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Do Nutritional Therapies Provide Benefit in Irritable Bowel Syndrome?

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Statement of Probity

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List of Abbreviations

ATI; Amylase trypsin inhibitor

AGA; Antigliadin antibodies

BAD; Bile acid diarrhoea

BDA; British Dietetic Association

BSG; British Society of Gastroenterology

CD; Coeliac disease

CI; Confidence Interval

CNAQ; Comprehensive Nutrition Assessment Questionnaire

COVID-19; Coronavirus disease of 2019

DBPC; Double-blind placebo-controlled

DI; Dysbiosis index

DNA; Deoxyribonucleic acid

DRV; Dietary reference values

FGID; Functional gastrointestinal disorder

FODMAPs; Fermentable oligo-, do-, mono- saccharides and polyols

FTE; Full Time Equivalent

GCD; Gluten containing diet

GFD; Gluten free diet

GI; Gastrointestinal

GOS; Galacto-oligosaccharides

GSRS; Gastrointestinal Symptom Rating Scale

HADS; Hospital Anxiety and Depression Scale

HLA; Human leukocyte antigen

IBD; Inflammatory bowel disease

IBS; Irritable bowel syndrome

IBS-C; Constipation-predominant irritable bowel syndrome

IBS-D; Diarrhoea-predominant irritable bowel syndrome

IBS-M; Mixed-type irritable bowel syndrome

IBS-QOL; Irritable bowel syndrome quality of life

IBS-SSS; Irritable bowel syndrome symptom severity score

IBS-U; Unclassified irritable bowel syndrome

IMD; Index of Multiple Deprivation

ITT; Intention-to-treat

LFD; Low FODMAP diet

MLC; Myosin II regulatory light chain

MLCK; Myosin light chain kinase

mITT; Modified intention-to-treat

mNICE; Modified National Institute for Health and Care Excellence

MRI; Magnetic resonance imaging

NCGS; Non-coeliac gluten sensitivity

NHS; National Health Service

NICE; National Institute for Health and Care Excellence

OR; Odds Ratio

PEI; Pancreatic exocrine insufficiency

PHQ; Patient Health Questionnaire

pLFD; Personalisation phase of low FODMAP diet

PCR; Polymerase Chain Reaction

PP; Per protocol

QOL; Quality of Life

RCT; Randomized Controlled Trial

REC; Regional ethics committee

rRNA; ribosomal ribonucleic acid

SD; Standard deviation

SIBO; Small intestinal bacterial overgrowth

sLFD; Strict reduction phase of low FODMAP diet

TDA; Traditional dietary advice

UK; United Kingdom

US; United States

VAS; Visual analogue scale

WFD; Wheat free diet

WGA; Wheat germ agglutinin

ZO-1; Zonula occludens-1

Abstract

Introduction: Irritable Bowel Syndrome (IBS) is common, with a global prevalence estimated at approximately 4%, with a young age of presentation and female preponderance. The pathophysiology of IBS is not fully understood, with the prevailing hypothesis being a disorder of the brain-gut axis. Diet appears to play an important role in individuals with IBS, triggering symptoms in up to 84 percent of individuals with IBS. As a result of this, there has been an interest in the role of nutritional therapies in IBS, with a recent focus on the role of traditional dietary advice (TDA), the low fermentable oligo-, di-, mono- saccharides and polyols (FODMAPs) diet and gluten-free diet (GFD) in IBS. The aim of this thesis was to determine to role of nutritional therapies in IBS.

Methods: The long-term effects of the low FODMAP diet were explored in patients with IBS. Individuals with IBS who had received dietetic-led low FODMAP advice were approached at long term follow up. Individuals were invited to complete questionnaires assessing gastrointestinal symptoms, adherence, nutritional intake, dietary acceptability and food related quality of life at least 6 months after having received dietetic-led low FODMAP advice. A randomised controlled trial was also performed, assessing the efficacy and convenience of TDA, the low FODMAP diet and GFD head-to-head. Individuals with Rome IV-defined IBS diarrhoea or mixed subtype were recruited via two centres in the United Kingdom, and block randomised in groups of up to 5 (mean of 3) to receive TDA, LFD or a GFD. Dietary therapy commenced following face-to-face or virtual dietetic-led education, which was delivered via group sessions. The primary endpoint was clinical response after 4 weeks of dietary intervention, as defined by ≥ 50-point reduction in IBS-SSS. Finally, the provision to deliver dietary therapies to patients with IBS was assessed, comparing this to individuals with coeliac disease and inflammatory bowel disease.

Hospitals within all National Health Service (NHS) trusts in England were approached. A custom-designed web-based questionnaire was circulated via contact methods of e-mail, post or telephone. Individuals/teams with knowledge of GI dietetic services within their trust were invited to complete.

Results: The low FODMAP diet appears to be effective at long term follow up, with 60% reporting adequate relief of symptoms at a mean follow up of 44 months. The majority appear to be on the personalisation phase (76%) of the diet at long term follow up, with no alteration in nutritional intake compared to those on a habitual diet. Many purchase 'free-from' products, with the purchase of gluten or wheat free products being the commonest (68%). From the RCT, at short term follow up of 4 weeks, TDA, low FODMAP diet and GFD all appear to be equally effective, with clinical response rates of 40%, 55% and 58% respectively (p=0.30). Individuals found TDA significantly cheaper, tastier, less time-consuming to shop, easier to implement and socially more convenient than the GFD and LFD. Reductions in macro- and micro- nutrient content were similar across the groups. Clinical characteristics, socioeconomic status and baseline stool dysbiosis index did not predict response to dietary therapy. From the assessment of provision of dietetic services, there appears to a variable number of dietitians between regions (median 3.64/100,000; p=0.03) with 50% of trusts failing to deliver specialist dietetic clinics for IBS.

Conclusion: This body of work has demonstrated that there is a role for nutritional therapies for IBS, with TDA, low FODMAP diet and GFD being equally effective at short term follow up. However, TDA appears to be easier to implement for patients and maybe preferred as first line dietary therapy in view of this. The low FODMAP diet appears to

be effective at long term follow up, with many individuals using gluten or wheat free products to achieve this. Despite the efficacy of dietary therapies, there appears to be inequity of dietetic services across England to deliver these therapies. Future research is required to assess dietary therapies against pharmacological options, with novel methods such as group delivery required to implement these therapies in view of the variable provision.

Chapter 1 Overview of Dietary Therapies in Irritable Bowel Syndrome

1.1 Irritable Bowel Syndrome

Functional gastrointestinal disorders (FGIDs) are chronic gastrointestinal (GI) symptoms that occur in the absence of organic pathology to explain their presence.[1] They account for approximately 40 percent of referrals to gastroenterology, with irritable bowel syndrome (IBS) being one such FGID.[2]

IBS is the most studied FGID,[2] with a global pooled prevalence of approximately 4 percent.[3] The prevalence of IBS is greater in women than men, as well as being more prevalent in individuals under the age of 50 years.[4] It is characterised by symptoms of abdominal pain and altered bowel habit.[1] It is associated with substantial healthcare impairment and healthcare utilisation,[5] with a total per capita cost estimated of almost 3,000 euros per year in Europe.[6]

IBS is diagnosed when patients with characteristic bowel symptoms have organic pathology excluded. This should be performed following a clinical history, physical examination and minimal laboratory tests. If alarm features are absent, then a positive diagnosis of IBS can be made. If alarm features are present then invasive investigations such as a colonoscopy or other appropriate tests are considered before a diagnosis of IBS is reached.[1] Alarm features include unexplained rectal bleeding, unintentional weight loss, anaemia or a family history of colorectal cancer.[1] Over the years, diagnostic criteria have been developed to make the diagnosis of IBS. Initially the Manning and Kruis criteria were used,[7,8] but have fallen out of favour. The Manning criteria may have fallen out of favour as it was unable to distinguish between subtypes of IBS, whilst the Kruis criteria

was found to be too cumbersome to use in clinical practice.[2] Since the 1990s, a multinational working party of international experts in the field for FGIDs, termed the Rome foundation (after the birthplace of its conception), provide expert guidance on the diagnosis and management of FGIDs such as IBS. The Rome criteria have been updated over the years since, following increasing scientific evidence, and as of 2016 published its fourth iteration.[2]

The Rome IV criteria states that recurrent abdominal pain must be present at least 1 day per week, and in association with two or more of the of the following criteria: change in frequency of stool, change in form of stool, or related to defecation.[1] Criteria must be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.[1] The main subtypes of IBS are diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C) and mixed-type (IBS-M). Individuals who do not fit these classifications are labelled as unclassified IBS (IBS-U).[1]

