de symptomatische behandeling van het prikkelbare darm syndroom (PDS). Het laag FODMAP dieet is een intensief dieet bestaand uit drie fasen. In de eerste fase worden alle voedingsmiddelen die fermenteerbare oligosachariden, disachariden, monosachariden en/of polyolen (FODMAPs) bevatten, vermeden in het dieet. Die eliminatiefase wordt gevolgd door een re-introductiefase en een stabilisatiefase. Studies die de effecten van dit dieet op prikkelbare darm syndroom en de therapietrouw op lange termijn bestuderen, zijn schaars. Deze studie heeft als doel de therapietrouw van en de tevredenheid over het dieet te bestuderen, alsook de levenskwaliteit en symptoomcontrole op lange termijn.

Methode: Alle patiënten die gediagnosticeerd zijn met PDS door een gastro-enteroloog en die verwezen zijn naar een ervaren diëtist van het UZ Gent tussen januari 2014 en maart 2016 voor dieetadvies en educatie over het LFD, worden uitgenodigd om deel te nemen aan de studie. Het informed consent is verkregen van alle studie deelnemers of hun legale voogden voordat ze deelnamen aan de studie. De vragenlijsten worden opgestuurd via e-mail en bevatten de IBS-QOL vragenlijst ontwikkeld door Drossman et al. en een zelf opgestelde vragenlijst die polst naar de therapietrouw op lange termijn, de tevredenheid met het dieet, eventuele moeilijkheden in het volgen van het dieet, het verloop van de ziekte en de symptomen gerelateerd aan PDS. Het patiëntendossier wordt geraadpleegd als het informed consent verkregen is. Geslacht, leeftijd, IBS-subtype, aantal dieetconsultaties en de aanwezigheid van een opgeblazen gevoel en flatulentie op het moment van de verwijzing naar de diëtist voor een laag FODMAP dieet worden geïncludeerd in het data bestand. Statistiek werd verricht met het SPSS 24 pakket (SPSS Inc. Chicago IL, USA). De studie is goedgekeurd door het Ethisch Comittee van het UZ Gent.

Resultaten: Van de 234 potentiële deelnemers vulden 90 de vragenlijsten in. De gemiddelde tijdsduur tussen de eerste dieetconsultatie en het invullen van de vragenlijsten is 99.5 weken, of bijna 2 jaar (min 49 w, max 168 w). 80% geeft aan nog altijd een dieet te volgen waarin bepaalde FODMAP-rijke voeding vermeden wordt. 15.3% geeft aan nooit af te wijken van het dieet. Een van de belangrijkste redenen om af te wijken van het dieet is de afwezigheid van symptomen (50%). 55.6% wijken af van het dieet wanneer ze op vakantie zijn of op restaurant gaan eten. Eten met andere mensen en sociale druk voelen, en eten bij vrienden of eten bij familie zijn ook mogelijke redenen om af te wijken van het dieet (52.1% and 50%, respectively). 62.2% geeft aan dat ze het moeilijk vinden het dieet te integreren in

hun dagelijkse leven. 88.9% is echter tevreden dat ze het dieet volgen of hebben gevolgd. De gemiddelde levenskwaliteit van de deelnemers is 72.3. Deze levenskwaliteit verschilt niet significant tussen zij die het dieet zeer strikt volgen en zij die regelmatig afwijken van het dieet (p=0.669). Het meest voorkomende ziekteverloop bij de studiedeelnemers is mild IBS met indolent verloop (43.0%). Een opgeblazen gevoel werd gescoord als het meest ernstige symptoom door de deelnemers (gemiddelde score 5.5/10), gevolgd door flatulentie en buikpijn (gemiddelde score respectievelijk 5/10 en 4.5/10). Patiënten die nog altijd het dieet volgen ervaren significant minder ernstige buikpijn dan patiënten die gestopt zijn met het dieet of er nooit aan begonnen zijn (p= 0.044).

Conclusie: De levenskwaliteit op lange termijn van mensen met PDS lijkt gelijkaardig of zelfs iets beter dan de levenskwaliteit op korte termijn. De therapietrouw en tevredenheid over het LFD op lange termijn is hoog. Desondanks geven patiënten aan dat het moeilijk is het LFD dagelijks te volgen. Praktische factoren, sociale factoren en de afwezigheid van symptomen worden aangegeven als de hoofdredenen voor een daling van de therapietrouw.

INTRODUCTION

1. IBS

1.1 Definition

Irritable Bowel Syndrome (IBS) is a functional bowel disorder. Functional gastrointestinal disorders are disorders of the gut-brain interaction. They are classified by gastro-intestinal symptoms related to any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and altered central nervous system (CNS) processing. (1, 2)

IBS is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit, with features of disordered defecation. The criteria currently used to determine the presence of IBS are the ROME IV criteria. These criteria define IBS by recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following:

a. Related to defecation

b. Associated with a change in frequency of stool

c. Associated with a change in stool form (appearance)

and with no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms. The criteria should be fulfilled for the last 3 months and symptoms must have started at least 6 months ago. (1, 2) Other symptoms that occur frequently but are not part of the diagnostic criteria include: abnormal stool frequency (≤3 bowel movements per week or >3 bowel movements per day), abnormal stool form (lumpy hard stool or /loose/watery stool), defecation straining and urgency or also a feeling of incomplete bowel movement, passing mucus and bloating. (1)

Most commonly, IBS is categorized in 4 subtypes: IBS-C: IBS with predominant constipation, IBS-D: IBS with predominant diarrhea, IBS-M: IBS with mixed bowel habits and IBS-U: unclassified IBS. The classification in subtypes is based on the patient's perception of their predominant type of abnormal stool consistency. (1-3)

1.2 Epidemiology

The mean global prevalence of IBS is estimated to be 11.2%. (4) There are however large differences in prevalence, partly related to differences in study populations (geographic location) and diagnostic criteria. Figure 1 displays the prevalence of IBS according to country. The lowest prevalence was measured in Southeast Asia (7.0%) and the highest in South America (21.0%). Lovell. et al. also reports a female predominance (14% vs 8.9%) and

a decrease with age. There is no association with socioeconomic status. (4)

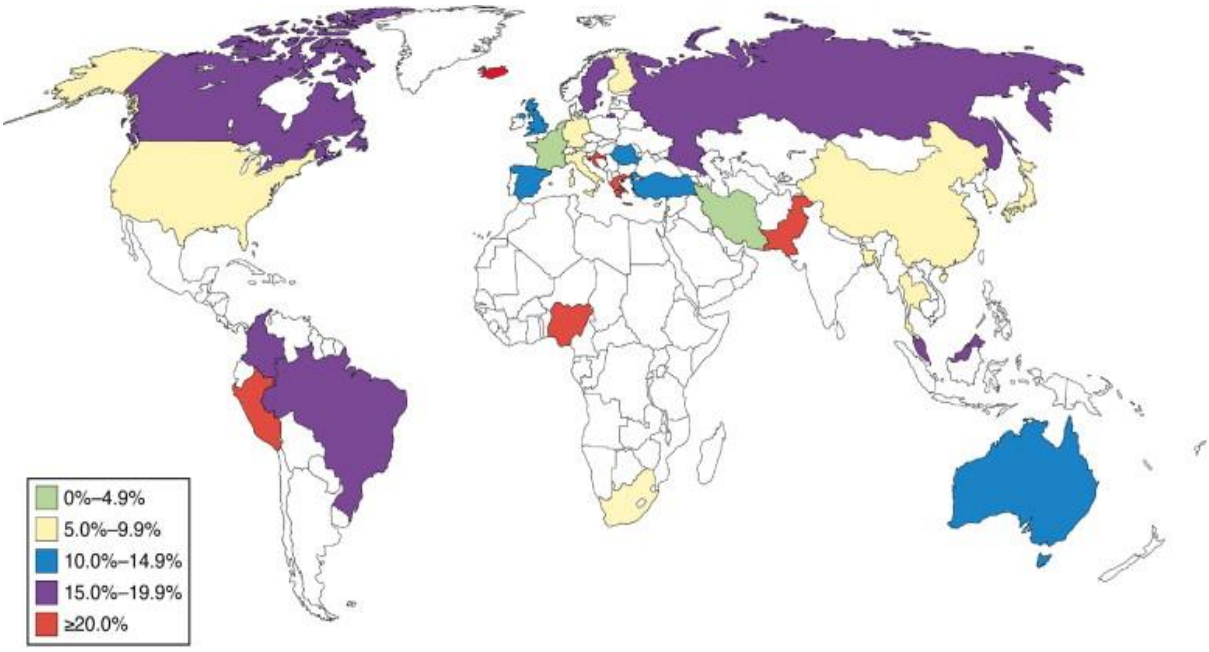

Figure 1. Global prevalence of IBS according to country, extracted from Lovell et al. (4)

1.3 Pathophysiology

A wide variety of factors are associated with IBS symptoms. Biological factors include altered motility, visceral hyperalgesia, disturbance of brain-gut interaction, abnormal central processing, autonomic and hormonal events, genetic factors, post-infectious sequels, increased intestinal permeability and dysbiosis. (1, 3) Psychosocial factors include psychiatric disorders, sleep disturbance and dysfunctional coping. (1) Environmental factors described as associated with IBS symptoms include food components, the use of antibiotics and enteric infections. (3)

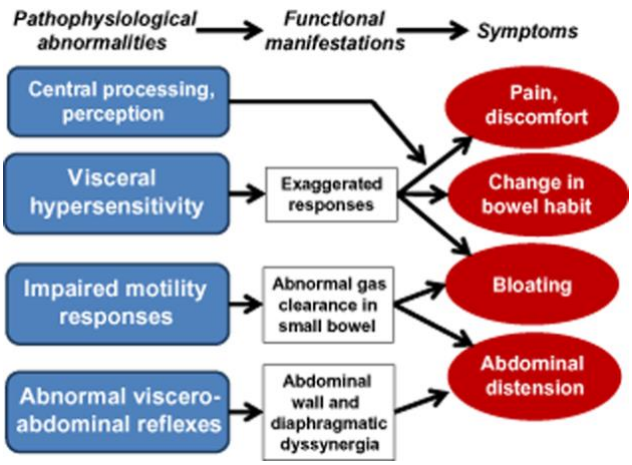

Figure 2. Conceptual framework through which the pathophysiological basis for the genesis of symptoms can be understood. Extracted from Gibson et al. (5)

The way pathophysiological abnormalities result in symptoms is well illustrated in figure 2. More recently, alterations in gut immune activation, in intestinal permeability, and in intestinal and colonic microbiome have been identified in some IBS patients. Supporting the role of an altered gut immune reaction is an increased prevalence of IBS symptoms in patients with celiac disease or inflammatory bowel disease. (4)

The functions of gut microbiota include protection of the host from enteropathogens, development of the host immune system, participation in host metabolism and contribution to nutrition. (6) Rajilici-Stojanovic et al. have investigated the microbiota of 62 patients with IBS and compared them with the microbiota of 46 healthy individuals. They found that gut microbiota of IBS patients differed significantly from that of controls. They detected an increased number of bacteria secreting proteases, causing abdominal pain in the gut through sensory afferents. On the other hand, microbiotic species having anti-inflammatory effect were significantly lower in numbers. (7) This difference in luminal and mucosal microbiota was also reported by Staudacher et al. (8) Crouzet et al. were able to induce features of IBS such as visceral hypersensitivity by transplanting stool from IBS sufferers into germfree mice, suggesting an important role of microbiota in IBS. (9) The increased likelihood of persistent functional GI symptoms after a gastro-intestinal infection, the so called post infectious IBS, also suggests a role of microbiota in IBS. (8) However, it is not yet clear whether changes in the gut microbiota directly induce symptoms of IBS as the composition of the microbiota differs largely between persons and between studies and is furthermore influenced by numerous factors including study methodology.

Along with these factors, various morbidities are associated with IBS, such as somatic pain syndromes (fibromyalgia, chronic fatigue syndrome and chronic pelvic pain), other gastrointestinal disorders (gastroesophageal reflux disease and dyspepsia) and psychiatric disorders (major depression, anxiety and somatization). (3)

1.4 Quality of life

IBS has a large impact on the quality of life. Several studies have compared the health-related quality of life (HRQOL) between IBS patients and healthy controls. According to Agarwal et al., IBS patients have the same physical HRQOL as patients with diabetes and a lower physical HRQOL compared to patients who have depression or gastroesophageal reflux disease. (10)

Aside from a large impact on the quality of life, IBS also has a large burden of illness. Studies estimate that over $20 billion of the health care budget is consumed by IBS in the United States. (11) Such large expenditures suggest not only that IBS is highly prevalent, but also

that the use of resources to control the disease is disproportionate. A major part of this budget goes to redundant diagnostic tests, invasive procedures and abdominal operations. Aside from the direct expenditure to diagnose and control the disease, society also suffers a high cost due to indirect expenditures. Patients with IBS are more likely to miss work or suffer impaired work performance. (10)

1.5 Food and IBS

Several studies show that food has an impact on the severity of the symptoms associated with IBS. According to Capili et al., over half of the investigated IBS patients report food intolerances or worsening of symptoms with certain foods. This worsening of symptoms occurs most often within 3 hours after eating, with gas problems and abdominal pain being the most frequently reported symptoms. (12) Over two-thirds of the patients report restricting their diet to alleviate the symptoms of IBS or turning to alternative sources for dietary advice. (6) Simrén et al. report that 63 % of IBS patients attribute their gastrointestinal symptoms to specific food intake and Monsbakken et al. report that 62 % limit or exclude specific products from their diet (table 1). Only a small percentage of the patients seek professional guidance in restricting their diet. (6, 13)

Table 1. Dietary Surveys of Patients with Irritable Bowel Syndrome.

Study	Dietary Survey	Results
Simrén et al, 2001 (14)	Patients with IBS (n=330) grade their perceived symptoms against a list of 35 foods.	63% attribute their GI symptoms to foods, especially carbohydrates and fats.
Monsbakken et al, 2006 (15)	Patients with IBS (n=84) have completed a survey based on symptoms related to food, foods limited or avoided, and adequacy of diet.	62% limit or exclude food from their diet. 12% have an inadequate diet.
Ostgaard et al, 2012 (16)	Patients with IBS (n=36) and patients with IBS given dietary guidance (n=43) have completed FFQs detailing intakes of macro- and micronutrients and providing information on meal patterns.	Patients have significantly lower intakes of certain food groups due to self-restriction compared with patients with IBS given dietary advice by a healthcare professional.
Hayes et al, 2013 (17)	Patients with IBS (n=135) have completed a dietary survey on their perceptions of the role of diet in their symptoms and whether they restrict their diet accordingly.	90% attribute their symptoms to certain foods, with 9.6% restricting milk products, 7.4% restricting fruit, and 5.2% restricting vegetables. Only a small percentage of patients have sought professional dietary guidance.

Adapted from Hayes et al. (6)

While the role of food in general in IBS is well-known, discovering which food groups in particular cause or aggravate symptoms is a difficult process. (13) Common food groups reported by patients as a trigger for IBS symptoms are fruits (citrus and banana), grains

(wheat, barley, rye, oats and corn), vegetables (onions, peas and potatoes), dairy products (yoghurt, milk, cheese, eggs and butter), legumes (beans and lentils), wine, chocolate, coffee, tea and fried foods. To investigate the characteristics of a food trigger, the full assortment of both physical and chemical components, as well as the absorbable and poorly absorbed components have to be investigated, thus making this method not suitable for day-to-day medical practice. (12) This explains the fact that dietary recommendations are based on trial and error, more so than guideline consensus or randomized clinical trials.
There is a number of mechanisms through which food triggers GI symptoms in IBS. The first mechanism that is proposed is food hypersensitivity. Dunlop SP et al. suggests that an increase in epithelial barrier permeability can lead to immune activation and low-grade inflammation. (18)
Secondly, the bioactivity of chemicals in food themselves have been proposed to trigger GI symptoms in IBS. These chemicals are believed to trigger these symptoms through direct stimulation of neural components and/or mast cells. (19) There is little evidence supporting this theory and further investigation is needed. Restricting food containing bioactive components has to be done with caution, as it can lead to nutritional deficiencies. (19)
Luminal distention is a third mechanism proposed to cause gastrointestinal symptoms in IBS and can be caused by an increase of water or gas in the bowel. Partially absorbable dietary components such as fructose, polyols and oligosaccharides attract water through osmosis. Furthermore, dietary components such as fructose and inulin are fermented by the gut microbiota and produce gas. This causes a distention of the lumen and symptoms such as abdominal pain and bloating occur. (6, 19)

1.6 Current management options of IBS

Numerous treatment options for IBS have been studied in the past years. The management of IBS consists generally of a combination of non-pharmacological and pharmacological treatment and is more specified according to the predominant symptoms. Non-pharmacological therapy options include lifestyle interventions, psychological therapies and diets. Pharmacological therapy can act peripherally and target the dominant symptoms, can act centrally or it can modify the gastrointestinal microbiome.

1.6.1 Pharmacological therapy

The pharmacological agents discussed below are mainly based on American Gastroenterological Association Institute guideline on the pharmacological management of IBS (2014), JAMA IBS clinical review of 2015 and the NICE guidelines of IBS in adults in primary care (updated in 2015).

Peripherally acting agents

Because peripherally acting agents target the predominant symptoms of IBS, pharmaceutics are classified according IBS-D and IBS-C.

IBS-D

Loperamide

Loperamide is antidiarrheal medication that inhibits peristalsis, makes the gut transit slower and diminishes the faecal volume. (3, 20) Only two randomised controlled trials have studied the effect of loperamide on IBS. (21, 22) Both studies showed lower failure rate of abdominal pain improvement (RR, 0.41; 95% CI, 0.20–0.84) and of improvement of stool consistency (RR, 0.06; 95% CI, 0.01–0.43) for treatment with loperamide compared with placebo. (20-22) Hodvenak et al. did not find a lower failure rate of global symptom relief with treatment with loperamide in patients with IBS compared to a placebo treatment (RR, 0.73; 95% CI, 0.29–1.86). (20, 21) Lavo et al. studied the effect of loperamide in urgency situations and loperamide showed no significant improvement of the failure rate (RR, 0.61; 95% CI, 0.13–2.92). (20, 22) There is no direct evidence of the benefit of the use of loperamide over placebo in reducing stool frequency. (3, 20) However, the efficacy of loperamide is proven in other settings. (3, 20) Because of the indirect evidence, minimal side effects and low cost, loperamide is considered valuable as adjunct therapy when a patient anticipates diarrhea. (3, 20)

Alosetron

Alosetron is a 5-HT_3-receptor antagonist. Serotonin (5-HT) is a gut hormone that influences gastrointestinal motility and visceral sensation. (3, 20) Eight randomized controlled trials have shown that alosetron improves abdominal pain (n total=4227; failure rate of relief of abdominal pain compared with placebo: RR, 0.83; 95% CI, 0.79–0.88) (20, 23-30) and two RCTs have proven IBS-related global symptom relief (n total=1506; failure rate of global improvement with alosetron compared with placebo: RR, 0.60; 95% CI, 0.54–0.67). (20, 27, 30) Alosetron has important potential adverse effects such as dose-dependent constipation and idiopathic non-dose dependent ischemic colitis (circa 1 case/1000 patient-years). (20, 31) Therefore, the use of alosetron is only approved by the FDA for treating women with severe IBS-D who do not respond to other medical therapies and is currently not on the market in Europe. (3, 20)

Antispasmodics

Antispasmodics may have an effect on IBS-symptoms by relaxing the gut smooth muscle. This pharmacological group includes anticholinergic drugs and drugs with a calcium-channel blocking effect. (3, 20) The American Gastroenterologic Association reported that antispasmodics are beneficial in the treatment of abdominal pain based on 13 RCTs (n=1392) and have a positive effect on the global assessment based on 22 RCTs (n=1983). (20) Compared with placebo, antispasmodics were associated with a lower failure rate of abdominal pain relief with a RR of 0.74 (95% CI, 0.59–0.93). (20) A RR of 0.67 (95% CI, 0.55–0.80) was found for the failure rate of global relief. (20) Especially postprandial abdominal cramping and loose stools can be treated by anticholinergics as some IBS symptoms are due to an inadequate gastrocolonic reflex that is partially cholinergically mediated. (3, 20) Anticholinergics should be used with caution in elder patients. Dose-dependent side events such as constipation, fatigue, dry mouth, dizziness and blurred vision have been reported by the Journal of the American Medical Association. (32) A drug with calcium-channel blocking properties is peppermint oil. Peppermint oil is available over the counter. Khanna R. et al. conducted a meta-analysis about the short-term efficacy and safety of enteric-coated peppermint oil capsules compared with placebo for the treatment of active irritable bowel syndrome (IBS) and included nine randomised controlled trials with a total number of 726 patients with IBS. Relief of global symptoms (5 studies, 392 patients, relative risk 2.23; 95% confidence interval, 1.78-2.81) and improvement of abdominal pain (5 studies, 357 patients, relative risk 2.14; 95% confidence interval, 1.64-2.79) was reported. (33) Adverse effects of peppermint oil include gastrointestinal disorders such as reflux. (3, 33)

IBS-C

Fibre supplements

Fibre supplementation has been used in the treatment of IBS for a considerable time. Recently however, it has lost popularity due to reports of exacerbation of symptoms in IBS-patients. (34) A meta-analysis of 14 RCTs involving 906 patients investigated the effects of fibres in the treatment of IBS. (34) Modest improvement of global IBS symptoms with soluble fibre (psyllium) treatment was reported. (3, 34, 35) No significant benefit of IBS treatment with insoluble fibre (wheat bran), compared with placebo, could be shown. (34) Insoluble fibre contains fructans that can worsen bloating and other IBS symptoms. (3)

Laxatives

Both osmotic laxatives (polyethylene glycol) and stimulant laxatives are used in the treatment of IBS-C. (3, 20) Polyethylene glycol (PEG) is a long-chain polymer of ethylene oxide. (20) Chapman et al. conducted a randomized controlled trial about the efficacy of PEG 3350 plus electrolytes in the treatment of IBS-C compared to placebo. (36) 68 patients received PEG 3350 +E for 28 days and 71 patients with IBS-C were included in the placebo group. (36) Chapman et al. reported a significant improvement of the mean number of complete spontaneous bowel movements per day in the last treatment week compared to placebo (95% CI: 1.17, 1.95; $P<0.0001$) leading to an improvement in stool frequency and consistency. (36) However, the American Gastroenterology Association found no significant statistical and clinical improvement after a post-hoc analysis using the modified FDA responder definition (with primary endpoint spontaneous bowel movements). (20) Furthermore, no evidence is found supporting the benefit of polyethylene glycol on abdominal pain and bloating. (20, 36) Adverse effects are minimal and include dose-dependent bloating, gas and loose stools. (3, 20, 36) Further high-quality RCTs studying the effects of PEG 3350 in the treatment of IBS-C are required. Less evidence of benefits in the treatment of constipation in IBS is reported for stimulant laxatives (e.g. oral bisacodyl). (3) Kamm et al. conducted a randomized, double-blind, placebo-controlled study of the effect of oral biscodyl in patients with chronic constipation according the Rome III criteria. (37) Treatment with oral bisacodyl is related to an increase of the number of complete spontaneous bowel movements for each single week, number of spontaneous bowel movement and constipation-associated symptoms. (37) No RCTs have studied the use of stimulant laxatives in the treatment of IBS-C. Thus, further research is needed.

Prosecretory agents

Linaclotide and lubiprostone are the two most commonly used luminally acting prosecretory agents. (3, 20) Linaclotide is a guanylate cyclase-C agonist that causes intestinal chloride and bicarbonate secretion via activation of the cystic fibrosis transmembrane conductance regulator (CFTR), which results in acceleration of intestinal transit. (3, 20, 38) Based on three RCTs comparing linaclotide with placebo for the treatment of patients with IBS-C, the American Gastroenterology Association reported improvement of global symptoms (failure rate: RR of 0.73 (95%CI, 0.65–0.82)), complete spontaneous bowel movements (failure rate: RR of 0.86 (95%CI, 0.83–0.89)) and abdominal pain (failure rate: RR of 0.83 (95%CI, 0.77–0.88)). (20, 39-41) The meta-analysis of Videlock et al. reported an improvement of the bowel function and reduction of abdominal pain in IBS-C patients treated with linaclotide,

compared to placebo. (42) The most common side effect is diarrhoea wherefore linaclotide should be taken 30 to 60 minutes before breakfast. (3, 20) Lubiprostone is a chloride-channel activator that, like linaclotide, increases the intestinal chloride secretion and thus accelerates the intestinal transit. (3, 20) Drossman et al. analysed the results of two randomised placebo-controlled trials studying the efficacy of lubiprostone including 1171 patients with IBS-C. (43) Lubiprostone was moderately associated with global relief of IBS symptoms (failure rate: RR of 0.93 (95%CI, 0.87–0.96)). (20, 43) Dose-dependent nausea can occur but can be avoided by combining the intake of lubiprostone with food. (3, 20)

Centrally acting agents

Tricyclic antidepressants (TCAs) and selective serotonin-reuptake inhibitors (SSRIs) are both used in the treatment of IBS as they have an effect on pain perception, mood and gut motility via modulation of brain interpretation of peripheral gut signalling. (3, 20, 44) Chang et al. reported a modest improvement of global symptoms and abdominal pain in patients with IBS treated with TCAs compared to placebo based on 8 RCTs. (20) The meta-analysis of Ford et al. concluded a number needed to treat with TCAs of 4 (95% CI, 3 to 8) in order to treat IBS symptoms in one patient. (45) An important adverse effect of tricyclic antidepressants is the risk for prolonged QT interval. (3, 20) Other side effects include dry mouth and urinary retention due to the anticholinergic properties of TCAs. (44) Sedation and sexual dysfunction can also occur. (44) There is less evidence of the beneficial effect of serotonin-reuptake inhibitors on IBS symptoms but improvement of abdominal pain has been reported. (3, 20, 44) Ford et al. studied the efficacy of SSRIs in IBS in a meta-analysis of 5 RCTs and found a number needed to treat of 3.5 (95% CI, 2-14). (45) Potential adverse effects include sexual dysfunction, agitation, nausea, drowsiness and diarrhea. (3)

Monoclonal antibodies

A recent study has suggested the use of the monoclonal antibody omalizumab, in the treatment of IBS. (46) This method of treatment seeks to interact with the mast cell activation through blockage of the IgE receptor possibly contributing to the symptomatology and etiology of IBS. The evidence is lacking though, as this hypothesis is a product of recent investigations and only 2 case reports so far have been published, both indicating spectacular response.(47, 48). More evidence is needed to investigate the possible effect of omalizumab in IBS.

Modification of the microbiota: Probiotics and Antibiotics

Since the discovery of the importance of the microbiome in the pathophysiology of IBS, studies on probiotics and antibiotics in the treatment of IBS have emerged. A meta-analysis of Ford et al. in 2014, including 43 RCTs, showed improvement in global symptoms, abdominal pain, bloating and flatulence in IBS patients treated with probiotics (RR of IBS symptoms persisting with probiotics compared to placebo was 0.79 (95%CI, 0.70-0.89)). (49) Unfortunately head-to-head comparisons of probiotics are lacking. RCTs studying the role of gut-specific antibiotics such as rifaximin and neomycin reported global benefit in non-constipated IBS. (3, 20, 44) Menees et al. conducted a meta-analysis of 5 studies investigating the efficacy and safety of rifaximin in the treatment of IBS and found a number needed to treat with rifaximin of 10.2 to have an improvement of global symptoms compared to placebo. (50) However, RCTs studying the long-term efficacy, the antimicrobial resistance and side effects of rifaximin and neomycin in the management of IBS are lacking.

1.6.2 Non-pharmacological therapy

It can be assumed that a trusting patient-doctor relationship and good communication are key factors in the management of IBS. Basic skills such as empathy, active listening and (non-)verbal communication should be used in order to build a sustainable relationship. As IBS is a symptom-based disease and its pathogenesis is multifactorial, an individual approach to the disorder is needed and goals, expectations and a plan of action should be set together with the patient. Better outcome of treatment can be expected when the patient is educated about his disease and is actively involved in the management.

Lifestyle interventions

Physical activity improves the gas transit and the abdominal distension in healthy persons. Johannessen et al. conducted a RCT including 102 IBS patients evaluating the effect of physical exercise (patients were followed by a physiotherapist) on IBS symptoms compared to a placebo group. A significant improvement of the IBS Severity Scoring System (IBS-SSS) was found in the group coached by the physiotherapist. (51) A daily walk of circa 20 minutes is recommended. (3)

Psychological therapies

Psychological therapies include cognitive behavioural therapy (CBT), hypnotherapy, multicomponent psychotherapy and dynamic psychotherapy. Meta-analysis of the effect of psychological therapies compared to a placebo group showed a significant improvement of global symptoms in patients treated with CBT (number needed to treat (NNT): 3),

hypnotherapy (NNT: 4) and multicomponent psychotherapy (NNT: 4). No conclusions could be made concerning the efficacy of dynamic psychotherapy. (45) Psychological therapies should be considered an alternative or adjunctive therapy for IBS. (3) Internet-based psychological programs are emerging. Two RCTs have studied the efficacy of CBT delivered via the internet, but, because significant heterogeneous results were found between those two, there is not yet conclusive evidence that online CBT can be an effective alternative to classic CBT. (3, 45)

Dietary interventions

Food components are often a trigger of symptoms in patients with IBS. IBS is frequently associated with food intolerances and sensitivities. The two most commonly followed diets to reduce IBS symptoms are the gluten free diet and the low FODMAP diet. The effect of a gluten free diet on IBS symptoms has been studied in patients with a history of non-celiac glutensensitivity and/or patients with a diarrhea-predominant IBS. Despite reports of improvement of IBS symptoms, the role of the diet in IBS is uncertain. As wheat contains besides gluten also fructans and other proteins that can cause IBS symptoms like bloating, diarrhea and abdominal pain, it is uncertain whether gluten is a primary trigger of IBS symptoms. (3)

2. Low FODMAP diet

2.1 FODMAPs

FODMAPs (Fermentable Oligo-, Di- and Mono-saccharides And Polyols) are short-chain carbohydrates and sugar alcohols that are poorly absorbed in the small intestine. The most common FODMAPs are fructans, galacto-oligosaccharides, lactose, fructose and polyols. (52) As these carbohydrates are poorly absorbed in the small intestine, they increase the osmotic load in the distal small bowel and proximal colon. This causes an increase in water delivery. (53) The increase of fluid collection in the small intestine may lead to luminal distention, and combined with visceral hypersensitivity can lead to abdominal pain. Secondly, FODMAPs are also highly fermentable, causing gas production in the colon, contributing to the symptoms of bloating and flatulence. (52, 53) A study has proven that the oral ingestion of the polyol mannitol causes an increase in the water content of the small bowel. (54) Fructose also increased the water content of the small bowel significantly in comparison to glucose. Inulin on the other hand had little to no effect on the small bowel water content. Both fructose and inulin caused a significant rise in colonic gas production compared to glucose or a glucose fructose mixture. (55) The effect of FODMAPs on gastrointestinal symptoms

seems to be dose-dependant, the effect of intake of several FODMAPs at once is additive and the gastro-intestinal symptoms seem to be affected by exposure duration. (56)

The group of oligosaccharides can be divided into fructo-oligosaccharides (chain of fructose molecules with a glucose endmolecule) and galacto-oligosaccharides (chain of galactose molecules with a glucose endmolecule). The fructo-oligosaccharides or FOS are frequently used as alternative sweeteners and are also present in specific fruits, vegetables and grains. Galacto-oligosaccharides or GOS can be found in specific nuts, legumes, lentils and beans (Table 2). The human gut does not have hydrolase enzymes for FOS and GOS and thus, they reach the colon intact where fermentation of FOS and GOS takes place into gas and short-chain fatty acids. This can cause the typical bloating symptoms and flatulence. GOS are considered prebiotics as well as they stimulate the growth of Lactobacilli and Bifidobacteria, two beneficial bacteria of the colon. (57, 58)

The disaccharide that can potentially trigger IBS symptoms is lactose. Lactose consists of a glucose and a galactose molecule and is metabolised in the small intestines by the lactase enzyme. Nearly all infants express the enzyme but the expression of lactase changes after weaning and can result in lactose malabsorption, which causes symptoms like bloating, flatulence and diarrhea. Lactose is found in milk, ice cream, yoghurt and soft and fresh cheese. Lactose intolerance can be diagnosed by a hydrogen breath test. (57, 58)

Fructose is a monosaccharide and can be absorbed via different pathways. There are two well-known pathways: a high-capacity pathway using GLUT-2 carrier, co-transporting fructose with glucose, and a low-capacity pathway using GLUT-5 carrier. Especially when fructose presents in excess of glucose and the low-capacity pathway is working less, fructose malabsorption may occur and is tested via a hydrogen breath test. Non-metabolised fructose reaches the colon and is fermented. In that case flatulence, bloating and diarrhea occur. Sources of fructose are apples, pears, peaches, watermelon, mango, raisins and honey. (57, 58)

Polyols include sorbitol, mannitol, lactitol and others and are sugar alcohols that are passively diffused through the epithelial barrier of the gut. They cause osmotic secretion in the small intestines and are fermented in the colon. Polyols are found in apples, pears, cherries, lychee, apricots, coconut milk, peaches, plums, prunes, watermelon, avocado, butternut pumpkin, cauliflower and mushrooms. They are as well an important sugar substitute in our modern processed food. (57, 58)

Table 2. FODMAPs overview		
FODMAP	**Malabsorption rates**	**Examples of food sources**
Fructose	30-40% of the population do not absorb fructose efficiently but not all report symptoms.	Apples, pears, peaches, watermelon, mango, raisins and honey
Lactose	Malabsorption is due to diminished presence of the enzyme lactase. Nearly 100% of children are born with this enzyme but a significant proportion of the population have reduced activity after early childhood.	Milk, ice cream, yoghurt and soft and fresh cheese
Fructooligosaccharides (fructans/FOS)	Malabsorption in all people	Wheat, rye, barley, onion, garlic, nuts.
Galactooligosaccharides (GOS)	Malabsorption in all people	specific nuts, legumes, lentils and beans
Polyols (sugar alcohols)	Malabsorption in 50% of people	Apples, pears, cherries, lychee, apricots, coconut milk, peaches, plums, prunes, watermelon, avocado, butternut pumpkin, cauliflower and mushrooms

Adapted from Wilson et al. (58)

2.2 The role of a low FODMAP diet in IBS

The low-FODMAP diet (LFD) is a therapeutic measure in the treatment of IBS. The aim of the diet is to eliminate all foods high in FODMAPs, with the intention of limiting the osmotically active and fermentable substrates, to minimize the water delivery and gas production in the intestine. (59) The reduction of water delivery and gas production reduces the luminal distension and provide GI symptom relief in IBS. (60)

The implementation of a low FODMAP diet can be divided into three phases: the restriction phase, the reintroduction phase and the stabilisation phase. During the restriction phase, all FODMAP rich food is eliminated. This phase lasts between 4-8 weeks and should give relieve of symptoms. If not, the diet is stopped. If the patient experiences relieve of symptoms, the reintroduction phase starts. In this phase, FODMAP rich foods are reintroduced one by one to detect which of the foods induce symptoms. This phase takes about 8 weeks. The last phase is the stabilisation phase, in which the patient tries to find a balance between the intake of FODMAP rich food and the control of the symptoms of IBS with the help of a dietician. This is the so-called top-down approach to a LFD and is mostly indicated in people who are very symptomatic and who usually do not consume a large amount of FODMAPs. (61)

The implementation of a LFD can also be done through a bottom-up approach. The subject starts with the restriction of food that contains a very large amount of FODMAPs and gradually food that contains less FODMAPs is eliminated until a tolerance level is achieved. This approach is mostly indicated in people who have a diet that contains a high amount of FODMAPs and that are mildly symptomatic. (61)

Studies have shown that the low FODMAP diet alters the gastrointestinal microbiota. After following a LFD, patients tend to become more dysbiotic than at baseline. (59) Staudacher et al. also found a significant drop in bifidobacteria concentrations following a LFD diet. (62) Halmos et al. described a reduction in total bacterial abundance of 47% compared to the typical Australian diet. (63) The relevance of the alterations in gut microbiota and the clinical effects on IBS are still mostly unknown and need to be investigated further.