The pathophysiology of IBS is still not fully understood, but the prevailing hypothesis is that it is a disorder of brain-gut interaction, as characterised by alterations in visceral hypersensitivity, gut immunity, enteric motor function disturbances and central processing. The intestinal microbiota has also been shown to be perturbed in a subset of IBS subjects compared to healthy controls, with its interactive crosstalk at the intestinal mucosal border possibly contributing towards the pathophysiology of IBS. Factors that may contribute to this dysregulated brain-gut axis include genetic predisposition, chronic stress, inflammation/infection, and environmental triggers such as diet, motility, visceral hypersensitivity, genetic and psychosocial factors.[9,10]

1.2 The Role of Diet in Irritable Bowel Syndrome

The majority of individuals with IBS experience symptoms following the ingestion of food, with approximately two thirds of individuals noting this.[11-13] Food intolerances are defined as non-immunological responses to food or components of food at doses that would normally be tolerated.[14] They have been described for over 30 years,[15] with exclusion diets leading to symptomatic improvement in individuals with IBS.[16] Despite promise being shown several years ago with regards to exclusion and elimination diets, concerns remained. This was highlighted by a systematic review of eight studies, which demonstrated a wide response rate, which could be attributed to factors including inadequate patient selection, poor exclusion diets and poor adherence.[17] It appears that the historical 'lamb, rice, pears' diet in the early 1980s could not be replicated with success.[18] This was a diet of lamb, rice and pears in studies of 182 patients between 1979 and 1982, which resulted in a 67% success rate.[18]

Over the last decade, there has been a renewed interest in the role of dietary therapies in IBS. First line dietary advice for IBS has focussed on healthy eating and lifestyle management, which is recommended both by the National Institute for Health and Care Excellence (NICE) and British Dietetic Association (BDA) guidelines.[19,20] However, research recently has focussed on the role of the low fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) diet and gluten free diet (GFD) in IBS.

1.3 Traditional Dietary Advice in IBS

Both the BDA and NICE guidelines recommend traditional dietary advice (TDA) as first line dietary therapy, based upon dietary and lifestyle management.[19,20] Practical considerations from the BDA suggest reducing common dietary triggers of IBS such as

alcohol, caffeine, spicy meals, and fatty foods. The evidence statements for these interventions are graded as Grade C evidence by the BDA, meaning that the statements are supported by limited evidence or expert opinion. Whilst no studies met the criteria for a systematic review of fluid intake due to a lack of evidence, a gradual increase in fluid intake is recommended by the BDA as a practical consideration.[19]

The BDA guidelines also reviewed the restriction of milk and/or dairy products, with the practical consideration of lactose restriction to be considered as part of the low FODMAP diet, rather than in isolation. Lactose restriction was only demonstrated to provide marginal symptom benefit in isolation. There was no high quality evidence that a milk-free diet improves IBS symptoms, with cow's milk protein elimination in atopic individuals being recommended to be conducted by allergy-experienced dietitians only.[19]

Evidence statements have also been made by the BDA with regards to fibre, being graded as Grade C evidence. Wheat bran fibre, as well as increasing dietary fibre from cereals and fruits failed to demonstrate symptom improvement in IBS. Ground and whole linseeds as a dietary supplement in IBS are well-tolerated, but evidence on effectiveness is conflicting. The BDA suggested that the evidence for dietary supplementation of psyllium husk to improve symptoms in IBS and IBS-C was insufficient,[19] although a systematic review and meta-analysis, not included in the BDA guidelines, demonstrated empirical evidence for its use.[21]

Like the BDA, NICE has also outlined quality standards for the dietary management of IBS.[20] These include general lifestyle and dietary advice, increasing activity levels, relaxation time, regular meals, increased fluid intake, limiting alcohol and caffeine, less

than three portions of fresh fruit per day, avoiding sorbitol (a sugar commonly found in sweeteners and chewing gum) and adjustments to fibre (**Table 5**).[20]

It is worth noting that the evidence for TDA is based upon a combination of clinical experience and case-control studies, rather than RCTs assessing this approach against a control treatment.[5]

1.4 The low FODMAP Diet in IBS

1.4.1 Evidence to Date

A low FODMAP diet is recommended currently as a dietary therapy that can be used in IBS,[19,22] with it being recommended as second-line dietary therapy by the BDA, NICE and British Society of Gastroenterology (BSG) guidelines.[5,19,20]

FODMAPs consist of oligosaccharides, such as fructans (e.g. wheat, garlic and onion) and galacto-oligosaccharides (e.g. pulses and legumes), disaccharides including lactose (e.g dairy products), monosaccharides including fructose in excess of glucose (e.g. fig, honey) and polyols, such as mannitol (e.g. cauliflower), sorbitol (e.g. stoned fruit) and xylitol (e.g. sugar-free gum).[23,24]

In terms of FODMAP composition, extensive work has been performed by Monash University Department of Gastroenterology in determining the quantity of FODMAP composition for hundreds of foods.[25] Examples of low FODMAP foods include oranges, courgettes and gluten-free bread. Likewise, high FODMAP foods include apples, onions, and haricot beans (**Table 5**).[25]

There are two primary mechanisms by which FODMAPs are thought to be involved in symptom generation in IBS. Firstly, small intestinal water content has been shown to be increased in individuals following FODMAPs.[26] A randomised cross-over single-blinded study in twelve ileostomates demonstrated an increase in water content by 20% on individuals on a high FODMAP diet compared to a low FODMAP diet.[27] Likewise, the polyol, mannitol, has been shown to increase small bowel water content compared to glucose.[28] It is thought that the increase in luminal water content may induce abdominal pain and bloating in individuals with visceral hypersensitivity.[26] It has also been hypothesised that the increase in small intestinal water content may contribute to loose stools and diarrhoea.[26] Secondly, as FODMAPs are fermented in the large bowel, which leads to the accumulation of colonic gas, including hydrogen and methane.[26] Both healthy individuals, as well as individuals with IBS, have been shown to have similar luminal distention following fructans (a FODMAP), as demonstrated by magnetic resonance imaging (MRI).[29] However, patients with IBS may have increased visceral hypersensitivity, which is likely to be the pathophysiological mechanism in symptom generation.[30]

The implementation of a low FODMAP diet can be either via the 'top-down' or 'bottom-up' approach. The 'top-down' approach involves a strict reduction initially of all FODMAP groups for 4 to 8 weeks, with 4 weeks being generally recommended as the time frame for clinical practice.[31] Individuals are advised on food sources for each FODMAP group and how these can be excluded without impacting on dietary quality. At the end of the first appointment, individuals should be advised on how to incorporate the FODMAP restriction into their daily life, including planning shopping, adherence and food-related social activities. It is advised that 45-60 mins is required for this first appointment.[23] After

the FODMAP restriction phase is complete, there is a period of FODMAP re-introduction, where if symptoms have improved on a strict low FODMAP diet, specific FODMAP triggers and doses that generate symptoms are identified. This stage involves maintaining a strict reduction of FODMAPs whilst undergoing food challenges, where a food high in one FODMAP is tested over 3 days at increasing doses. This is used to assess tolerance to each FODMAP group. If the challenge results in no symptoms, the food can be incorporated into their diet. However, if there is a substantial increase in symptoms, the challenge is stopped. A decision is then made whether the food group should be avoided partially or completely, dependent upon the severity of the symptoms. It is advised that an appointment of 20-30 minutes of duration is required to advise on initiation of this process.[23] The final phase is FODMAP personalisation, where a less restrictive diet is followed, where FODMAPs which induce symptoms are excluded in addition to a varied and nutritionally adequate dietary intake.[31] Individuals who have already undergone the re-introduction phase generally can implement this phase without the need for a further appointment for advice. In this phase, individuals should aim to follow a diverse diet, where FODMAP restriction if continued, but FODMAPs which did not induce symptoms during the reintroduction phase are included. [23]

The 'bottom-up' approach, which is less commonly used,[32] and less well studied,[33] involves the reduction of a few targeted FODMAPs, or a reduction of a few foods which contain a very high FODMAP content for 4-8 weeks, followed by further restrictions of FODMAPs only if required.[34]