There are several risks involved in following a low FODMAP diet. Böhn et al. have investigated the dietary intake of people following a low FODMAP diet and have concluded that people following a low FODMAP diet have a lower energy intake. This effect has not only been observed in the low FODMAP group but also in the IBS group following a traditional dietary treatment. This is presumably more due to the risk of following a detailed diet than that of the low FODMAP diet in particular. (64) A few studies also report a higher prevalence of eating disorders in IBS patients, although this phenomenon is still understudied. (65) As described in the previous paragraph, the low FODMAP diet may alter the gastrointestinal microbiota. As it is likely that a change in microbiome will result in functional changes of the bowel, the diet might have adverse effects, such as a shift in microbial composition, decreasing the resistance against potential harmful bacteria, although more studies are required. (64, 66) Lastly, the low FODMAP diet has an effect on fibre intake and constipation. As the diet restricts some of the high fiber foods, this can result in constipation. It is therefore important, especially in patients with IBS-C, that they are informed thoroughly about high fibre alternatives that do not contain FODMAPs. (5)

One of the first studies investigating the effects of a low FODMAP diet in IBS patients are Barret et al. and Ong et al. Barret et al. have used an ileostomy model to confirm that FODMAPs, conserved within meals, are poorly absorbed in the small intestine. (53) Ong et al. have discovered a significant reduction in breath hydrogen during low FODMAP diet in healthy volunteers and IBS-patients, compared to a high FODMAP diet. (67)

Relevant studies have been searched on the Pubmed database with the search term low FODMAP diet and IBS and published before December 2016 and only English articles have

been included. A list of 87 articles has been generated. The abstracts of these articles have been reviewed. 5 randomized controlled trials and 2 randomized crossover trials have been found investigating the effectiveness of a low FODMAP diet (LFD) in the treatment of IBS (see Addendum B, table 1). All these studies contain level 1 or level 2 evidence, based on the levels of evidence for therapeutic studies, designed by the Centre for Evidence Based Medicine.

Pedersen et al., Halmos et al. and Staudacher et al. compare the low FODMAP diet with a normal diet. They all observe a reduction in IBS symptoms in patients following the low FODMAP diet, compared to the normal diet ($p<0.01$, $p<0.001$, $p<0.006$). (62, 68, 69) Hustoft et al. and McIntosh et al. compare a low FODMAP diet with a high FODMAP diet. Both studies report a significant decrease in global symptom scores in patients on low FODMAP diet compared to baseline using the IBS-SSS ($p<0.001$, $p<0.001$). (59, 66) When comparing the low FODMAP diet group with the high FODMAP diet group, McIntosh et al. report a statistically significant difference in post-diet symptom scores ($p=0.01$). (66) Hustoft et al. report a significantly higher VAS score of nausea/or vomiting, headache, and belching and/or passing gas in the high FODMAP group compared with the low FODMAP group ($p=.002$, $p=.04$, and $p<.001$ respectively). (59) It is to be noted that in the study of Hustoft et al. the high FODMAP diet consists of a low FODMAP diet supplemented with 16g of fructo-oligosaccharides. This has been compared to a low FODMAP diet with a placebo intervention. Hustoft et al. compare a fixed amount of one specific FODMAP with a low FODMAP diet, while McIntosh et al. compare a low FODMAP diet with a high FODMAP diet in general. Eswaran et al. compare a low FODMAP diet with a diet based upon the modified National Institute for Health and Care Excellence (NICE) guidelines. (70) The Nice guidelines for IBS recommend eating small and regular meals, avoiding trigger foods and avoiding alcohol and caffeine, without eliminating high FODMAP foods specifically. Eswaran et al. report adequate relief of overall IBS symptoms during 50% or more of the last 2 weeks of the study period in 52% of the low FODMAP group, and 41% in the mNICE group ($p=0.31$). They also report a ≥30% reduction in mean abdominal pain in 51% in the low FODMAP group, compared to 23% in the mNICE group ($p=0.008$). (70) Böhn et al. compare the low FODMAP diet with a traditional diet recommended for IBS patients (encouraging small but regular meals, reduce intake of fat, discourage excessive fiber intake, reduce caffeine and avoid gas-producing foods). (64) The IBS symptom severity, measured by IBS-SSS, is reduced in both groups at the end of the intervention period, compared to baseline ($p=0.002$). Comparing the reduction in symptoms between both intervention groups, no significant difference is noted ($p=0.62$). (64)

It can be concluded that the low-FODMAP diet is an effective therapeutic measure in treating IBS. To determine whether or not the low FODMAP diet is significantly more effective than the traditional IBS diet or the NICE dietary guidelines, more evidence is needed. Studies investigating the long-term effects of following a low FODMAP diet are required to evaluate the adverse effects of a low FODMAP diet and their potential influence on adherence.

There are a few limitations in the studies. Halmos et al. and Hustoft et al. are crossover studies, so there is a possibility of carry-over effects. As with most studies investigating dietary treatment, blinding is very difficult. Most studies used dietary consultations to help the patients follow the respective diet. As such, patients could have suspected which diet they were following. None of the studies were double-blinded. Krogsgaard et al. conducted a systematic review to evaluate the quality of RCTs studying the effect of LFD in patients with IBS. (71) They report lack of blinding and the choice of control group as the most important domains contributing to bias. When comparing LFD with habitual diet, the results can be biased due to placebo effect caused by positive expectations of the LFD and by the care that is given by the dietician to the patient. It is difficult to compare the LFD with other treatment options as there is limited evidence for standard of care for IBS in general. (71) A possible alternative is to research the effect of a LFD in a subtype of IBS and to give active treatment with proven efficacy for that IBS subtype in the control group. (71) However, Krogsgaard et al. suggest that placebo response primarily explains the effects of a LFD on IBS symptoms. (71) Further, none of the studies have a fixed low FODMAP diet. As such dietary intake can be highly variable between subjects and is dependant of adherence. This setup is however much closer to reality than a study with fixed dietary intake. As such, the results of these studies can teach a lot about the effectiveness of the implementation of a low FODMAD diet in a medical setting, more so than a study-based setting. It should also be noted that the study duration of the studies included is too short to evaluate long-term effect of a LFD on IBS symptoms. Furthermore, the intervention period of the RCTs has never contained the re-introduction phase of the LFD. It is however very difficult if not near impossible to conduct an adequately blinded and high-quality study over such a long period of time. Besides, most of the patients in RCTs have been recruited from tertiary care and thus, no firm conclusions can be made for the role of LFD in the treatment of IBS in primary care. (71)

The aim of this study is to investigate the long-term adherence to a low FODMAP diet and to investigate associations between LFD and quality of life, IBS symptoms and disease course on the long-term, as well as discovering potential factors associated with adherence.

MATERIALS AND METHODS

1. Study design

A retrospective cross-sectional study is conducted investigating the long-term effects of the low FODMAP diet and long-term adherence to the diet in patients with IBS. The study design, the informed consent and the questionnaires have been presented to the Ethical Committee of the Ghent university hospital and approved by the committee.

2. Study population

All patients, diagnosed with IBS by a gastroenterologist and having subsequently received dietary advice and education concerning the LFD by an experienced dietician in the UZ Gent are invited to participate in the study. All patients have had their first dietary consultation concerning the low FODMAP-diet in the treatment of IBS between January 2014 and March 2016. Informed consent is acquired from all study participants, or their legal guardians, before participating in the study.

3. Data collection

Patients eligible to participate in the study are sent an email by their dietician, containing the informed consent, an invitation to participate and the link to the questionnaire. Patients who are eligible to participate in the study but who do not have a registered email address known to their dietician, are sent a letter, giving them the possibility to send an email to the study conductors to receive the link to the questionnaire along with the informed consent or to have the questionnaire and the informed consent sent by regular mail. Two weeks later, a reminder email is sent to the patients who have not completed the questionnaire. A second reminder by email is sent 4 weeks after the first reminder. The third and last reminder is sent 4 weeks after the second reminder email. Patients who do not have a registered email address and who do not answer to the first letter as well as patients with incorrect email address, are sent the questionnaires and informed consent by regular mail.

After receiving informed consent, the electronic data files of the participants are accessed regarding additional treatment and investigations. Gender, age, IBS-subtype, number of dietary consultations and presence of abdominal bloating and flatulence at the moment of referring of the patient to the dietician for LFD are included in the data file. Each face-to-face consultation with the dietician specialised in LFD is counted as a dietary consultation.

Furthermore, every conversation between the dietician and the patient by e-mail or phone concerning the LFD is also considered a dietary consultation.

4. Dietary advice and education

All patients included in the study have at least had one consultation concerning the low FODMAP diet with a dietician of Ghent university hospital specialized in IBS. This consultation was either an individual session or a group session.

An individual session includes a general history (nature of symptoms, duration of symptoms, gastroenterological reports and results of performed investigations), a nutritional history (dietary assessment, effect of previous diets, avoidance of certain nutrients) and education on IBS and the low FODMAP diet. The dietician explains the symptoms and pathogenesis of IBS, the relation between IBS and food and the three phases of the LFD, more specifically the first phase or elimination phase. More education is given on which foods contain which FODMAPs, on the correct interpretation of food labels, on the implementation of a LFD when eating outdoors, and examples of products and recipes for breakfast, lunch and dinner are presented. A patient folder on IBS and the LFD is given. At the end of the consultation, a second consultation is planned.

If the patient chooses to attend a group session (maximum 12 participants) instead of the first individual consultation, the general and nutritional history are not repeated by the dietician, but consulted in the electronic patient file. At the group session, the same education about IBS and LFD is given as in an individual consultation. A second (individual) consultation with the dietician can be scheduled on demand.

A second consultation takes place six to eight weeks after the first consultation. An evaluation of the effect of the elimination phase is done. The degree of implementation of the elimination of FODMAPs in the daily life of the patient is enquired. IBS symptoms and complaints are assessed. When the symptoms have improved according to the patient, the second phase or reintroduction phase is explained and a written manual is given. If there is no improvement in the course of the disease, possible mistakes in the implementation of the diet are considered and another consultation with a gastroenterologist is scheduled in order to consider an alternative treatment or diagnosis.

The third consultation is planned twelve weeks after the second consultation. Symptoms after reintroduction of fructans, galactans, lactose, fructose, sorbitol and/or mannitol are

assessed. According to the influences of each FODMAP on the IBS symptoms, personalised dietary advice is given. Patients are also given the option to contact their dietician through mail and phone during all three phases to answer further questions regarding the diet.

5. Questionnaires

The questionnaires consist of 1 validated translation of an internationally validated questionnaire and 1 self-developed questionnaire (Addendum A).

The internationally validated questionnaire is the IBS Quality Of Life (IBS-QOL) questionnaire developed by Drossman et al. (72) The questionnaire consists of 34 questions regarding health-related quality of life in patients with non-subtyped IBS. The answers to every one of the 34 questions are scored using a 1-5 Likert scale and is transformed to a scale ranging from 0 to 100, with 100 being a perfect quality of life. The IBS-QOL of study participants who do not complete all 34 questions, is calculated based on the amount of questions they have filled in. Based on the subscale structure of the IBS QOL questionnaire of Drossman et al, the scores of the eight different subscales (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationship) are calculated as well. (72) For each subscale only the scores of the patients who have answered all the questions for that subscale, are evaluated. The maximum score for each subscale is 100.

The self-developed questionnaire consists of 4 parts: General information, long-term adherence to the LFD, disease course and IBS symptoms.
The general information part addresses habits and medical information deemed important for the study and contained 3 questions: “Do you take chronic medication? If yes, which medication(s)?”, “Did you suffer from bowel symptoms for longer than 6 months when starting the diet?” and “Do you smoke?”.
The part about long-term adherence to the LFD explores the adherence to the diet, deviations from the diet and the reasons for (non-)adherence. This part contains 18 questions and is based on an extensive literature study.
The course of disease part is adapted from the Copenhagen IBS disease courses, developed by Maagaard et al. (73) The figures are translated and adapted to only address the course of disease since the intervention until the time of completing the questionnaire. Patients are presented with 4 pictures of possible disease courses and are asked to choose which picture represents their disease course.
IBS symptoms are evaluated through six questions based on the IBS-Symptom Severity Scale (74). The six questions include: “1. How severe was the abdominal pain you

experienced during the last 10 days?", "2. How many days did you experience abdominal pain during the last 10 days?", "3. How severe was the abdominal distension (bloating, swollen or tight tummy) that you experienced during the last 10 days?", "4. How severe was the flatulence that you experienced during the last 10 days?", "5. How many times in average did you defecate per day during the last 10 days?" and "6. Did you feel urge to defecate during the last 10 days?". On the questions 1, 3 and 4 the patients have to score the severity on a scale from 0 to 10, on the questions 2 and 5 they have to answer with a number and question 6 is a yes-or-no question.

6. Statistical analysis

Statistical analysis is performed using SPSS statistics 24 (SPSS Inc. Chicago IL, USA). Different statistical tests are performed in order to have an idea of possible long-term effects of the LFD in patients with IBS and of the factors influencing the adherence to a LFD. Possible long-term effects are hypothesised by researching associations between LFD and quality of life, LFD and disease course, and LFD and IBS symptoms. Factors potentially influencing the adherence that are studied are: number of dietary consultations, potential causes of deviation from the diet and the possible difficulties in implementation of the LFD in daily life. The fact if people are still following the diet or not and the frequency of deviating from the LFD are considered the two variables representing the adherence to the low-FODMAP diet in the statistical analyses.

For all statistical analysis, significance level α is set to 0.05. Normality of distribution is tested with the Kolmogorov-Smirnov and the Shapiro-Wilk test for the continuous variables, more specifically IBS-QOL, IBS-QOL subscales and IBS symptoms questions 1 to 5. Only non-parametric tests are used as none of the continuous variables follow a normal distribution. The Mann-Whitney U test is used to study a continuous variable in two unpaired non-parametric samples and the Kruskal-Wallis test to study a continuous variable in more than two unpaired non-parametric samples. Possible correlation between two continuous non-parametric variables is studied using the Spearman's ranks correlation coefficient. The χ^2-test and Fisher's Exact test are done when comparing a categoric variable in two or more than two unpaired samples. When the conditions to execute the χ^2-test (not more than 20% of the expected frequencies in the cells can be less than 5 and no expected count less than 1 may occur) are not fulfilled, only the Fisher's Exact Test is interpreted.

7. Ethical considerations

The study was approved by the Ethical Committee of the UZ Gent the 14th of July 2016. The informed consent is acquired by means of completing the questionnaires. Participants who want to fill in the questionnaires but who do not want to give access to their electronic patient files are given the option to send an email which states that they refuse to give access to their electronic patient files or to fill in the questionnaires anonymously.

RESULTS

1. Descriptive data

1.1. Recruitment of participants

234 patients fulfilled the inclusion criteria for participation in this study. 161 patients were first contacted by e-mail and 73 patients, who did not have a registered email address, were contacted by regular mail. Of the 161 patients who were contacted by e-mail, 65 persons had filled in the questionnaires after three reminders, 4 persons had an invalid email address, 2 patients preferred not to participate in the study and 6 patients did not fill in the questionnaires because of another diagnosis or treatment (figure 3). Of the 73 patients who were contacted by regular mail, 13 patients filled in the questionnaires by sending the study coordinators an e-mail to obtain the link of the online questionnaires, 1 person did not have a valid address and 1 person answered that he/she had another diagnosis. A second letter was sent, with the questionnaires and an informed consent, to the 4 patients who had an invalid e-mail address and to the 58 patients who did not have an e-mail address and did not answer the first letter. 12 patients agreed to the informed consent and sent the filled-in questionnaires back. 8 participants filled in the questionnaires, but did not consent to extraction of data from their electronic patient records. Therefore, only data acquired through the questionnaires was available for those 8 patients.

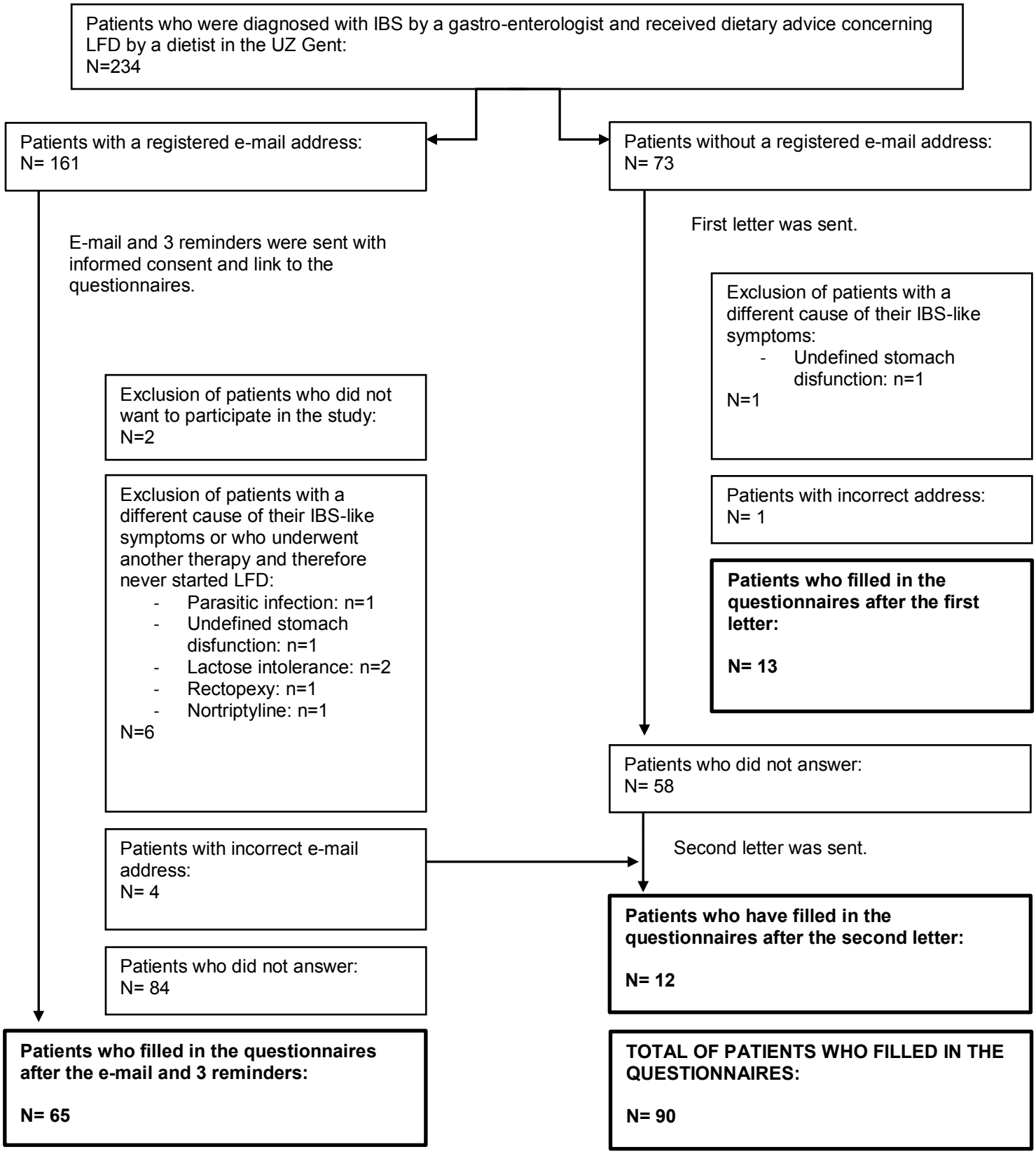

Figure 3. Flowchart of the participants' recruitment.

1.2 Demographic data

In line with the general demographic data regarding IBS, participants of this study are mainly female (79,3%). The median age is 41,5 years with a range from 17 to 69 years. 11,1% of all participants are current smokers. IBS-M is the dominant subtype (46,3%) followed by IBS-D (39,0%), IBS-C (9,8%) and IBS-U (4,9%). Data of presence of abdominal bloating and flatulence at the moment of referring of the patient to the dietician for LFD were extracted from the electronic patient reports. 28 (34,1%) patients were having symptoms of bloating and flatulence and 54 (65,9%) patients were not.

8 (9,8%) patients had 1 consultation with the dietician, 19 (23,2%) patients had 2, 29 (35,4%) patients had 3 and 26 (31,7%) patients had 4 or more. As mentioned earlier, three dietary consultations are required to complete the three phases of a low FODMAP-diet. Accordingly, 67.1% of all the participants completed the three phases of the diet. The median number of dietary consultations is 3, minimum dietary consultations are 1 and maximum 9.

The median time span between the first dietary consultation and the day of completing the questionnaires is 99,5 weeks or nearly 2 years, minimum time span is 49 weeks and maximum is 168 weeks. When only the cases who are still following the LFD are selected, a median duration of the diet of 99,5 weeks is found and a minimum of 53 weeks and maximum of 152 weeks.

96,7% of the participants report suffering from bowel symptoms for at least 6 months prior to starting the diet.

Table 3. Demographic data	
Patients, N (%)	90 (100%)
Sex, N (%)	
Male	17 (20,7%)
Female	65 (79,3%)
Missing	8
Age, years	
Median	41,5
Minimum	17
Maximum	69
Smoking, N (%)	
Smokers	10 (11,1%)
Non-smokers	80 (88,9%)
IBS subtypes, N (%)	
IBS-U	4 (4,9%)
IBS-D	32 (39,0%)
IBS-C	8 (9,8%)
IBS-M	38 (46,3%)
Missing	8
Abdominal bloating and flatulence at dietary referral, N (%)	
Yes	28 (34,1%)
No	54 (65,9%)
Missing	8
Dietary consultations, N (%)	
1	8 (9,8%)
2	19 (23,2%)
3	29 (35,4%)
4 or more	26 (31,7%)
Missing	8
Median	3
Minimum	1
Maximum	9
Range	8
Interquartile range	2
Time span between first dietary consultation and filling in the questionnaire, weeks	
Median	99,5
Minimum	49
Maximum	168

1.3 Adherence and satisfaction

80 percent of the participants still follow a diet in which certain FODMAP-rich food types are avoided. 17 (18,9%) patients used to avoid certain FODMAP-rich food types but do not avoid any food types anymore. 1 (1,1%) participant did not start with the diet due to pregnancy. The main reasons for quitting the diet are inability to adhere due to practical reasons (e.g. time management) (7 participants) and the absence of effect (6 participants). Other reasons are loss of weight (1 participant) and inability to identify what food types to avoid (1 participant). 2 participants didn't have symptoms anymore and therefore stopped the diet.

Of those who are still following the LFD, only 15,5% of the participants still follow the diet strictly (table 4). 28,2% deviate from the diet less than once a week, 21,1% once a week and

28,2% twice or more a week. 7,0% indicate that they follow the diet periodically, meaning that they alternate periods following the diet strictly with periods not following the diet at all.

Table 4. How often do you deviate from the low FODMAP-diet?			
		Frequency	**Percent**
Valid	Never	11	15,5
	Less than once a week	20	28,2
	Once a week	15	21,1
	Twice or more a week	20	28,2
	I follow the diet periodically	5	7,0
	Total	71	100
Missing	.	1	

Possible reasons for deviating from the diet are diverse. 50 percent of persons still following the LFD indicate they follow the diet less strictly when they do not have any symptoms. 52,1 percent state that they do not follow the diet when eating with other people and being subjected to social pressure. 50 percent respond that they do not follow the diet when having dinner with friends and family. 55,6 percent agree that they do not follow the diet when going to a restaurant and 55,6 percent when they are on holiday.

A questionnaire asking about the general difficulty of applying the diet was administered to all participants. 62,2 percent indicate that they have trouble applying the diet in daily life. 34,8 percent responded that low FODMAP ingredients are hard to find and 57,8 percent respond that low FODMAP foods are expensive. 41,1 percent agree that it is difficult to know what food types to avoid even though only 12,2 percent indicate that they received too little information about what food types they should and shouldn't avoid. 46,7 percent of the patients are enjoying their meal less when they are eating low FODMAP food (table 5).

However, 88.9 percent of all participants are satisfied that they follow or have followed the diet.

Table 5. Statements concerning difficulties in the adherence to LFD.			
Statement	**Agree**	**Disagree**	**Total**
1. When I don't have any symptoms, I follow my low FODMAP diet less strictly.	36 (50%)	36 (50%)	72 (100%)
2. I deviate from my low FODMAP diet when I'm eating with other people and when I feel social pressure.	37 (52,1%)	34 (47,9%)	71
3. I deviate from my low FODMAP diet when I'm eating at my friends' or at my family's place.	36 (50%)	36 (50%)	72
4. I deviate from my low FODMAP diet when I'm eating in a restaurant.	40 (55,6%)	32 (44,4%)	72
5. I deviate from my low FODMAP diet when I'm on holiday.	40 (55,6%)	32 (44,4%)	72
6. Low FODMAP food is difficult to find.	31 (34,8%)	58 (65,2%)	89
7. Low FODMAP food is expensive.	52 (57,8%)	38 (42,2%)	90
8. I find it difficult to know which food I can eat and which food I can't.	37 (41,1%)	53 (58,9%)	90
9. I' m enjoying my meal less when I am eating low FODMAP.	42 (46,7%)	48 (53,3%)	90
10. I don't feel informed enough to know what I can and cannot eat.	11 (12,2%)	79 (87,8%)	90
11. I find it difficult to apply the low FODMAP diet in real life.	56 (62,2%)	34 (37,8%)	90

1.4 Disease course

When asked about their disease course from the start of the diet to the time of filling in the questionnaire, the predominant disease course in the participants of this study is mild IBS with indolent course (43.0%), followed by chronic IBS with continuous course (31.4%), chronic IBS with intermittent course (22.1%) and the mild IBS with aggressive course (3.5%) (Figure 4).

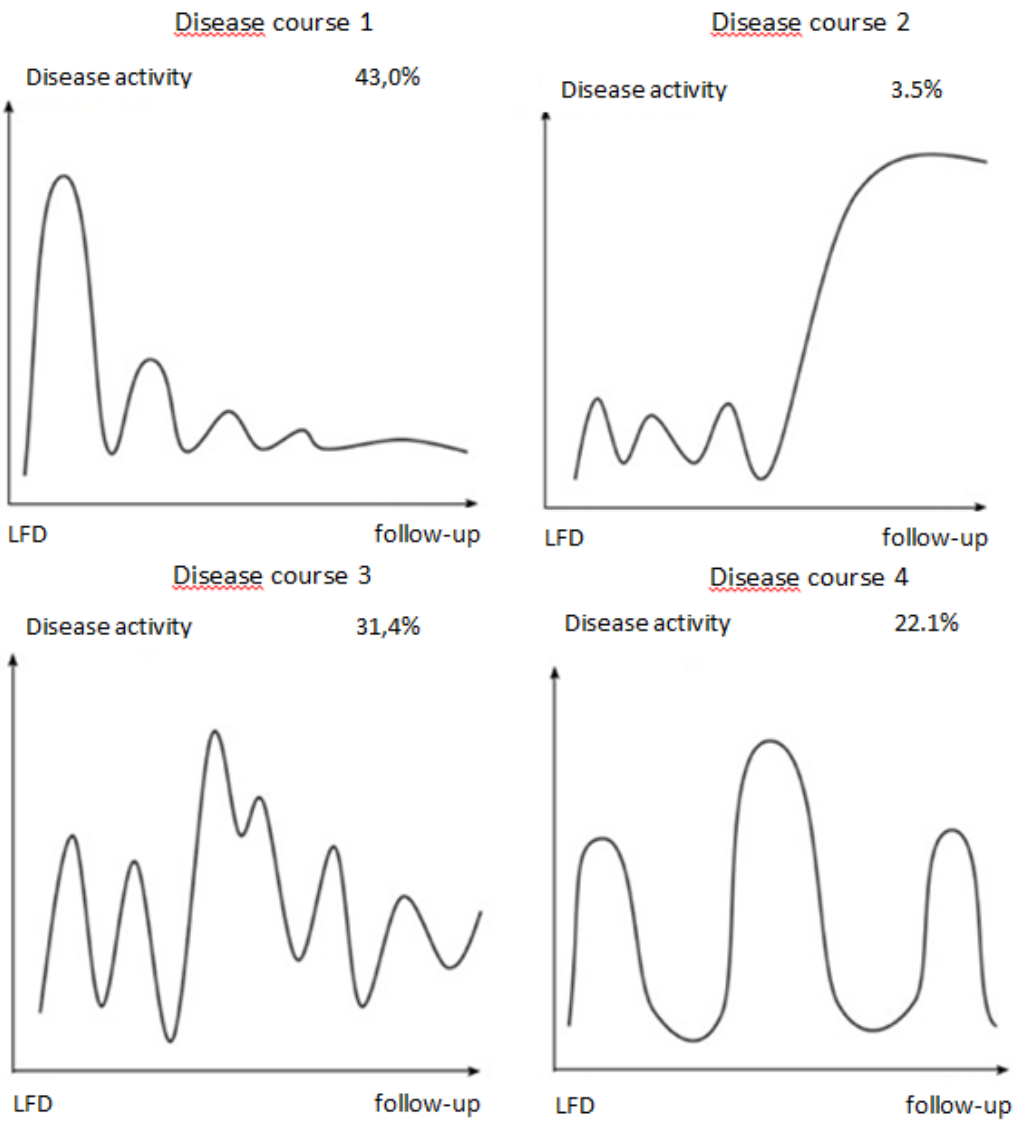

Figure 4. Disease courses: Disease course 1: mild IBS with indolent course, Disease course 2: mild IBS with aggressive course, Disease course 3: chronic IBS with continuous course, Disease course 4: chronic IBS with intermittent course.

1.5 Quality of life

78 study participants answered all 34 questions of the validated IBS-QOL questionnaire, 12 participants did not complete the full questionnaire. The mean quality of life of our participants in the last 30 days is 72,3 with a minimum of 31,2 and a maximum of 94,4 (figure 5). The standard deviation is 14,0. Both Kolmogorov-Smirnov ($p<0,001$) and Shapiro-Wilk normality tests ($p=0,001$) show that the IBS-QOL does not follow a Gaussian distribution.

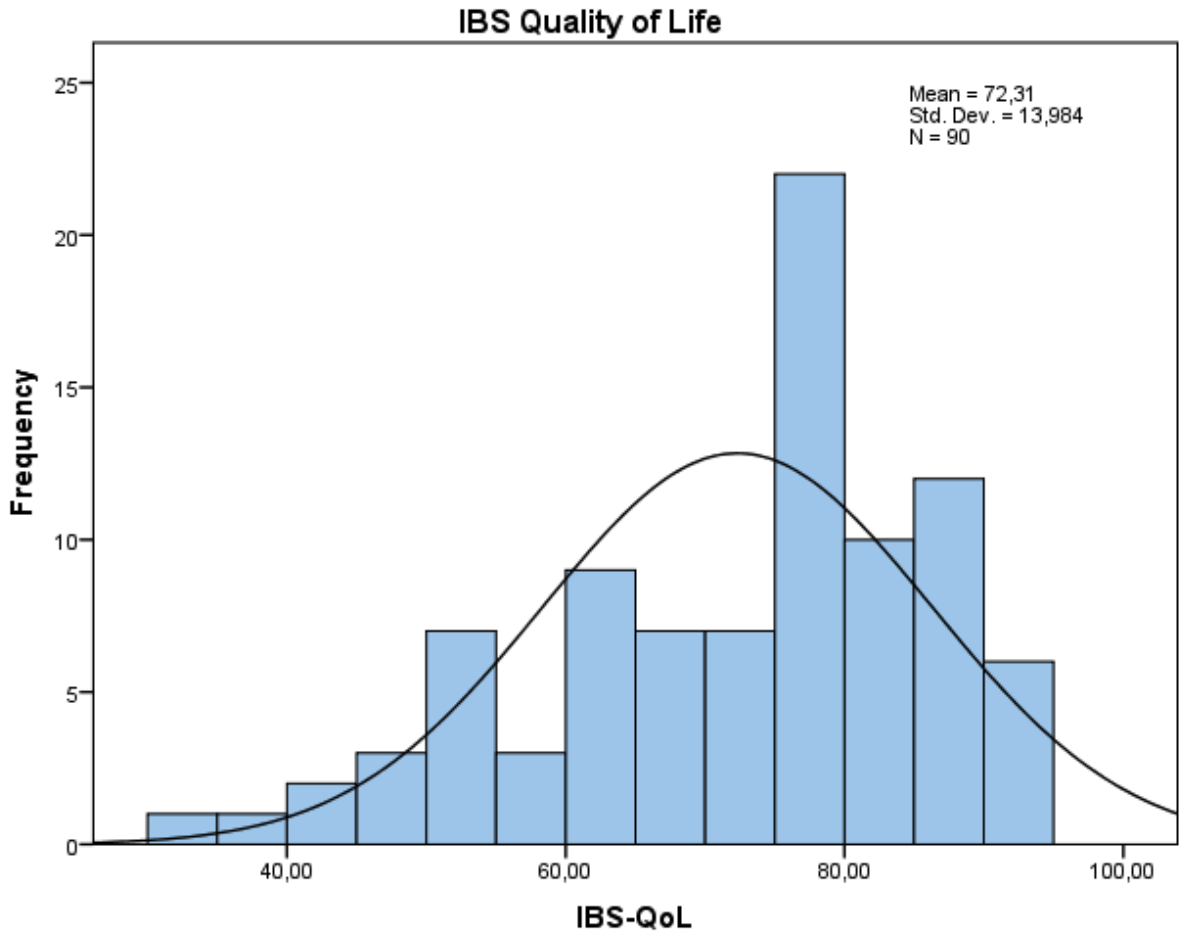

Figure 5. Histogram of IBS Quality of Life.

The IBS-QOL subscale scores were calculated as well. An overview of the mean scores, standard deviations, minimum and maximum scores, range and interquartile range is presented in table 6. The lowest mean score was found for the IBS-QOL subscale Food avoidance (53,0). It is also the subscale with the lowest minimum score (20,0). However, it can be noticed that the subscale has the biggest range with a value of 80,0. The highest mean score is found in the subscale sexual well-being with a mean score of 85,7, followed by relationship (82,0). The IBS-QOL subscale “Social reaction” has the highest minimum score of quality of life with a value of 35,0. None of the participants reach a perfect quality of life score for body image. Body image also has the lowest standard deviation (15,5) compared to the other IBS-QOL subscales.

Table 6. IBS – Quality of Life Subscale scores							
	N	Mean	Std. Deviation	Minimum	Maximum	Range	Interquartile range (IQR)
Dysphoria	86	70,5	18,7	22,5	100,0	77,5	27,5
Interference with activity	87	71,1	19,5	25,7	100,0	74,3	31,4
Body image	89	70,6	15,5	25,0	95,0	70,0	20,0
Health worry	88	75,9	16,1	33,3	100,0	66,7	20,0
Food avoidance	88	53,0	16,9	20,0	100,0	80,0	26,7
Social reaction	88	74,2	16,0	35,0	100,0	65,0	20,0
Sexual	87	85,7	20,2	30,0	100,0	70,0	20,0
Relationship	90	82,0	18,1	26,7	100,0	73,3	20,0

Normality tests have been performed for each IBS-QoL subscale. All subscales have a non-Gaussian distribution according to the Kolmogorov Smirnov and the Shapiro Wilk test. ($p < 0.05$).

1.6 IBS symptoms

The mean score of severity of abdominal pain (question 1) is 4,5 on a scale from 0 to 10, with the lowest score 0 and the highest score 10. The median number of days with abdominal pain (question 2) in the participants group is 3 days, with no days being the lowest value and 10 days the highest. The mean rate of how severe the patients experienced abdominal distension (question 3) is 5,5 and for flatulence (question 4) 5,0. For both questions the lowest answer is 0 and the highest answer is 10. The scores of severity of abdominal pain, abdominal distension and flatulence have a wide distribution with a range of 10 and an interquartile range of respectively 5, 5 and 4. Abdominal distension is rated on average the most severe symptom, followed by flatulence and abdominal pain. The median of average number of defecations per day (question 5) is 2. The lowest average number of defecations per day is 0, the highest 18. After analysis of the frequencies and the boxplot of the average number of defecations (figure 6), the value 18 is considered an outlier and is recoded into missing variable in further analyses. Without including the outlier in the descriptive analysis, the median number of the average number of defecations per day is 2 with the lowest number being 0, the highest 9 and the interquartile range 2. An overview of the IBS symptoms (questions 1 to 5) can be found in table 7 and in figure 7. 67,8% of the participants indicate that they had felt urge to defecate during the past 10 days (question 6) (figure 7).