The potential benefits of a low FODMAP diet were hypothesised by Gibson and colleagues at Monash University, Australia.[35] This was followed by the group focussing on the effect

of implementing the low FODMAP diet in IBS.[36] The group initially set out to evaluate an effective dietary therapy in patients with fructose malabsorption and IBS. In this retrospective study, 62 patients presenting consecutively with IBS and fructose malabsorption underwent dietary instruction, comprising avoidance of substantial free fructose and short-chain fructans, as well as total dietary fructose load. Individuals were identified as having fructose malabsorption having had a positive hydrogen breath test.[37] Glucose was also balanced with free-fructose, as in the presence of luminal glucose, fructose absorption is markedly enhanced. Adherence and effect on abdominal symptoms were assessed via telephone interview, with a positive response to abdominal symptoms being identified in those adherent to the diet versus those non-adherent (85% versus 36%, $p<0.01$).[37] The same group subsequently conducted a double-blind placebo-controlled (DBPC) re-challenge trial in 26 patients with IBS and fructose malabsorption, recruited over a 5-month period from a hospital based dietetic practice. Patients were provided all food, low in free fructose and fructans, with random graded introduction of fructose, fructans, alone or in combination, or glucose. Patients receiving fructose, fructans or a combination noted symptoms of IBS were not adequately controlled in comparison to those receiving glucose ($p<0.002$). This study demonstrated that dietary fructose or fructans was likely to be responsible for symptom generation in IBS.[38]

Since these initial studies, there have been several studies evaluating the role of a low FODMAP diet in IBS. Feeding studies, often seen as the gold standard in dietary intervention trials, have shown symptom improvement in patients receiving a low FODMAP diet. A controlled cross-over feeding study demonstrated lower GI symptom scores in patients given a low FODMAP diet, compared with a typical Australian diet and the participants' own diet.[39] Thirty patients with IBS, and 8 healthy controls were

recruited for the study. Participants, who had not received dietary advice previously, received 3 weeks of a diet low in FODMAPs, or typical Australian diet, with a washout period of at least 3 weeks before crossover. The study demonstrated lower gastrointestinal symptom scores on a diet low in FODMAPs in comparison with an Australian diet ($p<0.001$). Despite this statistically significant result, the benefits of the low FODMAP diet from this study have been debated. Krogsgaard et al noted that participants on the control diet had a significant difference in overall gastrointestinal symptoms on a 100mm visual analogue scale (VAS) compared with the baseline diet (VAS 44.9mm versus 36.0mm, $p<0.001$).[40] It was suggested that this may have been attributed to the higher FODMAP content of the control diet versus the baseline diet, which may have led to favourable benefits of the low FODMAP diet seen in the study.[40]

There have been several Randomized Controlled Trials (RCTs) published demonstrating the benefits of a low FODMAP diet in IBS, with **Table 1** outlining some of these.[39,41-48] The first meta-analysis of the low FODMAP diet in IBS, analysing 6 RCTs and 16 non-randomized studies demonstrated its benefits. A statistically significant decrease in IBS symptom severity scores (IBS-SSS), IBS-quality of life score, symptom severity for abdominal pain, bloating and overall symptoms were demonstrated in both the RCTs and non-randomized studies.[49] Out of all the GI symptoms reviewed in the meta-analysis, a low FODMAP diet led to the least improvement in symptoms of constipation, which may be attributed to the low fibre content of the diet,[49] with the low FODMAP diet being shown to reduce small intestinal water.[27] Therefore, it is possible that patients with symptoms of IBS and constipation may need other adjuncts in addition to a low FODMAP diet to derive benefits. However, recently there has been evidence to suggest there is no significant difference in fibre content between a habitual diet and adapted low FODMAP

diet in the longer term.[50] It has also been suggested that the Rome IV sub classification is of little use when assessing the effect of the low FODMAP diet, as the therapy is not directed at specific effects on bowel habits in view of its mechanism of action.[51]

However, a systematic review focusing on the quality of nine RCTs of a low FODMAP diet in IBS suggested a high risk of bias in trials.[52] Concerns raised included small numbers of patients being used, with patients being recruited primarily from tertiary centres, as well as issues regarding blinding and choice of control group.[52] The control group has sometimes been a high FODMAP content diet,[45] thus exaggerating the effects of a low FODMAP diet. Also, feeding studies may not be pragmatic as they are not strictly 'real-life' as all meals are prepared for patients. A systematic review, where five studies of the low FODMAP diet in IBS were identified, deemed that the quality of evidence for the low FODMAP diet was only fair (Level II), with little evidence to support a recommendation for or against a low FODMAP diet in IBS (Grade C) on the basis of the studies reviewed.[53]

In terms of magnitude of benefit of the low FODMAP diet, a recent meta-analysis, where nine parallel trials and three crossover studies were included, demonstrated that IBS severity was reduced by a moderate to large extent, when compared to a control diet.[54] When studies using the IBS-SSS were analysed, the magnitude of improvement was noted to be 45 points (**Figure 1**).[54] Of note, the IBS-SSS is measured on a scale of 0-500, with a reduction in 50 points noted to be clinically significant in the literature.[55] In view of the heterogeneity of outcome measures used in studies, it is currently difficult to quantify the true magnitude of benefit of the low FODMAP diet.

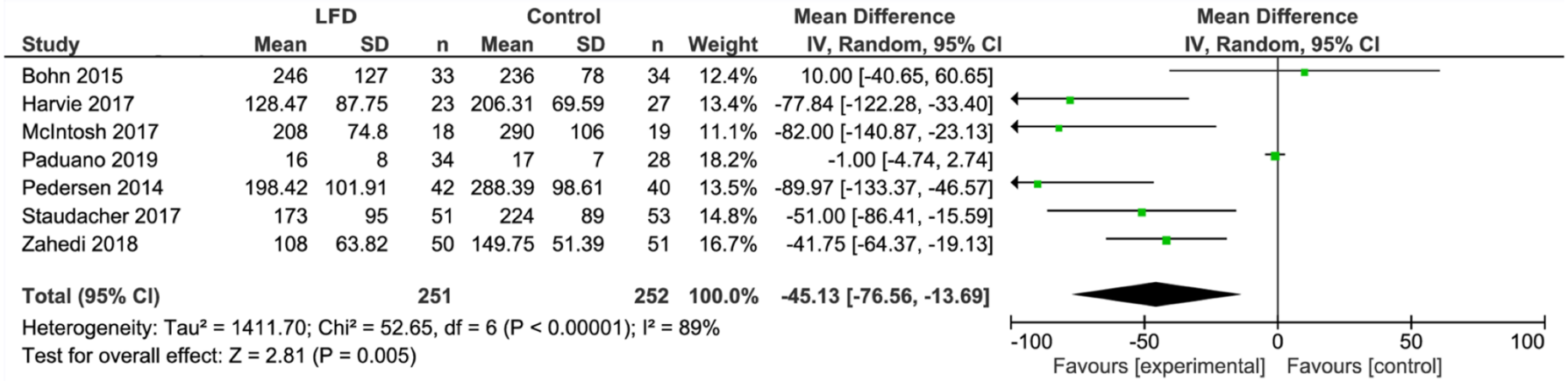
Table 1 Summary of key RCTs investigating the short-term effect of the low FODMAP diet in patients with IBS[24,56]

Lead Author for Study	Year	Study Design	Study Duration	Total Number of Participants in Study	Intervention	Outcome
Staudacher [41]	2012	Unblinded RCT	4 weeks	41 patients with IBS	Habitual diet n=22 Low FODMAP diet n=19	Greater adequate control of GI symptoms on patients with low FODMAP diet (13/19) versus habitual (5/22) (p=0.005)
Pedersen [42]	2014	Unblinded RCT	6 weeks	123 patients with IBS	Low FODMAP diet n=42 Lactobacillus rhamnosus GG diet (probiotic) n=41 Normal diet (Danish) n=40	Reduction in IBS-SSS in low FODMAP diet in comparison to Danish diet (IBS-SSS 75, p<0.01)
Halmos [39]	2014	Single blind crossover RCT	21 days	30 patients with IBS and 8 healthy individuals	All participants received diet low in FODMAPs and Australian diet	Reduction in overall gastrointestinal symptom score on low FODMAP diet versus Australian diet (22.8 versus 44.9, p<0.001)
Bohn [43]	2015	Single blind RCT	6 weeks	75 patients with IBS	Low FODMAP diet n=38 Traditional dietary advice n=37	No difference in IBS-SSS between low FODMAP diet and traditional diet (p=0.62)
Eswaran [44]	2016	Unblinded RCT	4 weeks	92 patients with IBS-D	Low FODMAP diet n=45 Modified NICE guidelines n=39	No significant difference between low FODMAP diet and modified NICE guidelines with regards to adequate relief of symptoms (p=0.13)
McIntosh [45]	2017	Single blind RCT	3 weeks	37 patients with IBS	Low FODMAP diet n=19 High FODMAP diet n=18	Significant difference between proportion of patients defined as responders (IBS symptom reduction >50) between low FODMAP group versus high FODMAP group (p=0.01)

Staudacher [46]	2017	Single blind RCT	4 weeks	104 patients with IBS	Sham diet/placebo n=27, Sham diet/probiotic n=26, Low FODMAP diet/placebo, n=24, Low FODMAP diet/probiotic n=27	Significantly lower IBS-SSS in patients on low FODMAP diet versus sham diet (p=0.001)
Hustoft [48]	2017	Double blind crossover RCT	6 weeks	20 patients with IBS-D/IBS-M	All participants received placebo and low FODMAP diet	Significant improvement of all symptoms following 3 weeks of low FODMAP diet with mean reduction of IBS-SSS 163.8
Zahedi[57]	2017	Unblinded RCT	6 weeks	110 patients with IBS-D	Low FODMAP diet n=55 General dietary advice n=55	Greater improvement in IBS-SSS on low FODMAP diet versus general dietary advice (IBS-SSS at 6 weeks, 108 vs 150; p<0.001)
Patcharatrakul[58]	2019	Unblinded RCT	4 weeks	70 patients with IBS	Low FODMAP diet n=33 Commonly recommended diet to reduce IBS symptoms n=33	60% response rate to low FODMAP diet (defined as 30% decrease in average of daily worst abdominal pain/discomfort after 4 weeks) in comparison to 28% on commonly recommended diet (p=0.001)
Goyal[59]	2021	Unblinded RCT	16 weeks	101 patients with IBS-D	Low FODMAP diet n=52 Traditional dietary advice n=49	Response (defined as reduction in IBS-SSS of ≥50 points) to low FODMAP diet significantly higher than TDA group at week 4 (63% vs 41%, p=0.04) and week 16 (53% vs 31%, p=0.03)

RCT: Randomised controlled trial; IBS: Irritable bowel syndrome; FODMAP: Fermentable oligo-,di-,mono- saccharides and polyols; NICE: National Institute of Clinical Excellence; IBS-SSS: Irritable bowel syndrome symptom severity score

Figure 1 Forest plot showing mean IBS-SSS scores from meta-analysis by van Lanen et al[54]



This figure has been reproduced from van Lanen AS, de Bree A, Greyling A. Efficacy of a low-FODMAP diet in adult irritable bowel syndrome: a systematic review and meta-analysis. Eur J Nutr. 2021 Sep;60(6):3505-3522. doi: 10.1007/s00394-020-02473-0. This is Figure 3 within this article.[54]

1.4.2 Low FODMAP diet versus other therapies

With the emerging data about the role of a low FODMAP diet in IBS, a number of questions still remain. It is currently unclear whether the low FODMAP diet provides greater symptom benefit versus other dietary therapies.

To date, there have been four studies comparing a low FODMAP diet to TDA for IBS.[43,44,57,59] A multi-centre single-blind study in Sweden demonstrated no significant difference in clinical response - defined as a 50 point reduction in IBS severity score - between a low FODMAP diet versus traditional IBS diet over a 6 week period (50% vs. 46% p=0.72).[43] There was also no difference seen in a single-centre study from the United States between a low FODMAP diet and a modified NICE diet (52% reported adequate relief of symptoms in low FODMAP group versus 41% of modified NICE diet, p=0.13).[44] However, in this study, the low FODMAP diet did result in a higher proportion of abdominal pain responders versus the modified NICE diet (51% versus 23%, p=0.008).[44] In contrast, a RCT from Iran found the low FODMAP diet to be significantly superior to TDA with regards to improving overall gastrointestinal symptom scores (IBS-SSS at 6 weeks, 108 vs 150, p<0.001).[57] Most recently, a study in India demonstrated superiority of the low FODMAP diet (defined as a 50 point reduction in IBS severity score) at both the short term restrictive phase (4 weeks), as well as following the re-introduction phase (16 weeks) in comparison to TDA (week 4; 63% vs 41%, p=0.04, week 16; 53% vs 31%, p=0.03).[59]

The discrepancy in results between these studies may be accounted for by differences in the amount of gas-producing foods (i.e. FODMAPs) being eliminated within the TDA

control group. For example, the study from Sweden advised individuals to reduce intake of beans/cabbage/onions based on historical traditional dietary guidance, [43] whereas the studies from the United States, Iran and India allowed for their consumption.[44,57] It is worth noting that the BDA guidance from 2016 does not recommend reducing gas-producing foods as part of TDA, as this would be considered as being within the realms of a low FODMAP diet approach.[19] Further research in this area is required before definitive conclusions can be made.

Currently, there are no RCTs comparing the efficacy of the low FODMAP diet in comparison to the GFD. However, there has been a recent study in Italy, where 42 consecutive outpatients with IBS were recruited, receiving the low FODMAP diet, gluten free diet and Mediterranean diet, each over a 4 week period, with a 4 week washout period.[60] Whilst all three diets showed improvements in abdominal bloating, abdominal pain and IBS-SSS score, individuals on the low FODMAP diet showed superiority in improving abdominal bloating in comparison to the GFD.[60] Interestingly, the majority of participants (86%) expressed preference for the Mediterranean diet, in comparison to the GFD (11%) and low FODMAP diet (3%); $p<0.01$.[60] This study highlights the challenges of adhering to more complex diets, such as the low FODMAP diet and GFD.

It is unclear whether the low FODMAP diet has any benefit in comparison to alternate non-dietary therapies currently. A RCT comparing yoga versus a low FODMAP diet did not demonstrate difference in outcomes between groups,[61] with another study demonstrating no difference in overall gastrointestinal symptoms between the low FODMAP diet and gut-directed hypnotherapy.[62]

1.4.3 Long-term outcomes

The majority of data have focused on the role of the low FODMAP diet in IBS, with short term endpoints, and a lack of long-term data. However, long-term adherence to the low FODMAP diet appears to be good, with a prospective observational study demonstrating 75% adherence to an adapted low FODMAP diet after a median follow up of approximately 16 months, with 70% of patients satisfied with their symptoms.[63] This is also supported by other studies, with adherence reported as 77% (46/62 patients) in a retrospective study of IBS patients, where there was avoidance of short chain fructans and excess free fructose. Adherence in this study was assessed via telephone interview with a median follow up of 14 months.[37] A retrospective pilot study in 72 consecutive patients with inflammatory bowel disease (IBD) and concurrent functional symptoms demonstrated adherence between 54% and 70%, depending on the food group excluded, with a median follow up, via telephone interview, of 17 months.[64]

There are concerns that patients may continue on a strict low FODMAP diet long-term, without adequate re-introduction of FODMAPs as tolerated. A retrospective study demonstrated that a minority of patients (16%, 29/180) continued on a strict low FODMAP diet without re-introduction at long-term (median 16 months).[65]

However, there are also data emerging, demonstrating the benefits of a low FODMAP diet in the long term. A prospective questionnaire study (n=103) following dietitian-led low FODMAP education demonstrated 57% of patients reported relief of symptoms at long-term follow-up, with 82% continuing on an 'adapted' low FODMAP diet, with no compromise in terms of nutritional adequacy.[50] The long-term benefits of an 'adapted' low FODMAP diet have also been demonstrated in a recent parallel design study. Fifty

patients with IBS were recruited through gastroenterology outpatient clinics, with 23 patients being commenced on a low FODMAP diet at baseline, followed by a re-challenge of FODMAPs at 3 months. A statistically significantly lower IBS-SSS was noted at 3 months in the low FODMAP group ($p<0.0002$), which was sustained at 6 months, at the re-introduction phase of the long-term low FODMAP diet.[47] A recent retrospective study in 90 patients highlighted that patients following the low FODMAP diet experienced less abdominal pain compared to those who had stopped following the diet ($p=0.044$).[66] In addition, the majority of individuals (80%) were on the low FODMAP diet at long term follow up.[66] Interestingly, only 15.5% of individuals were following the diet strictly, highlighting the challenges of strict adherence to the low FODMAP diet.[66]

The emerging data currently suggests the efficacy of a low FODMAP diet in the long-term, with an 'adapted' low FODMAP diet. However, studies performed have been variable in study design, with different dietary protocols, making it difficult to make comparisons between studies.[67] **Table 2** outlines some of the key studies assessing the low FODMAP diet at long term follow up.