Severity of abdominal pain, number of days with abdominal pain and severity of abdominal distension do not follow a normal distribution. The p-values for the three questions are smaller than or equal to 0,001 for both Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Severity of flatulence has a p-value of 0,080 when tested with the Kolmogorov-Smirnov

test and a p-value of 0,006 when tested with the Shapiro-Wilk test. As the Shapiro-Wilk normality test has more power than the Kolmogorov-Smirnov normality test and is more reliable for small sample sizes, this test is taken into consideration. Therefore, severity of flatulence does not follow a normal distribution. The distribution of the average number of defecations per day is tested without including the outlier. Both Kolmogorov-Smirnov and Shapiro-Wilk tests show p-values smaller than 0,001 and thus it can be stated that the average number of defecations per day does not follow a Gaussian distribution.

Table 7. IBS – Symptoms (Questions 1 to 5)								
	N	Mean	Median	Std. Deviation	Min.	Max.	Range	IQR
1. Severity of abdominal pain	90	4,5	5,0	2,8	0	10	10	5
2. Number of days with abdominal pain	85	3,4	3,0	2,8	0	10	10	3
3. Severity of abdominal distension	90	5,5	6,0	2,9	0	10	10	5
4. Severity of flatulence	90	5,0	5,0	2,9	0	10	10	4
5. Average number of defecations per day	90	2,4	2,0	2,4	0	18	18	2

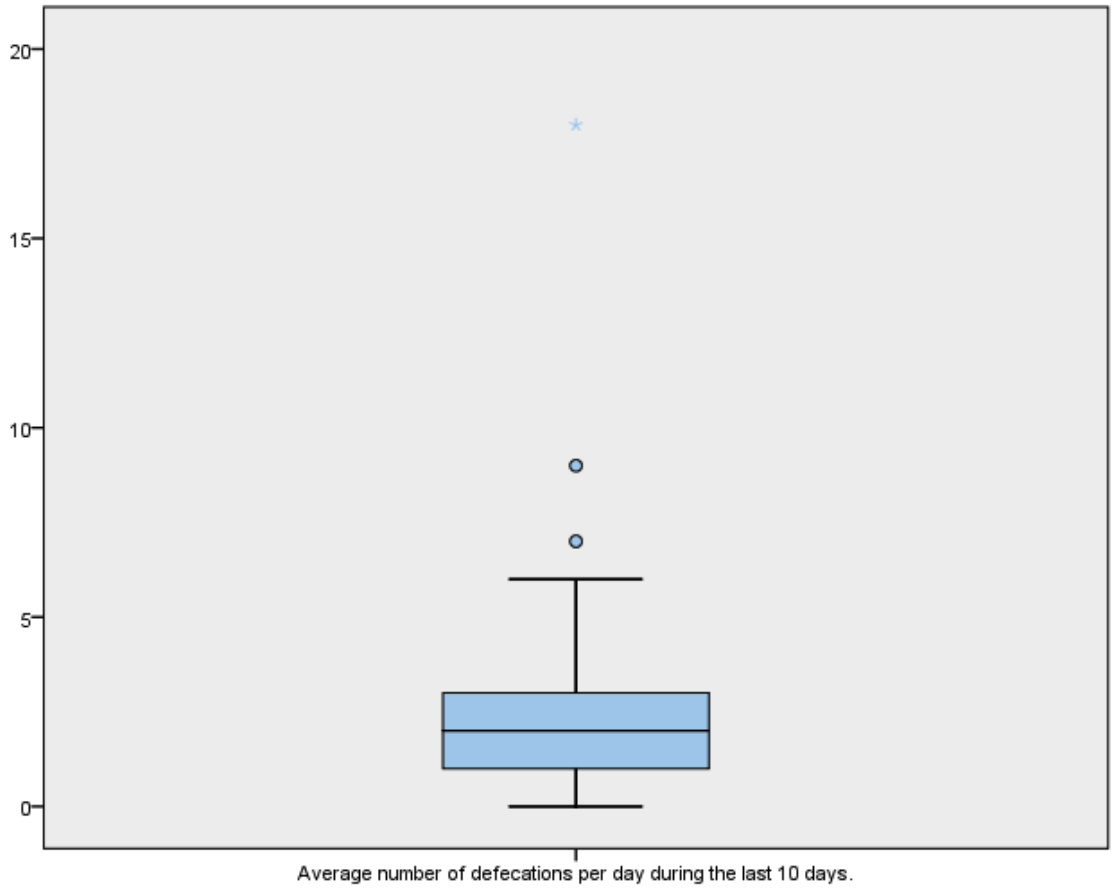

Figure 6. Boxplot of average number of defecations per day.

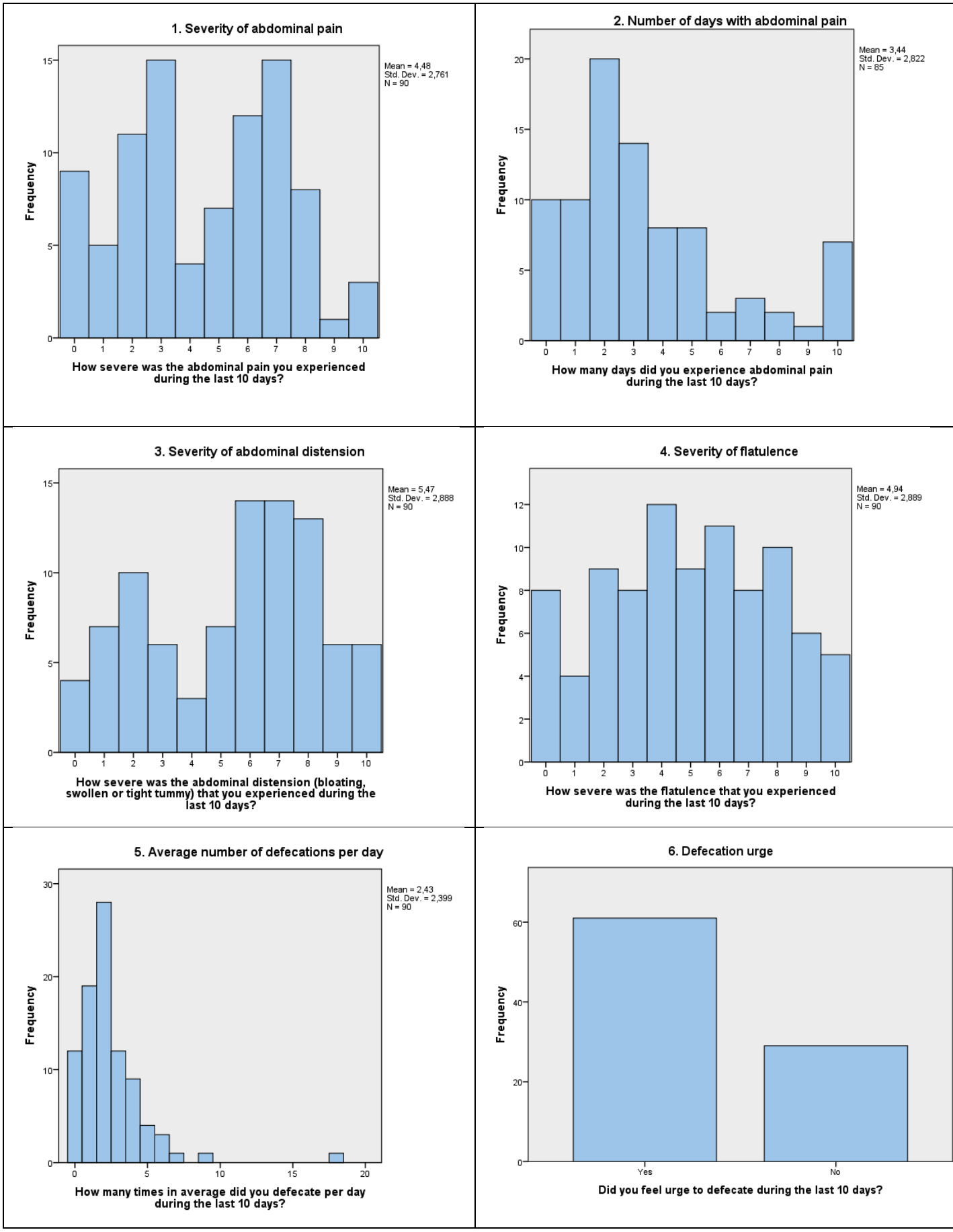

Figure 7. Histograms and bar chart of IBS symptoms (Questions 1 to 6).

2. Statistical analysis

2.1 Long-term effects of LFD

2.1.1 Associations with Quality of Life

The Mann-Whitney U test, two-tailed tested, does not show a significant difference in quality of life between people who are still following a diet in which certain FODMAP-rich food types are avoided and people who have never started the LFD or who have definitely stopped following the LFD (p= 0,639) (table 8).

Table 8. Difference in IBS-QoL between patients still following the LFD and patients not following.

		N	Mean rank	Sum of ranks
IBS - QoL	Patients still following the LFD.	72	44,9	3229,5
	Patients not following the LFD.	18	48,1	865,5
	Total	90		

The IBS-QOL has been compared between patients who never deviate from their diet, patients who deviate from the diet less than once a week, patients who deviate once a week, patients who deviate twice or more a week and patients following the diet periodically (table 9). The Kruskal-Wallis test shows a p-value of 0,669 and thus no significant difference could be shown in quality of life between the different groups of patients.

Table 9. Difference in IBS-QoL according the degree of deviation from the LFD.

		N	Mean rank
IBS - QoL	Patients who never deviate from LFD	11	34,0
	Patients who deviate less than once a week from LFD	20	35,9
	Patients who deviate once a week from LFD	15	35,7
	Patients who deviate twice a week or more from LFD	20	40,2
	Patients who follow LFD periodically	5	25,0
	Total	71	

A possible correlation between the number of dietary consultations and IBS-QOL has been tested with the Spearman's rank correlation coefficient. The Spearman's rho test shows a p-value of 0.592, tested two-tailed. It can be concluded that there is no significant correlation between the two variables. In addition, the Mann-Whitney U test has been done to research a difference in quality of life between the patients who completed the three phases of the low-FODMAP diet (3 dietary consultations or more) and the patients who didn't complete the process with help of the dietician of the Ghent University Hospital (1 or 2 dietary consultations) (table 10). The test shows a p-value of 0,921; two-tailed tested. Thus, no significant difference in quality of life could be proven between people who have completed the three phases of the LFD with help of their dietician and people who haven't.

Table 10. Difference in IBS-QoL between patients who completed the LFD and patients who did not.				
		N	Mean rank	Sum of ranks
IBS - QoL	Patients who completed the 3 phases of the LFD.	55	41,7	2292,5
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	27	41,1	1110,5
	Total	82		

The same tests have been executed for the eight different subclasses of IBS-QOL (table 11). The Mann Whitney U test, two-tailed tested, does not show a significant difference in quality of life between people still following the LFD and people who aren't, in the subgroups Dysphoria, Interference with activity, Body image, Health worry, Social Reaction, Sexual and Relationship (respective p-values: 0,953; 0,749; 0,420; 0,463; 0,571; 0,631; 0,638). A significant lower quality of life on food avoidance level in patients still following the LFD was observed. (p = 0.001).

Table 11. Differences in each IBS-QOL subclass between patients still following the LFD and patients not following.				
		N	Mean rank	Sum of ranks
Dysphoria	Patients still following the LFD.	68	43,4	2952,5
	Patients not following the LFD.	18	43,8	788,5
	Total	86		
Interference with activity	Patients still following the LFD.	69	43,6	3005,5
	Patients not following the LFD.	18	45,7	822,5
	Total	87		
Body image	Patients still following the LFD.	71	46,1	3273,5
	Patients not following the LFD.	18	40,6	731,5
	Total	89		
Health worry	Patients still following the LFD.	70	43,5	3045,0
	Patients not following the LFD.	18	48,4	871,0
	Total	88		
Food avoidance	Patients still following the LFD.	70	40,1	2809,0
	Patients not following the LFD.	18	61,5	1107,0
	Total	88		
Social reaction	Patients still following the LFD.	70	43,7	3060,5
	Patients not following the LFD.	18	47,5	855,5
	Total	88		
Sexual	Patients still following the LFD.	69	43,4	2993,0
	Patients not following the LFD.	18	46,4	835,0
	Total	87		
Relationship	Patients still following the LFD.	72	44,9	3230,0
	Patients not following the LFD.	18	48,1	865,0
	Total	90		

The potential differences in each IBS-QOL subclass have been studied as well between patients who never deviate from their diet, patients who deviate from the diet less than once a week, patients who deviate once a week, patients who deviate twice or more a week and patients following the diet periodically (see Addendum B table 2). No significant differences between the groups of patients are observed in any subclass. The p-values of the Kruskal-

Wallis-test are 0,659 for Dysphoria; 0,581 for Interference with activity; 0,668 for Body image; 0,899 for Health worry; 0,054 for Food avoidance; 0,097 for Social Reaction; 0,478 for Sexual and 0,115 for Relationship.

At last, differences in each quality of life subclass have been investigated between the patients who completed the three phases of the low-FODMAP diet and the patients who didn't complete the process with help of the dietician of the Ghent University Hospital (see Addendum B table 3). No significant differences in any quality of life subclasses between the two patient groups could be proven, when the Mann-Whitney U test was done for each quality of life subclass and tested two-tailed. The p-values are 0,559 for Dysphoria; 0,654 for Interference with activity; 0,512 for Body image; 0,148 for Health worry; 0,252 for Food avoidance; 0,943 for Social Reaction; 0,118 for Sexual and 0,896 for Relationship.

2.1.2 Associations with disease course

First, a possible significant difference in disease course has been studied between patients still following a diet in which certain FODMAP-rich food types are avoided and patients who have never started the LFD or who have stopped following the LFD (see Addendum B table 4). As the conditions for interpreting the χ^2-test are not met (4 cells (50,0%) have expected count less than 5 and the minimum expected count is 0.52) only the Fisher's Exact Test is interpreted. The Fisher's Exact Test reveals a p-value of 0,153. As a result, no significant difference in disease course can be concluded.

Secondly, a difference in disease course has been researched in relation to the number of times patients, still following the diet, have deviated from the LFD (table 12). The Fisher's Exact Test has been done as the conditions for interpreting the χ^2-test are not met (14 cells (70,0%) have expected count less than 5 and the minimum expected count is 0,14). The two-sided p-value of the Fisher's Exact Test is 0,018. A significant difference in disease course according to the number of times of deviation from the low-FODMAP diet was found.

Table 12. Crosstabulation disease course*times of deviation from LFD							
		How many times do you deviate from your diet?					
		Never	Less than once a week	Once a week	Twice or more a week	I follow the diet periodically	Total
Mild IBS with indolent course	Count	8	8	11	4	2	33
	% within disease course	24,2%	24,2%	33,3%	12,1%	6,1%	100,0%
	% within patient group	72,7%	40,0%	73,3%	21,1%	40,0%	47,1%
Mild IBS with aggressive course	Count	1	0	0	1	0	2
	% within disease course	50,0%	0,0%	0,0%	50,0%	0,0%	100,0%
	% within patient group	9,1%	0,0%	0,0%	5,3%	0,0%	2,9%
Chronic IBS with continuous course	Count	2	6	1	10	1	20
	% within disease course	10,0%	30,0%	5,0%	50,0%	5,0%	100,0%
	% within patient group	18,2%	30,0%	6,7%	52,6%	20,0%	28,6%
Chronic IBS with intermittent course	Count	0	6	3	4	2	15
	% within disease course	0,0%	40,0%	20,0%	26,7%	13,3%	100,0%
	% within patient group	0,0%	30,0%	20,0%	21,1%	40,0%	21,4%
Total	Count	11	20	15	19	5	70
	% within disease course	15,7%	28,6%	21,4%	27,1%	7,1%	100,0%
	% within patient group	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

Further analysis to detect which disease course is more or less present than what is expected in which group of patients has been done. The adjusted residual (A.R.) has been calculated (table 13). The null hypothesis states that the two variables are independent and consequently, the adjusted residuals follow a normal distribution with mean value 0 and standard deviation 1. When significance level α=0,05 is adopted, an adjusted residual higher than 1,96 indicates that the observed count is significantly larger than expected if the variables would be independent and an adjusted residual lower than -1,96 indicates that the observed count is significantly smaller than expected. Accordingly, mild IBS with indolent course is significantly more present (A.R.= 2,3) in patients deviating once a week from their diet and significantly less present (A.R.= -2,7) in patients deviating twice or more than twice a week. Patients who deviate twice or more than twice a week from the LFD experience

significantly more chronic IBS with continuous course in comparison with the other patient groups (A.R.= 2,7). Patients deviating once a week from their diet, on the other hand, have significantly less chronic IBS with continuous course (A.R.= -2,1).

Table 13. Expected count and Adjusted residual of disease course*times of deviation from LFD

		How many times do you deviate from your diet?				
		Never	Less than once a week	Once a week	Twice or more a week	I follow the diet periodically
Mild IBS with indolent course	E.C.[a]	5,2	9,4	7,1	9,0	2,4
	A.R.[b]	1,9	-0,8	**2,3**	**-2,7**	-0,3
Mild IBS with aggressive course	E.C.	0,3	0,6	0,4	0,5	0,1
	A.R.	1,4	-0,9	-0,7	0,7	-0,4
Chronic IBS with continuous course	E.C.	3,1	5,7	4,3	5,4	1,4
	A.R.	-0,8	0,2	**-2,1**	**2,7**	-0,4
Chronic IBS with intermittent course	E.C.	2,4	4,3	3,2	4,1	1,1
	A.R.	-1,9	1,1	-0,2	0,0	1,1

[a] E.C.= Expected Count
[b] *A.R.= Adjusted Residual*

Lastly, the distribution of the disease courses has been compared between patients who had 3 or more dietary consultations and people who had less than 3 consultations (see Addendum B table 5). The Fisher's Exact Test has been executed because the conditions for performing a χ^2-test are not met (3 cells (37,5%) have expected count less than 5 and the minimum expected count is 0,59). A two-sided tested p-value of 0,320 is shown. No significant difference in disease course can be found between patients who completed the three phases of LFD and patients who did not.