Table 2: Key Studies Assessing the Long-Term Effects of the Low FODMAP Diet in IBS[24]

Study	Year	Location	Study Duration	Number of participants on low FODMAP diet	Proportion of individuals adherent to 'adapted' low FODMAP diet	Long-term Findings
de Roest[63]	2013	New Zealand	Mean follow up of 15.7 months	90	Not stated	Symptom improvement including abdominal pain, bloating, flatulence and diarrhoea ($p<0.001$)
Peters[62]	2016	Australia	6 months	24	All but 2 participants failed to achieve 'adapted' low FODMAP diet	Reduction in overall gastrointestinal symptoms at 6 months on low FODMAP diet (-30, $p<0.0001$)
Maagaard[65]	2016	Denmark	Median follow up 16 months	131	84% of individuals on 'adapted' low FODMAP diet	Patient reported efficacy reported as partial in 54% and full in 32% of individuals of low FODMAP diet
Harvie[47]	2017	New Zealand	6 months	23	Not stated	Reduction in IBS-SSS on low FODMAP diet vs normal diet at 3 months ($p<0.0002$), reduction in IBS-SSS sustained at 6 months.
O'Keeffe[50]	2017	United Kingdom	6-18 months	103	82% of individuals continued on 'adapted' low FODMAP diet	57% patients received satisfactory relief of symptoms at long term
Schumann[61]	2018	Germany	6 months	29	Not stated	Statistically significant improvement in IBS-SSS for both low FODMAP diet and yoga at weeks 12 and 24, with no difference between groups at week 12 ($p=0.151$) and week 24 ($p=0.08$)
Weynants[66]	2019	Belgium	Median follow up of 99.5 weeks	90	15.5% of participants still on strict phase of low FODMAP diet	Patients still following low FODMAP diet experienced less severe abdominal pain than those who stopped the diet or those who never started the diet ($p=0.044$)
Bellini[67]	2020	Italy	6-24 months	73	81% advised to go on 'adapted' low FODMAP diet	83% reported a clinically significant relief of symptoms at long term. However, 44% drop out rate from baseline.

FODMAP, fermentable oligo-, di, mono- saccharides and polyol; IBS-SSS, irritable bowel syndrome symptom severity score; RCT, Randomised Controlled Trial

1.4.4 Nutritional adequacy

Nutritional inadequacies are a potential concern using the low FODMAP approach. A RCT in 41 patients with IBS demonstrated a statistically significant reduction in calcium intake ($p=0.016$) in those on a low FODMAP diet, compared with their habitual diet, after 4 weeks.[41] A significant reduction in energy intake has also been demonstrated in patients following a low FODMAP diet ($p<0.001$), in a RCT comparing the low FODMAP diet with TDA.[43] This may be a potential concern in those at risk of under nutrition who continue to follow this diet in the long-term. However, there was also a significant reduction in energy intake in those following TDA ($p=0.009$), which suggests that this concern is not unique to a low FODMAP diet.[43]

In contrast, a RCT in 104 patients with IBS demonstrated no difference in total energy intake, macronutrient intake or fibre intake between the low FODMAP diet and a sham diet at short term follow up.[46] The sham diet was designed to be an exclusion diet that restricted a similar number of staple and non-staple foods as the low FODMAP diet, as well as being of a similar difficulty, intensity and duration of the low FODMAP diet, whilst not adversely impacting on nutrient, fibre and FODMAP intake.[46] The findings from this study were supported by another study, in 26 patients with IBS, where no significant changes in energy, macronutrient and fibre intake were noted following 8 weeks of a low FODMAP diet,[68] highlighting the uncertainty in this area.

A recent study, where post hoc analysis of a RCT comparing the modified NICE (mNICE) diet and low FODMAP diet demonstrated fewer daily kilocalories being consumed with a lower carbohydrate intake.[69] There was a significant decrease from baseline with several

micronutrients on the low FODMAP diet, which was not seen with the mNICE diet. However, interestingly, the only difference which remained significant after correcting for calorie intake was riboflavin, when correcting for calorie-adjusted nutrient intake.[69] This study highlighted that many micronutrient deficiencies reported may disappear when adjusting for energy intake.

In the long term, a study demonstrated a reduction in total energy and fibre intake whilst on the low FODMAP diet.[47] However, there is emerging data that utilization of an 'adapted' FODMAP diet may be nutritionally adequate, with a long term follow-up postal questionnaire study demonstrating no significant difference in carbohydrate and calcium intake between an adapted low FODMAP diet and habitual diet at long term follow up, between 6 to 18 months.[50] Recently, a RCT comparing the low FODMAP diet to traditional dietary advice, noted a reduction in energy, carbohydrate, fat and fibre intake, at short term follow up of 4 weeks with the LFD, although this gradually improved at 16 weeks.[59]

Currently, there is uncertainty with regards to nutritional intake following the low FODMAP diet, both at short and long term follow up, with further research required to explore this.

1.4.5 Gut microbiota

The microbiota are organisms that are presented in the environmental habitat, and can be bacteria, viruses or eukaryotes.[70] The human microbiota consists of 10-100 trillion symbiotic microbial cells, primarily bacteria in the gut.[71] In short-term studies, a reduction in the concentration and proportion of luminal Bifidobacterium has been

demonstrated on a low FODMAP diet,[41,72] as well as a reduction in total bacterial abundance.[73] Bifidobacterium is known to be an important butyrate-producer in the colon, with butyrate known to be a key modulator of colonic health.[74] A recent study demonstrated a lower abundance of Bifidobacterium in faecal samples on the low FODMAP diet, but demonstrated that co-administration of a multi-strain probiotic increased numbers of Bifidobacterium species.[46] This supplementation could potentially negate concerns of a reduction in Bifidobacterium whilst on a low FODMAP diet, although further studies are required.

It is possible that bacterial profiles and their metabolomic activity, may be used in the future to predict responsiveness to a low FODMAP diet and thus allow for personalised care.[72,75] A Swedish study found that responders to a low FODMAP diet could be discriminated from non-responders on the basis of faecal bacterial profiles, with non-responders having a higher baseline dysbiosis index score.[72] Elsewhere, a UK study reported of patterns of faecal volatile organic compounds, as analysed by a gas-chromatography, to predict responsiveness to a low FODMAP diet with almost 100% certainty.[75]

A recent systematic review and meta-analysis, where 8 studies were reviewed, which had assessed the low FODMAP diet and gut microbiome, noted that several different methods were used for assessment, including fluorescence in situ hybridisation, quantitative real-time polymerase chain reaction (PCR) and 16s rRNA (ribosomal ribonucleic acid) sequencing or combinations of.[54] Where microbial diversity was measured, no effects of the low FODMAP diet were noted. As mentioned above, the abundance of the

Bifidobacterium species, as well as its overarching phylum Actinobacteria were noted to be reduced following the low FODMAP diet.[54]

In view of the different methods employed to assess the gut microbiome, and current uncertainty, the effects of the low FODMAP diet on the gut microbiome are still unclear.

1.5 The Role of Wheat in IBS

1.5.1 Evidence to Date

Wheat avoidance has been reported to be common in the general population, with a cross-sectional population survey in Australian adults demonstrating that 10.6% (126/1184) were avoiding wheat.[76] This was where individuals were avoiding products containing wheat.[76] A proportion of individuals presenting with IBS may have sensitivity to wheat. In a large retrospective study involving 920 patients fulfilling the Rome II criteria for IBS, 30% (276/920) demonstrated wheat sensitivity or multiple food hypersensitivities (including wheat) (**Table 3**).[77] Patients identified as 'wheat sensitive' were on an elimination diet, but developed symptoms with wheat, given via capsules, using a DBPC challenge. This was where individuals received either the intervention or placebo, with participants and researchers unaware of what intervention participants received. Significant increases in the VAS for overall symptoms, bloating, abdominal pain and stool consistency were demonstrated following the wheat challenge. To date, this remains the only crossover DBPC trial assessing the WFD in IBS and has not been replicated.

Patients identified as being sensitive to wheat, in this large retrospective study,[77] were assessed at follow up, for adherence to a strict WFD using structured questionnaires.[78] This prospective study involved 200 of the previous study cohort participants, with a median follow up of 8 years 3 months. Findings demonstrated that 74% (148/200) were still adhering to a strict wheat free diet at follow-up; ten percent (21/200) were strictly avoiding wheat but consuming other gluten containing foods, including barley and rye, with the other 64% (127/200) on a strict GFD. Twenty-two patients from the study who were still on a WFD, consented to a repeat wheat challenge. It was noted that 20 of these 22 patients still reacted to wheat. This highlights that wheat sensitivity is likely to be persistent.

Dramatic mucosal responses to wheat have been noted via confocal endomicroscopy in patients with IBS. A study in 36 patients demonstrated immediate and dramatic mucosal responses to several antigens, including wheat (n=13), milk (n=9), yeast (n=6) and soy (n=4).[79] This interesting method may help identify patients who may benefit from a WFD, but further studies are required to assess this.

Table 3 DBPC trial investigating the effect of a wheat free diet in IBS patients [56]

Lead Author for Study	Year	Study Design	Study Duration	Total Number of Participants in Study	Intervention	Outcome
Carroccio [77]	2012	Crossover DBPC trial	5 weeks	276 patients with IBS identified as having wheat sensitivity	All participants received wheat or xylose (placebo) capsules	Increase in overall symptoms following introduction of wheat ($p<0.0001$)

DBPC: Double-blind placebo-controlled; IBS: Irritable bowel syndrome

1.5.2 Unanswered questions

There is little data currently on the risks of a WFD. Patients consuming a WFD commonly commence a GFD,[78] and it could be inferred that the risks are likely to be similar to those of a GFD. These risks include lower intakes of magnesium, iron, zinc, manganese and folate, noted from studies in CD.[80] Due to the lack of data, studies are required in this area to be able to elucidate the quantifiable risks.

1.5.3 Wheat components and IBS

Several components of wheat have been suggested as the causal agent for symptoms in IBS, including gluten, alpha-amylase trypsin inhibitors (ATIs), wheat germ agglutinins (WGAs), and fructans, which are part of the low FODMAP diet (**Figure 2**).[81] Studies have been performed to try to elucidate the pathophysiological mechanisms of these components in symptom generation.

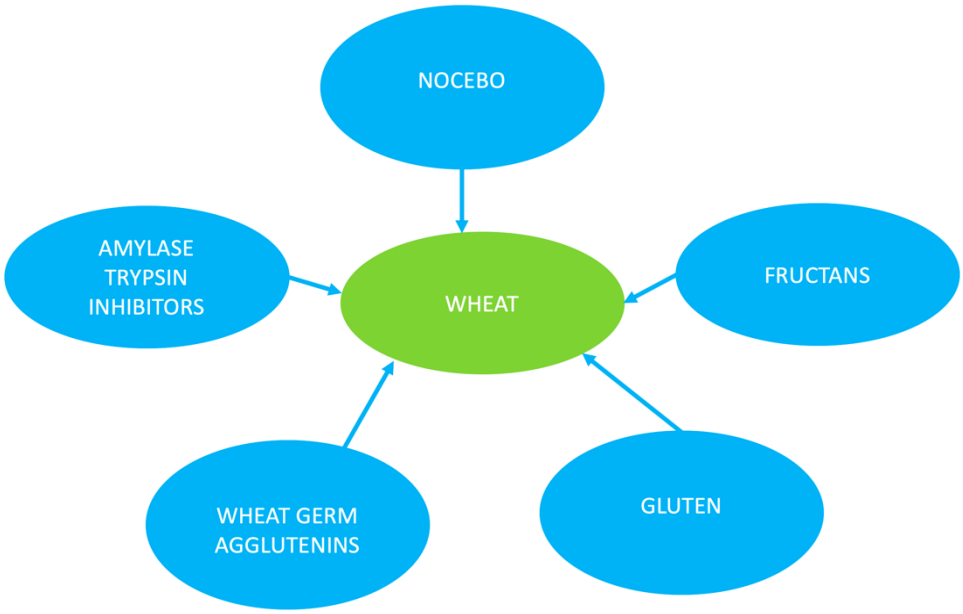


Figure 2 Components of wheat which may trigger symptoms in IBS

Gluten has been demonstrated to alter bowel barrier functions in patients with IBS. The expression of tight junction proteins (zonula occludens-1 (ZO-1), occludin, and claudin-1) have been demonstrated to be significantly lower in the colonic mucosa of individuals on a gluten containing diet (GCD), especially in individuals who are human leukocyte antigen (HLA) DQ2/ 8 positive.[82] Tight junction proteins, claudin-2, 8 and 15, as well as myosin light chain kinase (MLCK)-myosin II regulatory light chain (MLC) pathway have been demonstrated to be important in intestinal physiology and barrier function, regulating paracellular permeability. A study evaluating biopsies from 27 patients with IBS-D demonstrated alterations in MLC phosphorylation and claudin-15 and claudin-2 expression with gluten with intestinal permeability changes.[83] This also could potentially explain permeability responses to gluten challenge in patients with IBS .[83]

ATIs have been demonstrated to be strong induces of the innate immune responses, in vitro and in vivo, via the activation of the toll-like receptor 4, with the release of pro-inflammatory cytokines leading to intestinal inflammation.[84]

WGA is the best-studied cereal grain lectin. When delivered in vitro, WGAs have been demonstrated to stimulate monocytes and macrophages, which have the ability to initiate and maintain inflammatory responses.[85] WGA has been demonstrated to affect enterocyte permeability in vitro. However, it is important to note that human data demonstrating WGA on inflammatory markers are lacking.[85]

FODMAPs are short-chain carbohydrates which are rapidly fermentable and poorly absorbed, increasing the small bowel water content, passing unaltered into the colon,

where they are rapidly fermented, generating gas and distention.[30] FODMAPs are considered to be beneficial to epithelial cell integrity and health.[86]

1.6 The Gluten Free Diet in IBS

1.6.1 Evidence to Date

The concept of patients having symptoms following the ingestion of gluten outside a diagnosis of coeliac disease (CD) had been noted as early as the 1980s.[87,88] With regards to the mechanism of induction of symptoms with gluten, it has been suggested that gluten proteins may be insufficiently degraded by proteases, leading to undigested peptides with an innate immune response, which may trigger gastrointestinal symptoms. However, further research is needed to elucidate the mechanism.[89]

The GFD consists of the exclusion of dietary wheat, rye, barley and regular oats.[90] Obvious foods to avoid include pasta, pizza, regular bread products and cereals.[91] However, individuals also need to be aware of unexpected sources, such as soy sauce and beer.[91] Several types of cereals, grains, nuts, seeds and legumes can be used as part of a GFD, such as quinoa and chickpeas, which can improve the palatability of a GFD (**Table 5**).[90] In the UK, gluten free products are defined as having less than 20 parts per million (ppm or milligrams of gluten per kilogram of product).[90] It is also important that individuals are aware of potential cross contamination when undergoing a GFD, such as ensuring separation of gluten-free from gluten-containing kitchen gadgets and utensils.[90] It is also worth noting that there are non-food sources of gluten that individuals should be aware of, such as potentially toothpaste and lipstick.[90]

Recently, there has been research evaluating the role of a GFD in IBS. A prospective open-label study in 41 patients with IBS-D demonstrated a reduction in IBS-SSS from 286 to 131 after 6 weeks of a GFD ($p<0.001$), with a clinical response noted in 71% of participants.[92] A RCT in 45 patients with IBS-D, involved placing individuals on either a GFD or GCD for 4 weeks.[82] Patients placed on a GFD were noted to have a reduced bowel frequency ($p=0.04$).[82] However, it has been suggested that these findings may have been due to a reduction in fructans and galacto-oligosaccharides (GOS) content, which are closely associated with gluten, and are also part of the low FODMAP diet.[93]

There have been several double-blind placebo-controlled (DBPC) studies evaluating the GFD in IBS, as seen in **Table 4**.

Table 4 Summary of DBPC studies evaluating the effect of the GFD in patients with IBS[56]

Lead Author for Study	Year	Study Design	Study Duration	Total Number of Participants in Study	Intervention	Outcome
Biesiekierski[94]	2011	DBPC trial	6 weeks	34 patients with IBS symptomatically controlled on GFD	Placebo n=15 Gluten n=19	Worsening of overall symptoms on VAS (p=0.047), as well as pain (p=0.016), bloating (p=0.016), stool consistency (p=0.024) and tiredness (p=0.001) following gluten introduction
Biesiekierski[95]	2013	Crossover DBPC trial	2 week run in of low FODMAPs then 1 week of high-gluten, low gluten, or placebo for 1 week followed by 2 week washout period	37 patients with IBS and NCGS	All participants received high gluten, low gluten or placebo	No effect of gluten on GI symptoms
Shahbazkhani[96]	2015	DBPC trial	6 weeks	72 patients with IBS on GFD	Placebo n=37 Gluten n=35	Statistically significant worsening of symptoms in gluten-containing group versus placebo (p<0.001)
Zanwar[97]	2016	DBPC trial	4 weeks	60 patients with IBS who responded to GFD	Placebo n=30 Gluten n=30	Worsening of symptoms following intake of gluten (p<0.05)

DBPC: Double-blind placebo-controlled; IBS: Irritable bowel syndrome; GFD: Gluten free diet; VAS: Visual analogue scale; FODMAP: Fermentable oligo-, di-, mono- saccharides and polyols

A DBPC trial, in 34 patients who met the criteria for IBS and had improved on a GFD, demonstrated gluten causing gastrointestinal symptoms. In this study, individuals received gluten or placebo via muffins and bread. The gluten given in the muffins was analysed and were found to be free of FODMAPs. It was noted that following receiving gluten, overall symptoms worsened (p=0.047), as well as other parameters including pain (p=0.016), bloating (p=0.031), stool satisfaction (p=0.024) and tiredness (p=0.001).[94]