2.1.3 Associations with IBS symptoms

First, IBS symptoms have been compared between patients who are still following the LFD and patients who are not. No significant difference in number of days with abdominal pain, severity of abdominal distension, severity of flatulence and average number of defecations per day could be proven between the two different patient groups, when tested two-tailed with the Mann-Whitney U test (p-values are respectively: 0.247, 0.213, 0.065 and 0.872). However, a significant difference in severity of abdominal pain (p=0.044) was found between the two patient groups. Patients who are still following the LFD, experience less severe abdominal pain than patients who stopped following the diet or patients who have never started the LFD (table 14).

Table 14. Difference in IBS symptoms between patients who completed the LFD and patients who did not.				
		N	Mean rank	Sum of ranks
Severity of abdominal pain	Patients still following the LFD.	72	42,8	3078,0
	Patients not following the LFD.	18	56,5	1017,0
	Total	90		
Number of days with abdominal pain	Patients still following the LFD.	70	41,6	2910,0
	Patients not following the LFD.	15	49,7	745,0
	Total	85		
Severity of abdominal distension	Patients still following the LFD.	72	43,8	3152,5
	Patients not following the LFD.	18	52,4	942,5
	Total	90		
Severity of flatulence	Patients still following the LFD.	72	43,0	3094,0
	Patients not following the LFD.	18	55,6	1001,0
	Total	90		
Average number of defecations per day	Patients still following the LFD.	72	45,7	3292,0
	Patients not following the LFD.	18	44,6	803,0
	Total	90		

The frequencies of defecation urge have been compared as well between patients who still follow the LFD and patients who do not (figure 8). The χ^2-test was used as the conditions for the test were fulfilled (0 cells (0%) have expected count less than 5 and the minimum expected count is 5,80). When two-sided tested, the p-value is 0.576 and subsequently no significant difference in frequency of defecation urge can be concluded between the two groups of patients.

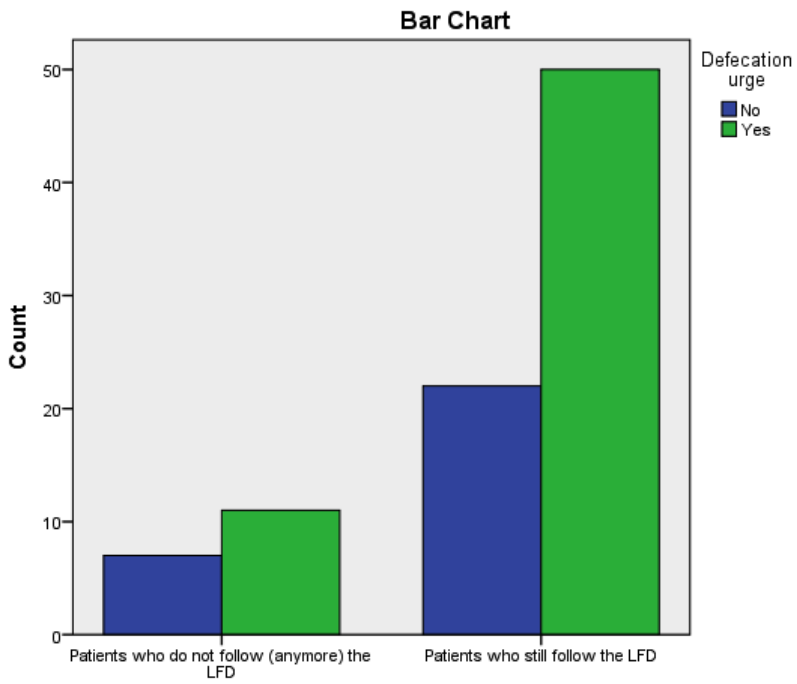

Figure 8. Bar Chart of defecation urge according to still following the LFD or not.

Further, a possible difference in IBS symptoms according to the frequency of deviation from the LFD, has been researched in the group of patients still following the diet by performing the Kruskal-Wallis test (see Addendum B table 6). The severity of abdominal pain, the number of days with abdominal pain, the severity of abdominal distension, the severity of flatulence and the average number of defecations per day all do not significantly differ between the groups of patients divided by frequency of deviation from the LFD. P-values are respectively 0.634, 0.923, 0.666, 0.957 and 0.968.

In similar way, the presence of defecation urge has been compared between the groups of patients divided by frequency of deviation from the LFD. The Fisher's Exact test, two-sided tested, shows that there is no significant difference in prevalence of defecation urge (P=0.936) between people who never deviate from their diet, people who deviate less than once a week, people who deviate once a week, people who deviate twice or more than twice a week and people who follow the diet periodically.

Lastly, we compared the difference in IBS symptoms between patients who completed the three phases of the diet and patients who did not (table 15). For severity of abdominal pain, the number of days with abdominal pain, severity of abdominal distension and average number of defecations per day, the Mann-Whitney U test cannot conclude a significant difference in those symptoms between patients who had 3 dietary consultations or more, and thus completed the phases of the LFD, and patients who only went to 1 or 2 dietary consultations. The p-values (two-tailed tested) are respectively 0.237, 0.403, 0.209 and 0.958. A significant difference in severity of flatulence (P=0.001) between patients who completed the LFD and patient who didn't, is found with the Mann–Whitney U test. When the mean rank of severity of flatulence is calculated for both groups, it can be concluded that patients who went 3 times or more to the dietician experience less severe flatulence than patients who went less than 3 times.

Table 15. Differences in IBS symptoms between patients who completed the LFD and patients who did not.				
		N	Mean rank	Sum of ranks
Severity of abdominal pain	Patients who completed the LFD.	27	45,9	1240,0
	Patients who did not complete the LFD.	55	39,3	2163,0
	Total	82		
Number of days with abdominal pain	Patients who completed the LFD.	25	42,1	1051,5
	Patients who did not complete the LFD.	52	37,5	1951,5
	Total	77		
Severity of abdominal distension	Patients who completed the LFD.	27	46,2	1247,5
	Patients who did not complete the LFD.	55	39,2	2155,5
	Total	82		
Severity of flatulence	Patients who completed the LFD.	27	53,3	1440,0
	Patients who did not complete the LFD.	55	35,7	1963,0
	Total	82		
Average number of defecations per day	Patients who completed the LFD.	27	41,7	1126,0
	Patients who did not complete the LFD.	55	41,4	2277,0
	Total	82		

The Fisher's Exact test has been done to study a difference in defecation urge between patients who have completed the LFD and patients who have not. No significant difference in defecation urge (P=1.000, two-sided tested) can be retained between the two groups of patients.

2.2 Factors influencing adherence to LFD

2.2.1 Number of dietary consultations

No significant difference in number of dietary consultations between patients still following the LFD and patients not eating low FODMAP anymore was found using the Mann Whitney U test (p=0.646) (see Addendum B table 7). There is also no significant difference in number of dietary consultations between patients who never deviate from their diet, patients who deviate from the diet less than once a week, patients who deviate once a week, patients who deviate twice or more a week and patients following the diet periodically using the Kruskal-Wallis test (p=0.559) (see Addendum B table 8).

2.2.2 Potential causes of deviation from the diet

A difference in frequency of agreeing to the five statements surveying possible reasons for deviating from the LFD, is studied between patients who never deviate from their diet, patients who deviate from the diet less than once a week, patients who deviate once a week, patients who deviate twice or more a week and patients following the diet periodically (see Addendum B table 9). The Fisher's Exact test is conducted for each statement. No significant

difference in agreement to the statement “2. I deviate from my low FODMAP-diet when I’m eating with other people and when I feel social pressure.” could be found (2-sided tested, P=0.225). For the statements “1. When I don’t have any symptoms, I follow less strictly my low FODMAP-diet.”, “3. I deviate from my low FODMAP-diet when I’m eating at my friends’ or at my family’s place.”, “4. I deviate from my low FODMAP-diet when I’m eating in a restaurant.” and “5. I deviate from my low FODMAP-diet when I’m on holiday.”, a significant difference in agreement is shown between the groups of patients defined by the frequency of deviating from the LFD. The two-sided p-values are respectively 0.021, 0.010, 0.011 and smaller than 0.001.

The adjusted residuals have been calculated in order to know in which group a significant difference in agreement is found. Patients who never deviate from the LFD, significantly agree less (A.R.=-2,3) that they don’t follow the LFD strictly when they don’t have any symptoms. On contrary, patients who deviate twice or more than twice a week agree significantly more (A.R.=2,0) (see Addendum B table 10). Patients who never deviate from their LFD and patients who deviate less than once a week significantly disagree more (A.R.=2.2 and A.R.=2.0 respectively) to deviate when they are eating at friends’ or family’s place. However, significantly more patients who deviate once a week from their diet agree to the statement (A.R.=2.1) (see Addendum B table 11). Patients who never deviate from their diet have significantly answered less (A.R.=-2.7) that they agree to deviate when they go on restaurant. No other significant correlations were observed (see Addendum B table 12). Significantly less patients who never deviate from their diet agree (A.R.=-3.3) to deviate when they are on holiday. On the contrary, significantly more patients who follow the diet periodically agree (A.R.=2.1) with the statement (see Addendum B table 13).

2.2.3 Possible difficulties in implementation of the LFD in daily life

A possible difference in answers to the six statements concerning difficulties in implementation of the LFD in real life, has been first researched between patients still following the diet and patients not eating low-FODMAP. No significant differences in answers could be shown with the Fisher’s Exact test between the two groups of participants to the statements: “6. Low FODMAP food is difficult to find.”, “7. Low FODMAP food is expensive.”, “8. I find it difficult to know which food I can eat and which food I can’t.”, “9. I’ m enjoying less my meal when I’m eating low FODMAP.”, “10. I don’t feel informed enough to know what I can and cannot eat.” and “11. I find it difficult to apply the FODMAP-diet in real life.” (see Addendum B table 14). The p-values, two-sided, are respectively 0.267, 1.000, 0.065, 0.195, 1.000 and 0.176.

Differences in agreement to the six statements, have been studied as well between patients who never deviate from their diet, patients who deviate from the diet less than once a week, patients who deviate once a week, patients who deviate twice or more a week and patients following the diet periodically. The two-sided p-values found with the Fisher's exact test are 0.702, 0.892, 0.084, 0.765, 0.884 and 0.470 in respective order of the statements. Thus, there are no significant differences in answers to the statements between the different groups of patients classified by the frequency of deviation.

2.3 The impact of dietary consultations

A possible influence of dietary consultations on the answers to the 11 statements concerning deviation and application of the LFD and a possible influence on satisfaction with the LFD was researched.

No significant difference in the number of dietary consultations can be found between patients who agree and patients who disagree for none of the statements concerning possible reasons to deviate from the LFD, when two-tailed tested with the Mann-Whitney U test (see Addendum B table 15). A p-value of 0.581 is found for the statement "1. When I don't have any symptoms, I follow less strictly my low FODMAP-diet.", a p-value of 0.824 for the statement "2. I deviate from my low FODMAP-diet when I'm eating with other people and when I feel social pressure.", a p-value of 0.807 for the statement "3. I deviate from my low FODMAP-diet when I'm eating at my friends' or at my family's place.", a p-value of 0.961 for "4. I deviate from my low FODMAP-diet when I'm eating in a restaurant." and a p-value of 0.726 for "5. I deviate from my low FODMAP-diet when I'm on holiday.".

A significant difference (p-value =0.017) in number of dietary consultations is found with the Mann-Whitney U test when comparing patients who agree that low-FODMAP food is difficult to find (statement 6) with patients who disagree. When calculating the mean rank of dietary consultations for the two groups of patients, it is found that patients who find low-FODMAP food difficult to find, went significantly to less dietary consultations than patients who disagree (table 16).

For the other statements regarding obstacles of implementation of LFD in real life, no significant difference in dietary consultations can be shown between patients who agree and patients who disagree (table 32). The p-value found when testing statement "7. Low FODMAP food is expensive." is 0.289, when testing "8. I find it difficult to know which food I can eat and which food I can't." 0.430, when testing "9. I' m enjoying less my meal when I'm eating low FODMAP." 0.854, when testing "10. I don't feel informed enough to know what I

can and cannot eat." 0.075 and when analysing "11. I find it difficult to apply the FODMAP-diet in real life." 0.928.

Table 16. Difference in number of dietary consultations between patients agreeing and patients not agreeing to statements 6 to 11.

			Number of dietary consultations	
		N	Mean rank	Sum of ranks
6. Low FODMAP food is difficult to find.	Agree	26	32,2	839,0
	Disagree	55	45,1	2482,0
	Total	81		
7. Low FODMAP food is expensive.	Agree	48	39,2	1882,5
	Disagree	34	44,7	1520,5
	Total	82		
8. I find it difficult to know which food I can eat and which food I can't.	Agree	32	39,0	1247,0
	Disagree	50	43,1	2156,0
	Total	82		
9. I' m enjoying less my meal when I'm eating low FODMAP.	Agree	37	41,0	1516,0
	Disagree	45	41,9	1887,0
	Total	82		
10. I don't feel informed enough to know what I can and cannot eat.	Agree	8	27,8	222,0
	Disagree	74	43,0	3181,0
	Total	82		
11. I find it difficult to apply the FODMAP-diet in real life.	Agree	50	41,3	2065,5
	Disagree	32	41,8	1337,5
	Total	82		

Finally, a significant difference (p-value = 0.002) in number of dietary consultations is found between patients who agree to be happy that they follow or have followed the LFD and patients who disagree. Patients who are satisfied with the therapy have received more dietary consultations than patients who do not (table 17).

Table 17. Difference in number of dietary consultations between patients who are satisfied with the LFD and patients who are not.

			Number of dietary consultations	
		N	Mean rank	Sum of ranks
I'm satisfied that I follow or that I have followed the LFD.	Agree	73	43,51	3176,00
	Disagree	8	18,13	145,00
	Total	81		

DISCUSSION

1. Discussion of results

1.1 Demographics

79% of the participants in this study are female, which is comparable to other studies researching the effect of LFD in patients with IBS, such as Hustoft et al. (75%) (59), Böhn et al. (79%) (64), McIntosh et al. (83%) (66), Pederson et al. (73%) (68), Halmos et al. (70%) (69) and Maagaard et al. (82%) (73). 39% of the participants have been diagnosed with IBS-

D, 9.8% with IBS-C, 46.3% with IBS-M and 4.9% are classified as IBS-U. Guilera et al. conducted a systematic review to study the distribution of IBS-subtypes, but no consistent prevalence could be concluded. (75) The distribution depends on the population that is evaluated, on the geographical location and on the criteria used to define the different IBS clinical subtypes. (75) Thus, no relevant comparison could be made of the in this study found distribution with other studies. However, the small percentage of patients with IBS-C is striking. This can imply that patients with IBS-C are less often referred by the gastroenterologist for a diet low in FODMAPs. Nevertheless, it should be taken into consideration that the participant group of this study is small and non-response bias may have occurred.

1.2 Adherence and satisfaction

With an adherence rate of 80%, the results are in line with several other studies such as de Roest et al. (76) and Shepherd et al. (77) (75 and 77 % respectively). These high adherence rates seem to suggest that the diet is easy to follow. However, the subjects of this study indicated that the diet did present them with several difficulties. Across all subjects that follow or have followed the diet, 62.2 percent indicated that they had trouble applying a LFD in real life, over 41.1 percent indicated that they experienced trouble knowing what food types to avoid and 34.8 percent responded that FODMAP-low ingredients were hard to find. 57.8% of the participants also indicated that low FODMAP food is expensive. These results about the difficulty in applicability and time management are conform the results in several other studies. O'Keeffe M et al. reported that 64% of their subjects following a LFD agreed to the statement that it takes extra time to shop for their current diet and 45 percent indicated that it takes them extra time to cook their meal. (78) However, the subjects of this study did not feel that the information that was given during the dietary consultations was lacking. Only 12,2 percent indicated that they had received too little information about what food types they should and shouldn’t avoid. Those numbers suggest that the dietary consultations seem to be very helpful, but that there is a need for help in applying a LFD in real life, such as cooking manuals or short comprehensive lists to show people quickly which everyday products contain which FODMAPs. Gearry et al. proved that distribution of FODMAP-specific cookbooks and a fructose malabsorption guide improved the adherence, due to enabling a larger variety in diet and the access to food lists and recipes containing low FODMAP food. (79) Other possible solutions can be found in the use of Ehealth apps. These apps are already commonly used to assess symptoms and could offer an easy to access help in implementing a LFD in daily life. A review conducted by Ankersen DV et al. (80) investigated the use of these apps in the treatment of IBS and IBD and these apps showed positive outcomes regarding adherence and quality of life, but the functionalities concerning patient

education and patient-provider communication were still lacking. With proper improvements, EHealth apps could have a considerable impact on improving the application of a LFD in the daily routine and on the time consumption of the diet.

Although the general adherence rate is high, most of the IBS patients following a LFD are not very strict in following the diet. Only 15,3 percent of the subjects that still follow the diet, eat low FODMAP every day of the week. Most people deviate once every few weeks or once a week. These deviations in adherence to the diet can possibly be attributed to several more social factors. People find it hard to follow their diet when eating at a friends' or family's place, eating with other people, when going to a restaurant and when going on a holiday (50%, 52.1%, 55.6% and 55.6% respectively). These findings are in agreement with O'Keefe M et al. (78) and Gearry et al. (79). This might suggest that people prefer to not openly talk about their diet and that they do not want to burden other people with the need to cook low FODMAP. The fact that people deviate from the diet when going to a restaurant and when going on holiday can also be attributed to the fact that low FODMAP meals are commonly described as bland. (79) 46,7% of the participants enjoy their meal less when eating low FODMAP. It seems that a tasty meal once in a while outweighs the benefits of following the diet strictly. 50% of the participants also state to deviate from their LFD when they do not have any symptoms.
Despite these remarks concerning the difficulty of applying the diet, 89 % is satisfied that they follow or have followed the diet. This high rate of satisfaction is seen in several other studies such as O'Keefe M et al. (78) and Staudacher et al. (81). This might suggest that the diet is an acceptable and tolerated treatment for IBS.