Interestingly the same group published another study contradicting these findings.[95] This crossover DBPC trial, in 37 individuals with IBS and non-coeliac gluten sensitivity (NCGS), demonstrated no effects of gluten. Individuals were randomly assigned, followed by a 2 week open-label diet of reduced FODMAPs, and then placed in a DBPC crossover manner on high gluten (16g gluten/day), low gluten (2g gluten/day and 14g whey protein/day) or control (16g whey protein/day).[95] Whilst this study failed to show any effects of gluten, this may have been due to the study design. Firstly, participants had a high VAS at baseline, which may not be truly representative of the population. Also, due to the study design, patients may have had an anticipatory nocebo response. An interesting observation was that participants continued to follow the GFD following completion of the study.[98] This may provide support for the ease of implementation of a GFD, with long term adherence to a GFD being shown at 64% at 12 months, in a recent study of 35 patients with IBS-D or IBS-M, in those who had responded symptomatically.[99]

There have been other trials demonstrating the benefit of a GFD in IBS. A trial in 148 patients with IBS, of whom 72 patients completed the study, evaluated the effect of a GFD in patients with IBS. After patients had been initially commenced on a GFD, a statistically

significantly lower symptom control was noted following re-introduction of gluten versus placebo ($p<0.001$), showing that patients are likely to be sensitive to gluten.[96] In a further trial, 60 Indian patients with IBS, who had responded a GFD for 4 weeks, were allocated to either placebo or gluten for 4 weeks, via bread (gluten free versus gluten containing). Significant worsening of symptoms was noted in patients who were re-challenged with gluten in comparison with a placebo ($p<0.05$).[97] A study in Italy, demonstrated that individuals on a GFD for 4 weeks, had improvements in symptom severity, bloating and abdominal pain, as well as improving quality of life.[60]

Recently, it has been proposed whether biomarkers may be used to assess predictors of response to a GFD.[100] 50 patients with IBS, as well as 25 healthy subjects were prospectively assessed, with symptom improvement noted following a four week GFD, in particular for those with antigliadin (AGA) IgG and IgA antibodies (75% vs 38%).[101] On post-hoc analysis, AGA positive patients were noted to have less diarrhoea than AGA negative patients.[101] Whilst AGA positivity may predict responsiveness to a GFD, the prevalence of AGA positivity in the IBS population is unclear. In this study, the prevalence was high, reported at 50%.[101] This was markedly higher than their validation cohort, which noted 21% AGA positivity in the IBS cohort.[101] Previous population estimates of AGA positivity in IBS has been reported between 7% to 18%,[102,103] which is higher than the general population, reported at 7%.[104] In this study, adherence to a GFD was assessed using dietetic assessment, as well as gluten immunogenic peptides.[101] Interestingly, benefits to a GFD were seen in individuals who had some gluten exposure, suggesting that strict adherence to a GFD may not be required in IBS, unlike coeliac disease (CD).[100] However, the threshold of gluten free reduction to derive symptom benefit in IBS is unclear currently.

Studies assessing the role of the GFD have been heterogenous. Different methods of delivering a GFD have been used, such as using feeding studies in some trials and dietary advice in others. In feeding studies, different doses of gluten have also been used. Different primary outcomes have been assessed, different population groups have been enrolled, as well as different study durations. Studies have also been performed in a wide variety of geographic locations which may lead to divergent results as different geographic locations may employ the GFD differently, which may potentially have an impact on their resident gut microbiota.[105] The design of these studies is important as this may result in different outcomes. For example, the studies by Biesiekierski and colleagues,[94,95] assessing the role of a GFD in IBS, led to different outcomes as mentioned earlier, which could be attributed to study design.

There have been a relatively small number of patients recruited to studies assessing the GFD in IBS. This is likely to be an issue for dietary studies in general, with a lack of pharmaceutical support for dietary therapy trials in comparison to pharmaceutical trials, as well as IBS not being a priority area for research.[106] Significant challenges remain, with a lack of guidelines for dietary trials, unlike drug trials which are closely regulated.[107] Issues also remain with regards to blinding, for example, as the GFD is well known to the general public, with up to 5 percent of individuals taking a GFD on their own volition.[108,109] In addition, other challenges remain in designing dietary trials, including difficulties in manipulating the diet and the adherence and modification of dietary habits. It is also difficult to practically implement the findings from dietary trials to the real world.[110]

Other components in a GFD can also be difficult to control in dietary studies, such as fructans.[93] A recent double-blind cross over challenge of 59 participants who had self-instituted a GFD demonstrated an increase in overall gastrointestinal symptoms in participants consuming fructans rather than gluten (p=0.049).[111]

1.6.2 Nutritional adequacy

Whilst there is growing evidence for the use of a GFD, questions still remain. Currently, there is little data on the nutritional adequacy of a GFD in patients with IBS. Nutritional adequacy is a potential concern, with evidence of this being extrapolated from individuals with CD, who undergo a GFD. A study in 139 patients with CD , in which 5-day food diaries were analysed, demonstrated that individuals on a GFD obtained a higher proportion of carbohydrate intake from non-milk extrinsic sugars, with lower intakes of magnesium and selenium in men and women.[80] A survey estimating three-day self-reported food records in individuals with CD on a GFD, demonstrated that recommended amounts of fibre and calcium were not met in men and women.[112] A GFD has also been shown to have an inadequate macronutrient intake, as well as micronutrient deficiencies such as vitamin D, vitamin B12 and folate.[113]

Nutritional concerns are not unique to the GFD itself. For example, in the UK, it has been demonstrated that 95% of men and women are non-adherent to fibre recommendations.[114] It is possible that the nutritional deficiencies of the GFD are due to habitual poor choices, rather than the GFD itself.[115] Also, the evidence of potential nutritional deficiencies has been extrapolated from individuals with CD, rather than IBS. A prospective open-label study in patients with IBS-D, patients maintaining the GFD at

long term follow up (average 18 months) had no alterations in body mass index or biochemical status relative to baseline.[92] It is therefore unclear whether a GFD may lead to nutritional deficiencies in individuals with IBS.

1.6.3 Gut microbiota

Another area of uncertainty of the GFD is the effect of the diet on the gut microbiota. There have been several studies evaluating the role of the GFD and in both healthy individuals and individuals with CD.[116-119] A study in ten healthy subjects, assessing faecal samples on a GFD, demonstrated reductions in beneficial gut bacteria populations, such as bifidobacterium.[119] Also, faecalibacterium prausnitzii proportions were shown to decrease after a GFD in this study, with these bacteria being noted to be a key modulator of colonic health.[120] As can be seen, this has therefore raised potential concerns of a GFD. Taxon-specific differences have been observed on a GFD. A study in 21 healthy volunteers, who has been on a GFD for four weeks demonstrated taxon-specific changes, most markedly noted in the family Veillonellaceae, which were significantly reduced.[116] Veillonellaceae is a pro-inflammatory family of bacteria, and therefore it is possible that this taxon-specific shift may cause the benefits seen on a GFD.[116] Therefore, it is possible that shifts in the microbiota on a GFD could potentially be beneficial.

It is important to note that currently it is not possible to draw conclusions on the role of a GFD on the gut microbiota. The faecal flora is spatially organised,[121] with bacteria not being evenly distributed in stools.[105] Therefore, it is unclear the significance of changes seen in faecal flora.

It is also possible that the changes seen on a GFD are not due to the GFD, but potentially due to other dietary alterations made by the individual. Individuals with IBS appear to have more restrictive diets than healthy controls, with individuals with IBS having been shown to have a greater abundance of Rikenellaceae, when adjusting for diet and race. However, no difference in microbial diversity was shown.[122]

Sample sizes used assessing the GFD and gut microbiota have been small, and changes seen from one population are unlikely to be extrapolated to another population due to the diversity of microbiota in different populations.[105] Further long-term data is required to assess the microbiota in both the short and long term, with studies in patients with IBS on a GFD needed.