1.3 Dietary consultations

61.1% of all participants had three consultations or more with the dietician of the Ghent university hospital. In order to complete the LFD, at least 1 consultation is needed for the restriction phase, 1 for the reintroduction phase and 1 for the stabilisation phase. It is remarkable that only 61.1% of the patients completed the whole process of the LFD, but 80% still follow the LFD. These results suggest that patients managed to adapt their diet to their symptoms and as such, developed their personalised LFD without the intensive guidance of a dietician or used other instruments than the dietary consultation provided in hospital to guide them. In line with those results, no significant difference in number of dietary consultations could be found between patients who are still following the LFD and patients who have quit. Neither is the number of dietary consultations associated with the frequency of deviating from the LFD nor with possible reasons for deviating.

No associations were found between the number of dietary consultations and IBS-QOL scores nor between the number of dietary consultations and disease course. An association was found between the number of dietary consultations and severity of flatulence. Patients who had at least 3 dietary consultations experienced less severe flatulence during the past 10 days than other patients (P=0.001).

Furthermore, patients who went to less dietary consultations, find it more difficult to find low-FODMAP food (P=0.017). This might suggest that the dietary consultations in their current form help people to know where to buy LFD-ingredients.

Patients who are satisfied with the therapy have received more dietary consultations than patients who do not. This may suggest that more dietary consultations can improve satisfaction with the diet, or, alternatively, that more satisfied patients return more easily to the dietician. However, it should be noted that only 3 patients of the 90 participants were not satisfied with the LFD and thus, this result should be interpreted with caution due to the small sample size.

1.4 IBS-QOL

The mean IBS-QOL was 72.3 in the last 30 days with a range of 63.4. This result is slightly better than the results of several short-term studies. (82-84)
The participants of this study scored highest on the sexual (mean= 85.7) and the relationship subscale (mean = 82.0) and lowest on the Food avoidance subscale (mean = 53.0). The low mean score on the Food avoidance subscale can be attributed to the fact that the questions concerning this subscale ask about the avoidance of food, which is inherent to a diet.

Surprisingly, there was no significant difference in IBS-QOL between participants that did not follow the diet anymore and participants that still followed the diet (p= 0.34). No baseline values were assessed to compare to and there might have been participation bias, especially in the group that did not follow the diet anymore. No studies were found that investigated the IBS-QOL of patients that quit the diet versus patients that still follow the diet long-term. More research is needed to investigate this particular finding. Neither was a significant difference in IBS-QOL found between study participants that followed the diet strictly and participants that were more lenient in following the diet (p= 0.671). This finding strengthens the belief that patients are not required to follow the diet strictly and that a deviation from the diet once in a while does not have an impact on the quality of life. However, it can only be hypothesized that this is the case, as the role of possible confounders was not investigated. In addition,

there were no studies found that thoroughly investigated this statement, thus more research is needed to determine the effects of the strictness of following a LFD on the quality of life.

1.5 Disease course

When asked how patients would describe their disease course from the start of the LFD to the completion of the questionnaires, the mild IBS with indolent course was the most prevalent in the group of patients still following the LFD (47.9 %), followed by chronic IBS with continuous course with only 28.2 %. This result suggests that the a low FODMAP diet helps in decreasing the disease activity over a long period of time and that the effect of a low FODMAP diet is one that requires a decent amount of time to reach its full effect. This means that even in patients with a small initial effect, it should be recommended to adhere to the diet for a sufficiently long duration before evaluating the effectiveness and deciding to change the treatment. This long-term improvement is something that is also observed in the few studies that evaluated the long-term effect of a LFD in IBS. (78) However, it can only be suggested that the disease course is the result of the diet, and not vice versa, as no information is available concerning the disease course prior to starting the diet. The fact that there is no significant difference in disease course between patients still following a LFD and patients not following a LFD diet anymore can suggest that even after quitting a LFD, the positive effects on the disease course are carried over for a period of time. This effect has not been studied thoroughly and requires further investigation. The lack of a significant difference can also be attributed to the fact that the group of patients not following a LFD anymore is rather small, and thus the test could lack power. Data concerning the disease courses prior to the start of the diet were not available, making it unable to identify whether the adherence to the LFD influenced the disease course, or the disease course influenced the adherence to the diet.

The strictness in following the diet also seems to be associated with the disease course. Chronic IBS with continuous course was significantly more present in patients following the diet less strictly (deviating twice or more a week from the diet). It is however not clear whether the patients adapt their diet to their disease course or vice versa, as no significantly larger presence of mild IBS with an indolent course was observed in the group that never deviated from the diet. Neither did the group of patients that follow the diet periodically, experience more chronic IBS with continuous course. This may suggest that when the LFD is followed for a longer period, a carry-over effect is possible.

1.6 IBS symptoms

According to the electronic patient files, 34.1% of the participants experienced abdominal bloating and/or flatulence when they were referred to the dietician. The investigation of the questionnaires shows that abdominal distension was in average the most severe symptom during the past 10 days (mean score= 5.5), followed by flatulence (mean score= 5.0) and abdominal pain (mean score= 4.5). There is no significant difference in severity of abdominal distension and flatulence between patients still following the LFD and patients who do not. However, as the severity of the symptoms was not assessed at the start of the LFD in this study, no clear conclusions on long-term improvements of abdominal distension and flatulence in the patients following a LFD can be made. In the existing literature about LFD and its effect on IBS, no long-term RCT's were conducted yet, but the results for improvement of severity of abdominal distension and flatulence on short-term are promising. In the study of Maagaard et al., 82% of the participants with IBS following a LFD answered a subjective improvement of abdominal bloating. The median time between the first dietary consultation and the completion of the questionnaire analysis was 15 months. (73) Hustoft et al. followed a group of 20 IBS-patients and investigated the effect of LFD after three weeks of implementation. The patient group experienced significantly less severe abdominal distension after the 3 weeks of LFD than at the start (P<0.001). (59) Böhn et al. concluded as well in their RCT that after 4 weeks, abdominal distension was significantly reduced in the patient group following the LFD compared to baseline (P<0.001). (64) Staudacher et al and Halmos et al found in their RCTs that after respectively 3 and 4 weeks of LFD, the intervention group following the LFD experienced significantly less severe bloating (P- values are respectively 0.002 and smaller than 0.001) than the control group (IBS-patients eating respectively their habitual diet or the typical Australian diet). (62, 69)

In this study, patients who are still following the LFD experience significantly less severe abdominal pain than patients who stopped following the diet or patients who have never started the LFD (P=0.044). However, this result should be interpreted with caution as patients may have stopped following the LFD when they didn't experience less severe abdominal pain when following the diet. In the study of Maagaard et al., 74% of the IBS-patients following the LFD (median duration 15 months) reported an improvement of abdominal pain. (73) Although long-term effects of LFD cannot be proven because of both study designs, a trend can be observed that following a LFD is associated with milder severity of abdominal pain. The results of the short-term RCTs are diverse. Staudacher et al. did not find a significant difference in intensity of abdominal pain after 4 weeks between patients following a LFD and patients following their habitual diet (P=0.07). (62) McIntoch et al. and Halmos et al., however, reported significantly less severe abdominal pain after 3

weeks in patients following LFD compared to a control group respectively following a high FODMAP diet (P=0.007) and a control group following a typical Australian diet (P<0.001). (66, 69) The severity of abdominal pain decreased significantly in patients following the LFD after 3 weeks in the study of Hustoft et al. (P<0.001), after 3 weeks in the RCT of McIntoch et al. (P=0.002) but did not decrease significantly after 4 weeks in the RCT of Böhn et al. (P=0.07). (59, 64, 66)

A median of 3 days with abdominal pain in the last 10 days was encountered in the patient group of this study. No significant difference in number of days could be found between patients still following the LFD and patients who do not (P=0.247). This result is not in line with the results of short-term RCT's. Staudacher et al. and McIntosh et al. found significant less days of abdominal pain when compared to their control group (habitual diet and high FODMAP diet) (P=0.02 and P=0.01). (62, 66) Hustoft et al. and Böhn et al. compared the frequency of abdominal pain in patients between baseline and after 3 or 4 weeks of following the LFD, and found a significant reduction in days of abdominal pain (P=0.001 and P=0.008). (59, 64) Mc Intoch et al., on the contrary, did not show a significant decrease in IBS patients following the LFD (P=0.07). (66)

67.8% of the participants in this study answered that they had felt urgent urge to defecate during the past ten days without a difference between patients still following a diet and patients who do not. Staudacher et al. compared in a short-term RCT defecation urge between patients following a LFD and patients following their habitual diet and could not find a difference either. (62)

2. Limitations and bias

There are several limitations which should be considered when interpreting the test results. The biggest limitation is the fact that no data were available concerning quality of life, symptom severity and disease burden of the study participants prior to starting the LFD. This hinders investigation of the long-term impact of the LFD on IBS-QOL, disease course and IBS symptoms. Another limitation is the fact that all recruited participants have been given information about the LFD by the same dietician. This means we can only speculate how much impact the quality of dietary consultations have on the adherence and effect of the diet. However, it also means that every patient had the same quality of dietary consultation and thus, a difference in answers cannot be attributed to a difference in dietician.
The response rate is rather low, 38%, and has perhaps led to a less diverse population.

However, the response rate is in line with other questionnaire studies that have sent questionnaires by e-mail or regular mail.(16, 76, 78) Patients who did not answer the questionnaires, did not give informed consent to access their electronic patient files and thus demographics of this patient group could not be evaluated. This makes it impossible to evaluate whether or not the study group was representative for the population and thus there is a chance of selection bias.

Dietary intake was measured using several questions asking about the adherence to the LFD and if certain food types were avoided/consumed less. As no standardized assessment was conducted concerning the dietary intake of patients who are following the LFD and patients who are not following a LFD anymore, the results might have been biased. This however contributes to the fact that the results are more in line with the way people will approach the long-term LFD in their everyday life and which results can be expected in an everyday life setting.

Most of the participants (80%) were still following a diet in which certain FODMAP-rich food types are avoided. The high percentage can be caused by participation bias. There is also a possibility of response bias, as only one questionnaire was validated and all of them were based on self-report and multiple choice. As all of the data about symptom severity were gathered by questionnaires, there was no way to objectively evaluate the severity of disease of the participants.

All of the participants were IBS patients in the Ghent University Hospital and thus may have had a more severe and therapy-resistant form of IBS than usually found in primary care. This makes it more difficult to extrapolate the results and to formulate suggestions for the management of IBS in the primary care setting.

To evaluate the long-term effect of LFD on IBS symptoms, disease course and IBS-QOL properly, a cross-over study should be conducted during a long period (at least until the end of the reintroduction phase). Symptoms, QOL and disease course should be assessed with a validated questionnaire at baseline and on a regular base during the follow-up term. It can be clinically relevant to evaluate the effect of LFD for each IBS-subtype separately and compare with a control group of the same IBS-subtype that receive the standard of care of that IBS-subtype.

3. Conclusion

This study investigated the long-term QOL, disease course and symptoms in patients with IBS and the long-term adherence and satisfaction to a LFD. With a mean IBS-QOL score of 72.3 on a scale of 100, the long-term IBS related quality of life seems to be similar to or even slightly better than the results found in short term studies. We were however not able to identify a significant difference in IBS-QOL between participants that did not follow the diet anymore and participants that still followed the diet. The predominant disease course in the participants of this study was mild IBS with indolent course (43.0%) No significant difference in disease course could be identified between patients who still followed the LFD and patients who did not. However, an association could be found between disease course and the degree of deviating from the LFD. Abdominal distention was rated the most severe IBS symptom by the participants, followed by flatulence and abdominal pain. Less severe abdominal pain was associated with still following the LFD. No conclusions on the long-term effect of LFD on QOL, disease course and the symptoms of IBS could be made in this study due to the study design and only hypotheses could be formulated. The high long-term adherence and satisfaction rates of this study show that the LFD is a diet people with IBS are willing to adhere to. Dietary consultations are a good medium to inform the IBS-patients on what they can and cannot eat and help patients to find their low FODMAP food. Despite these consultations however, people do indicate that they find it difficult to implement this diet in daily life and only 15,3% of the participants follow the LFD strictly. Practical issues, social factors and the absence of symptoms were indicated as the main reasons for a drop in adherence. Studies show that certain tools such as applications or product labelling can help in reducing the effort to adhere long-term to the diet and further improve the Quality of Life. These applications could also lead to a better education of the patient and could be used to enhance the patient-provider communication. These improvements however still require more investigation to evaluate the full effect of their implementation on the adherence to the LFD.

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ADDENDUM

ADDENDUM A

ALGEMENE VRAGENLIJST

Deel 1: Algemene informatie

1. Neemt u medicatie? Zo ja, welke?

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2. Had u al langer dan 6 maanden darmklachten voordat u het dieet gestart bent?

(Omcirkel het antwoord dat het meest voor u van toepassing is)

- Ja
- Neen
- Weet niet

3. Rookt u?

- Ja
- Neen

Deel 2: Therapietrouw bij laag FODMAP-Dieet

Deze reeks vragen peilt naar de striktheid waarmee u uw dieet volgt.

1. Gelieve het best passende antwoord te omcirkelen:

- Ik heb het dieet nooit gevolgd.
- Ik heb vroeger bepaalde FODMAP-rijke voedingsmiddelen vermeden, maar nu eet ik terug alles.
- Ik volg nog altijd een dieet waarbij ik bepaalde voedingsmiddelen vermijd.

2. Indien u "Ik heb het dieet nooit gevolgd" hebt geantwoord: Waarom bent u nooit begonnen aan het dieet na de consultatie? (Ga hierna verder met vraag 5 op pagina 5: FODMAP-arme voedingsmiddelen zijn moeilijk te vinden.)

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3. Indien u "ik heb vroeger bepaalde FODMAP-rijke voedingsmiddelen vermeden, maar nu eet ik terug alles." hebt geantwoord: Waarom bent u gestopt met het dieet? (Ga hierna verder met vraag 5 op pagina 5: FODMAP-arme voedingsmiddelen zijn moeilijk te vinden.)

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4. Indien u "Ik volg nog altijd een dieet waarbij ik bepaalde voedingsmiddelen vermijd" hebt geantwoord:

a. Welke voedingsmiddelen vermijdt u strikt?

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b. Van welke voedingsmiddelen eet u slechts een kleine hoeveelheid? (minder dan voorheen)

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c. Hoe frequent wijkt u af van uw FODMAP-arm dieet? (Omcirkel het meest passende antwoord)

- Nooit
- Minder dan 1 maal per week
- 1 maal per week
- 2 of meer dan 2 maal per week
- Ik volg het dieet periodiek(nu eens een week wel, dan weer een week niet)

d. Gelieve telkens het best passende antwoord aan te duiden bij de volgende stellingen:
Wanneer ik geen symptomen heb, houd ik me minder strikt aan mijn dieet.

- Akkoord
- Niet akkoord

Ik wijk af van mijn laag FODMAP-dieet wanneer ik met andere mensen samen eet en sociale druk ondervind.

- Akkoord
- Niet akkoord

Ik wijk af van mijn FODMAP-arm dieet wanneer ik bij vrienden of familie ga eten.

- Akkoord
- Niet akkoord

Ik wijk af van mijn FODMAP-arm dieet wanneer ik op restaurant eet.

- Akkoord
- Niet akkoord

Ik wijk af van mijn FODMAP-arm dieet wanneer ik op reis ben.

- Akkoord
- Niet akkoord

5. FODMAP-arme voedingsmiddelen zijn moeilijk te vinden.

- Akkoord
- Niet akkoord

6. FODMAP-arme voedingsmiddelen zijn duur.

- Akkoord
- Niet akkoord

7. Ik vind het moeilijk om te weten welke voeding ik wel en niet mag eten.

- Akkoord
- Niet akkoord

8. Ik vind mijn eten minder lekker als ik FODMAP-arm eet.

- Akkoord
- Niet akkoord

9. Ik vind dat ik te weinig geïnformeerd ben over wat ik wel en niet mag eten.

- Akkoord
- Niet akkoord

10. Ik vind het moeilijk om het FODMAP-arm dieet toe te passen in de praktijk.

- Akkoord
- Niet akkoord

11. Ik ben tevreden dat ik het FODMAP-arm dieet gevolgd heb.

- Akkoord
- Niet akkoord

Deel 3: Ziekteverloop

Onderstaande grafieken tonen vier mogelijke verlopen van prikkelbare darmsyndroom met op de verticale as de ernst van de ziekte, en op de horizontale as de tijd, vanaf de start van

het dieet tot nu. Gelieve het ziekte verloop aan te duiden dat het best uw ziekteverloop benadert. U kan slechts 1 ziekteverloop aanduiden.

Optie 1

Optie 2

Optie 3

Optie 4

Deel 4: IBS symptoom score

Deze reeks vragen is opgesteld om de ernst van u IBS symptomen to meten. Het is te verwachten dat uw symptomen variëren in de tijd, dus probeer gelieve de vragen te beantwoorden gebaseerd op hoe u zich over de LAATSTE TIEN DAGEN heeft gevoeld.

1. Hoe uitgesproken was de buikpijn die u ervaren heeft gedurende de laatste 10 dagen?

Helemaal niet uitgesproken	0	1	2	3	4	5	6	7	8	9	10	Heel erg uitgesproken

2. Hoeveel dagen had u last van buikpijn gedurende de laatste 10 dagen?
……. dagen

3. Hoe uitgesproken was het opgeblazen gevoel die u ervaren heeft tijdens de laatste 10 dagen?

Helemaal niet uitgesproken	0	1	2	3	4	5	6	7	8	9	10	Heel erg uitgesproken

4. Hoe uitgesproken was de winderigheid die u ervaren heeft gedurende de laatste 10 dagen?

Helemaal niet uitgesproken	0	1	2	3	4	5	6	7	8	9	10	Heel erg uitgesproken

5. Hoeveel stoelgangen heeft u gemiddeld per dag gemaakt gedurende de laatste 10 dagen?
…… stoelgangen per dag

6. Heeft u een gevoel van hevige aandrang voor stoelgang gehad gedurende de laatste 10 dagen? (omcirkel het meest passend antwoord)

- Ja
- Neen

ADDENDUM B

Table 1. Overview of RCTs studying the effect of LFD in IBS							
Study	**Design**	**Duration**	**LFD definition/IBS definition**	**Subjects with IBS**	**Method**	**IBS-type**	**Results**
Hustoft TN et al; 2016 (59)	randomized double-blinded, placebo-controlled crossover trial	9 week study period	IBS: ROME III criteria LFD: writtin and oral information by a dietician	20	LFD vs high-FOS(fructo-oligosaccharide) diet.	IBS-D IBS-M	When supplementing the LFD with 16g of high FODMAP or placebo, significantly more participants reported symptom relief in response to placebo (80%) than FOS (30%; *p*=.013).
Eswaran SL et al; 2016 (70)	single-center, randomized-controlled trial	4 week study period	IBS: ROME III criteria LFD: The Complete Low-FODMAP Diet: A Revolutionary Plan for Managing IBS and Other Digestive Disorders (Shepherd, Gibson)	84 LFD(n=45) mNICE diet(n=39)	LFD vs mNice diet	IBS-D	52% of the LFD vs. 41% of the mNICE group (70)reported adequate relief of their IBS-D symptoms (*p*=0.31)
McIntosh K et al;2016 (66)	randomized controlled, single blind study	3 weeks	IBS: ROME III criteria and symptoms greater than 6 months LFD: 60 min with a GI dietician and 5 sample meals	37 LFD(n=19) high FODMAP diet(n=18)	LFD vs high FODMAP diet	not specified	The IBS-SSS was reduced in the LFD group (p<0.001) but not in the high FODMAP group.
Böhn L et al; 2015 (64)	multi-center, parallel, single-blind randomized controlled trial	4 weeks	IBS: ROME III criteria LFD: Dietary advice by experienced dieticians and a brochure	67 LFD(n=33) traditional diet(n=34)	LFD vs a traditional IBS diet	not specified	At the end of the diet period, 19 patients (50%) in the LFD group had reductions in IBS severity scores ≥50 compared with baseline vs 17 patients (46%) in the traditional IBS diet group (*p* = .72).

Pedersen et al, 2014 (68)	randomized unblinded controlled trial	6 week study period	IBS: ROME III criteria LFD: 1 hour info session with dietician/nutritionist and a list with high FODMAP food	123 LFD(n=42) LGG(n=41) Normal Danish diet(n=40)	LFD vs a Lactobacillus rhamnosus GG probiotic(LGG) vs a normal Danish/Western diet(ND)	IBS-D, IBS-C, IBS-A	A statistically significant reduction in the IBS-SSS was observed in LFD and LGG groups compared to the ND group, mean IBS-SSS 133 ± 122 vs 68 ± 107, 133 ± 122 vs 34 ± 95, $p < 0.01$,
Halmos et al, 2014 (69)	randomized controlled, single-blind, cross-over trial	9 week study period	IBS: ROME III criteria LFD: 3 main meals and 3 snacks were provided, Low FODMAP of ≤ 0.5 g per sitting. Additional food lists were provided	30 and 8 healthy individuals	LFD vs a typical Australian diet	not specified	Subjects with IBS had lower overall gastrointestinal symptom scores on LFDs, compared with the Australian diet ($p < .001$) and the subjects' habitual diet.
Staudacher et al, 2012 (62)	randomized controlled trial	4 weeks	IBS: ROME III criteria LFD: advice by an experienced dietician: restrict foods high in fructan, GOS, polyols, lactose, and excess fructose	41 LFD(n=19) normal diet(n=22) 6 withdrew	LFD vs a habitual diet	Not specified	In the LFD population, more experienced a reduction in scores for bloating ($p = 0.007$), borborygmi ($p = 0.04$), urgency ($p = 0.047$), and overall symptoms ($p = 0.006$) compared with the control group

Table 2. Differences in each IBS-QoL subclass according the degree of deviation from the LFD.			
		N	**Mean rank**
Dysphoria	Patients who never deviate from LFD	9	38,6
	Patients who deviate less than once a week from LFD	19	33,3
	Patients who deviate once a week from LFD	15	35,7
	Patients who deviate twice a week or more from LFD	19	34,3
	Patients who follow LFD periodically	5	22,4
	Total	67	
Interference with activity	Patients who never deviate from LFD	11	31,1
	Patients who deviate less than once a week from LFD	19	34,1
	Patients who deviate once a week from LFD	15	37,0
	Patients who deviate twice a week or more from LFD	18	38,1
	Patients who follow LFD periodically	5	23,0
	Total	68	
Body image	Patients who never deviate from LFD	11	31,8
	Patients who deviate less than once a week from LFD	19	37,6
	Patients who deviate once a week from LFD	15	32,4
	Patients who deviate twice a week or more from LFD	20	39,6
	Patients who follow LFD periodically	5	28,4
	Total	70	
Health worry	Patients who never deviate from LFD	11	35,3
	Patients who deviate less than once a week from LFD	19	34,3
	Patients who deviate once a week from LFD	15	39,1
	Patients who deviate twice a week or more from LFD	19	33,6
	Patients who follow LFD periodically	5	30,1
	Total	69	
Food avoidance	Patients who never deviate from LFD	11	31,0
	Patients who deviate less than once a week from LFD	18	25,1
	Patients who deviate once a week from LFD	15	36,1
	Patients who deviate twice a week or more from LFD	20	43,2
	Patients who follow LFD periodically	5	43,3
	Total	69	
Social reaction	Patients who never deviate from LFD	11	31,4
	Patients who deviate less than once a week from LFD	18	28,2
	Patients who deviate once a week from LFD	15	31,4
	Patients who deviate twice a week or more from LFD	20	42,8
	Patients who follow LFD periodically	5	47,0
	Total	69	
Sexual	Patients who never deviate from LFD	10	42,5
	Patients who deviate less than once a week from LFD	20	34,7
	Patients who deviate once a week from LFD	14	35,1
	Patients who deviate twice a week or more from LFD	19	29,2
	Patients who follow LFD periodically	5	36,4
	Total	68	
Relationship	Patients who never deviate from LFD	11	26,0
	Patients who deviate less than once a week from LFD	20	35,8
	Patients who deviate once a week from LFD	15	41,4
	Patients who deviate twice a week or more from LFD	20	41,2
	Patients who follow LFD periodically	5	21,9
	Total	71	

Table 3. Differences in each IBS-QoL subclass between patients who completed the LFD and patients who did not.				
		N	**Mean rank**	**Sum of ranks**
Dysphoria	Patients who completed the 3 phases of the LFD.	27	41,6	1122,0
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	51	38,4	1959,0
	Total	78		
Interference with activity	Patients who completed the 3 phases of the LFD.	26	38,8	1009,5
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	54	41,3	2230,5
	Total	80		
Body image	Patients who completed the 3 phases of the LFD.	27	39,1	1054,5
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	55	42,7	2348,5
	Total	82		
Health worry	Patients who completed the 3 phases of the LFD.	26	35,2	914,5
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	54	43,1	2325,5
	Total	80		
Food avoidance	Patients who completed the 3 phases of the LFD.	27	45,2	1220,0
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	54	38,9	2101,0
	Total	81		
Social reaction	Patients who completed the 3 phases of the LFD.	27	40,2	1086,5
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	53	40,6	2153,5
	Total	80		
Sexual	Patients who completed the 3 phases of the LFD.	26	34,6	900,0
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	53	42,6	2260,0
	Total	79		
Relationship	Patients who completed the 3 phases of the LFD.	27	42,0	1133,5
	Patients who didn't complete the 3 phases of the LFD with help of the UZ Ghent dietician.	55	41,3	2269,5
	Total	82		

Table 4. Crosstabulation disease course*following the LFD				
		Patients still following the LFD.	Patients not following the LFD.	Total
Mild IBS with indolent course	Count	34	3	37
	% within disease course	91,9%	8,1%	100,0%
	% within patient group	47,9%	20,0%	43,0%
Mild IBS with aggressive course	Count	2	1	3
	% within disease course	66,7%	33,3%	100,0%
	% within patient group	2,8%	6,7%	3,5%
Chronic IBS with continuous course	Count	20	7	27
	% within disease course	74,1%	25,9%	100,0%
	% within patient group	28,2%	46,7%	31,4%
Chronic IBS with intermittent course	Count	15	4	19
	% within disease course	78,9%	21,1%	100,0%
	% within patient group	21,1%	26,7%	22,1%
Total	Count	71	15	86
	% within disease course	82,6%	17,4%	100,0%
	% within patient group	100,0%	100,0%	100,0%

Table 5. Crosstabulation disease course*completion of LFD				
		Patients completed the LFD.	Patients not completed the LFD.	Total
Mild IBS with indolent course	Count	7	28	35
	% within disease course	20,0%	80,0%	100,0%
	% within patient group	30,4%	50,9%	44,9%
Mild IBS with aggressive course	Count	1	1	2
	% within disease course	50,0%	50,0%	100,0%
	% within patient group	4,3%	1,8%	2,6%
Chronic IBS with continuous course	Count	9	16	25
	% within disease course	36,0%	64,0%	100,0%
	% within patient group	39,1%	29,1%	32,1%
Chronic IBS with intermittent course	Count	6	10	16
	% within disease course	37,5%	62,5%	100,0%
	% within patient group	26,1%	18,2%	20,5%
Total	Count	23	55	78
	% within disease course	29,5%	70,5%	100,0%
	% within patient group	100,0%	100,0%	100,0%

Table 6. Difference in IBS symptoms according to frequency of deviation from LFD.			
		N	Mean rank
Severity of abdominal pain	Patients who never deviate from LFD	11	38,5
	Patients who deviate less than once a week from LFD	20	34,1
	Patients who deviate once a week from LFD	15	39,1
	Patients who deviate twice a week or more from LFD	20	37,3
	Patients who follow LFD periodically	5	23,8
	Total	71	
Number of days with abdominal pain	Patients who never deviate from LFD	11	35,6
	Patients who deviate less than once a week from LFD	19	34,7
	Patients who deviate once a week from LFD	15	35,6
	Patients who deviate twice a week or more from LFD	19	36,6
	Patients who follow LFD periodically	5	27,3
	Total	69	
Severity of abdominal distension	Patients who never deviate from LFD	11	40,8
	Patients who deviate less than once a week from LFD	20	30,4
	Patients who deviate once a week from LFD	15	38,1
	Patients who deviate twice a week or more from LFD	20	36,8
	Patients who follow LFD periodically	5	38,5
	Total	71	
Severity of flatulence	Patients who never deviate from LFD	11	35,0
	Patients who deviate less than once a week from LFD	20	36,9
	Patients who deviate once a week from LFD	15	36,9
	Patients who deviate twice a week or more from LFD	20	36,7
	Patients who follow LFD periodically	5	29,3
	Total	71	
Average number of defecations per day	Patients who never deviate from LFD	11	35,2
	Patients who deviate less than once a week from LFD	20	35,8
	Patients who deviate once a week from LFD	15	36,8
	Patients who deviate twice a week or more from LFD	20	34,6
	Patients who follow LFD periodically	5	41,8
	Total	71	

Table 7. Difference in number of consultations between patients still following the LFD and patients who do not.				
		N	Mean rank	Sum of ranks
Number of dietary consultations	Patients still following the LFD.	66	42,1	2777,0
	Patients not following the LFD.	16	39,1	626,0
	Total	82		

Table 8. Difference in number of consultations according to the frequency of deviation from the LFD.			
		N	Mean rank
Number of dietary consultations	Patients who never deviate from LFD	10	35,9
	Patients who deviate less than once a week from LFD	18	33,9
	Patients who deviate once a week from LFD	15	38,8
	Patients who deviate twice a week or more from LFD	19	28,8
	Patients who follow LFD periodically	4	28,4
	Total	66	

Table 9. Crosstabulation frequency of deviation from LFD*statement 2					
			2. I deviate from my low FODMAP-diet when I'm eating with other people and when I feel social pressure.		
			Agree	Disagree	Total
How frequent do you deviate from your LFD?	Never	Count	4	7	11
		%	36,4%	63,6%	100,0%
	Less than once a week.	Count	8	12	20
		%	40,0%	60,0%	100,0%
	Once a week.	Count	10	4	14
		%	71,4%	28,6%	100,0%
	Twice or more than twice a week.	Count	10	10	20
		%	50,0%	50,0%	100,0%
	I follow the diet periodically.	Count	4	1	5
		%	80,0%	20,0%	100,0%
	Total	Count	36	34	70
		%	51,4%	48,6%	100,0%

Table 10. Crosstabulation frequency of deviation from LFD*statement 1					
			1. When I don't have any symptoms, I follow less strictly my low LFD.		
			Agree	Disagree	Total
How frequent do you deviate from your LFD?	Never	Count	2	9	11
		%	18,2%	81,8%	100,0%
		A.R.	**-2,3**	**2,3**	
	Less than once a week.	Count	7	13	20
		%	35,0%	65,0%	100,0%
		A.R.	-1,7	1,7	
	Once a week.	Count	10	5	15
		%	66,7%	33,3%	100,0%
		A.R.	1,4	-1,4	
	Twice or more than twice a week.	Count	14	6	20
		%	70,0%	30,0%	100,0%
		A.R.	**2,0**	**-2,0**	
	I follow the diet periodically.	Count	3	2	5
		%	60,0%	40,0%	100,0%
		A.R.	0,4	-0,4	
	Total	Count	36	35	71
		%	50,7%	49,3%	100,0%

Table 11. Crosstabulation frequency of deviation from LFD*statement 3					
			3. I deviate from my low FODMAP-diet when I'm eating at my friends' or at my family's place.		
			Agree	Disagree	Total
How frequent do you deviate from your LFD?	Never	Count	2	9	11
		%	18,2%	81,8%	100,0%
		A.R.	**-2,2**	**2,2**	
	Less than once a week.	Count	6	14	20
		%	30,0%	70,0%	100,0%
		A.R.	**-2,0**	**2,0**	
	Once a week.	Count	11	4	15
		%	73,3%	26,7%	100,0%
		A.R.	**2,1**	**-2,1**	
	Twice or more than twice a week.	Count	13	7	20
		%	65,0%	35,0%	100,0%
		A.R.	1,7	-1,7	
	I follow the diet periodically.	Count	3	2	5
		%	60,0%	40,0%	100,0%
		A.R.	0,5	-0,5	
	Total	Count	35	36	71
		%	49,3%	50,7%	100,0%

Table 12. Crosstabulation frequency of deviation from LFD*statement 4					
			4. I deviate from my low FODMAP-diet when I'm eating in a restaurant.		
			Agree	Disagree	Total
How frequent do you deviate from your LFD?	Never	Count	2	9	11
		%	18,2%	81,8%	100,0%
		A.R.	**-2,7**	**2,7**	
	Less than once a week.	Count	8	12	20
		%	40,0%	60,0%	100,0%
		A.R.	-1,6	1,6	
	Once a week.	Count	11	4	15
		%	73,3%	26,7%	100,0%
		A.R.	1,6	-1,6	
	Twice or more than twice a week.	Count	14	6	20
		%	70,0%	30,0%	100,0%
		A.R.	1,6	-1,6	
	I follow the diet periodically.	Count	4	1	5
		%	80,0%	20,0%	100,0%
		A.R.	1,2	-1,2	
	Total	Count	39	32	71
		%	54,9%	45,1%	100,0%

Table 13. Crosstabulation frequency of deviation from LFD*statement 5					
			5. I deviate from my low FODMAP-diet when I'm on holiday.		
			Agree	Disagree	Total
How frequent do you deviate from your LFD?	Never	Count	1	10	11
		%	9,1%	90,9%	100,0%
		A.R.	**-3,3**	**3,3**	
	Less than once a week.	Count	8	12	20
		%	40,0%	60,0%	100,0%
		A.R.	-1,6	1,6	
	Once a week.	Count	11	4	15
		%	73,3%	26,7%	100,0%
		A.R.	1,6	-1,6	
	Twice or more than twice a week.	Count	14	6	20
		%	70,0%	30,0%	100,0%
		A.R.	1,6	-1,6	
	I follow the diet periodically.	Count	5	0	5
		%	100,0%	0,0%	100,0%
		A.R.	**2,1**	**-2,1**	
	Total	Count	39	32	71
		%	54,9%	45,1%	100,0%

Table 14. Crosstabulation statements 6 to 11*following the LFD or not				
		Agree	Disagree	Total
6. Low FODMAP-food is difficult to find.	Patients still following the LFD.	31,9%	68,1%	100,0%
	Patients not following the LFD.	47,1%	52,9%	100,0%
	Total	34,8%	65,2%	100,0%
7. Low FODMAP-food is expensive.	Patients still following the LFD.	58,3%	41,7%	100,0%
	Patients not following the LFD.	55,6%	44,4%	100,0%
	Total	57,8%	42,2%	100,0%
8. I find it difficult to know which food I can eat and which food I can't.	Patients still following the LFD.	36,1%	63,9%	100,0%
	Patients not following the LFD.	61,1%	38,9%	100,0%
	Total	41,1%	58,9%	100,0%
9. I' m enjoying less my meal when I'm eating low FODMAP.	Patients still following the LFD.	43,1%	56,9%	100,0%
	Patients not following the LFD.	61,1%	38,9%	100,0%
	Total	46,7%	53,3%	100,0%
10. I don't feel informed enough to know what I can and cannot eat.	Patients still following the LFD.	12,5%	87,5%	100,0%
	Patients not following the LFD.	11,1%	88,9%	100,0%
	Total	12,2%	87,8%	100,0%
11. I find it difficult to apply the FODMAP-diet in real life.	Patients still following the LFD.	58,3%	41,7%	100,0%
	Patients not following the LFD.	77,8%	22,2%	100,0%
	Total	62,2%	37,8%	100,0%

Table 15. Difference in number of dietary consultations between patients agreeing and patients not agreeing to statements 1 to 5.				
			Number of dietary consultations	
		N	Mean rank	Sum of ranks
1. When I don't have any symptoms, I follow less strictly my low FODMAP-diet.	Agree	34	34,7	1181,0
	Disagree	32	32,2	1030,0
	Total	66		
2. I deviate from my low FODMAP-diet when I'm eating with other people and when I feel social pressure.	Agree	32	33,5	1073,0
	Disagree	33	32,5	1072,0
	Total	65		
3. I deviate from my low FODMAP-diet when I'm eating at my friends' or at my family's place.	Agree	32	32,9	1053,5
	Disagree	34	34,0	1157,5
	Total	66		
4. I deviate from my low FODMAP-diet when I'm eating in a restaurant.	Agree	36	33,6	1210,0
	Disagree	30	33,4	1001,0
	Total	66		
5. I deviate from my low FODMAP-diet when I'm on holiday.	Agree	36	34,2	1232,5
	Disagree	30	32,6	978,5
	Total	66		