Table 5 Key Components of Dietary Therapies Used in IBS

Traditional Dietary Advice	Low FODMAP diet	Gluten Free Diet
Single phase • Reduce alcohol intake • Reduce caffeine intake • Reduce spicy meals • Reduce fatty foods • General lifestyle advice (e,g, increasing activity levels, relaxation time) • Regular meals • Increase fluid intake • Consume less than three portions of fresh fruit daily • Avoid sorbitol (e.g. found in chewing gum) • Adjust fibre intake	***Restriction phase (1st)*** Avoidance of: • Oligosaccharides and galacto-oligosaccarides (e.g. onion and pulses) • Disaccharides (e.g. dairy products) • Monosaccharides (e.g. fig and honey) • Polyols (e.g. cauliflower) ***Reintroduction phase (2nd)*** • Food challenges, with food high in one FODMAP tested over 3 days at increasing doses ***Personalisation phase (3rd)*** • Personalisation of FODMAPs to tolerance	***Single phase*** • Advised to exclude wheat, rye, barley and regular oats (e.g. wheat pasta, bread, beer)

1.7 Discussion

There are now several heterogeneous randomized trials in IBS evaluating both the low FODMAP diet and GFD, with variable evidence for their use. The response rate to a low FODMAP diet has been recorded between 50% to 76% in the literature,[41,43,63,123] with a response rate to a GFD reported between 34% to 71%.[92,99] In IBS patients identified as wheat sensitive, reported as 30% in the literature,[77] response to a wheat or GFD has been demonstrated to be as high as 98%.[78] The evidence to date suggests that one diet alone is not effective for all patients with IBS, reinforcing the underlying heterogeneity of the condition.

It is likely that there is significant overlap between these dietary therapies, and they could be described as dietary 'cousins'. Controversy remains with regards to which component of wheat leads to the induction of symptoms in patients presenting with IBS.[124] Regardless of the mechanism, there appears to be evidence for the use of these diets in clinical practice.[77] **Table 6** outlines a comparison of the low FODMAP diet and GFD.

Currently, TDA is used as first line management for IBS, which is based upon a combination of clinical experience and case-control studies.[5] Whilst there have been RCTs comparing traditional dietary advice to the low FODMAP diet,[43,44,57,59] there have been no RCTs comparing its efficacy to a GFD or habitual diet.

Dietary advice for these therapies should be delivered by dietitians with a specialist interest in IBS, on the basis of the evidence base for the use of these diets being derived from dietitian-led studies, with this approach being supported by reviewers.[125] The delivery of TDA, the low FODMAP diet and GFD could lead to a strain on existing

resources, but could be achieved through different methods, such as group-based sessions rather than one-to-one education. This is supported by a large study (n=364) assessing dietitian-led group education versus traditional one-to-one education for a low FODMAP diet.[126] This study demonstrated no difference in patient satisfaction or difference in decrease in symptom severity following dietary advice in group education versus one-to-one education.[126] However, the provision of dietetic services is unclear, with further research required to see if these there is sufficient provision to deliver these dietary therapies.

1.8 Conclusion

There are currently no head-to-head trials evaluating TDA, the low FODMAP diet and GFD in IBS. There is variable evidence for the use of all three diets in IBS, but questions still remain, including concerns on the nutritional adequacy of all the diets, as well as the effects on the gut microbiota. Further long-term efficacy data are required. The provision of dietetic services to deliver these therapies is also unclear.

Table 6 Comparison of low FODMAP and GFD in IBS [56]

	Low FODMAP diet	**Gluten Free Diet**
Advantages of diet	Increasing public awareness of diet Re-introduction of FODMAPs can be tailored to patients' symptoms	Well known diet to public[127] Easy to implement Good availability of diet in supermarkets in UK[128] Restriction of one food group
Concerns of diet	Restrictive diet in initial phase[31] Reduction in calorie and calcium intake reported[41] Unclear efficacy in comparison to other dietary therapies[43,44] Costly to implement[50] Reduction in potentially beneficial gut bacteria reported[41]	Can be costly to implement[128] Lower intake of nutrients including magnesium, iron, zinc, manganese and folate reported[80] Reduction in beneficial gut bacteria populations reported[119] Poor palatability[129]
Adherence	Adherence reported at 75-77 percent in literature[37,63]	Adherence reported at 64 percent in literature[99]

1.9 Declaration of Published Work Used

Sections of this chapter have been published and been reproduced or published in part with minor changes. The following papers have been used for this chapter;

1. **Rej A**, Avery A, Ford AC, Holdoway A, Kurien M, McKenzie Y, Thompson J, Trott N. Whelan K, Williams M, Sanders DS. Clinical Application of Dietary Therapies in Irritable Bowel Syndrome. *J Gastrointestin Liver Dis* 2018; 27(3): 307-16
2. **Rej A**, Aziz I, Sanders DS. Breaking bread! *Proc Nutr Soc* 2018; Oct 16: 1-8
3. **Rej A**, Sanders DS. Gluten-Free Diet and Its 'Cousins' in Irritable Bowel Syndrome. *Nutrients* 2018; 10: 1727
4. **Rej A**, Trott N, Sanders DS. Self-Reported Wheat Sensitivity and Chronic Gastrointestinal Symptoms: Recent advances in understanding. *Clinical Nutrition* 2019; 11(1): 13-15
5. **Rej A**, Aziz I, Tornblom H, Sanders DS, Simren M. The Role of Diet in Irritable Bowel Syndrome: Implications for Dietary Advice. *J Intern Med* 2019; 286(5): 490-502

Chapter 2 Hypothesis, Aims and Methods

2.1 Null hypothesis

As outlined in chapter 1, there is growing evidence for the use of dietary therapies in IBS, but questions still remain. The null hypothesis is that there is no role for nutritional therapies for individuals with IBS.

2.2 Aims

1. To determine to role of nutritional therapies in IBS
2. To assess current dietetic provision in England for people with IBS

2.3 Objectives

1. Assess long term outcomes for patients with IBS following the low FODMAP diet. This will be achieved by:
    a) Assessing the efficacy of the low FODMAP at long term follow up
    b) Examining the nutritional and FODMAP intake of the low FODMAP diet in the long term
    c) Assessing the effects of the low FODMAP diet on sociability

2. Perform an RCT comparing the effectiveness and acceptability of differing dietary therapies for IBS. This will include:
    a) Assessing the efficacy of dietary therapies in IBS
    b) Compare the efficacy of TDA, low FODMAP diet and GFD in IBS
    c) Examine the nutritional intake, FODMAP intake, gut microbial changes following TDA, low FODMAP diet and GFD
    d) Assess the acceptability of dietary therapies in IBS
    e) Assess whether there are any predictors for response to dietary therapies

3. Determine the provision of dietetic services in England for IBS. This outcome will be compared to dietetic provision for individuals with CD and inflammatory bowel disease (IBD)

2.4 Materials and Methods

Study design, and statistical analysis is outlined in each individual chapter.

Chapter 3 The low FODMAP diet for IBS; A multicentre UK study assessing long term follow up

3.1 Summary

Background: The low FODMAP diet is effective in managing IBS in the short term. This study assessed the long-term effect of the low FODMAP diet on symptoms, nutritional composition and socialising.

Methods: Patients with IBS who received dietetic-led low FODMAP advice were approached at long term follow up (>6 months post low FODMAP diet advice) from six centres across the United Kingdom. Participants completed questionnaires prospectively assessing gastrointestinal symptoms, adherence, nutritional intake, dietary acceptability and food related quality of life (QOL) at long term follow up. In addition, where available, symptoms at long term follow up were compared to baseline data collected as part of routine dietetic care retrospectively. The primary outcome was to assess adequate symptom relief at long term follow up.

Results: 205 participants completed the study, with a mean follow up of 44 months (3.7 years). Adequate symptom relief was noted in 60% of individuals at long term follow up, with 76% being on the personalisation phase of the low FODMAP diet (pLFD). Mean nutritional intake did not differ between individuals on the pLFD versus habitual diet, with no difference in fructan intake (2.9g/d vs 2.9g/d, p=0.96). The majority (80%) of individuals on the pLFD consumed specific 'free-from' products at the long term, with the purchase of gluten or wheat free products being the commonest (68%).

Conclusion: The majority of patients follow the pLFD in the long term, with a large proportion purchasing gluten or wheat free products to manage their symptoms.

3.2 Introduction

IBS is a prevalent functional gastrointestinal disorder, affecting around 5 percent of the population.[3,130] It is characterised by symptoms of abdominal pain and change in bowel habit, in the absence of organic disease.[1,4] The pathophysiology of IBS is not fully understood, but is thought to include alterations in gut microbiota, central pain processing, visceral hypersensitivity, immune dysregulation and gut dysmotility.[9] The impact of IBS is significant, with negative effects on quality of life and work productivity.[131]

Options for the management of IBS include treatments such as antispasmodics, antidiarrhoeals and laxatives, as well as psychological therapies, lifestyle and dietary advice.[131] Diet appears to be a key trigger for symptom generation in IBS, with food related symptoms being reported in around 60-80% of individuals.[11-13,132] There has been significant interest in the role of dietary therapies over the last decade, with increasing evidence for the use of a low FODMAP diet to manage the symptoms of IBS. The low FODMAP diet has been recommended as second line dietary therapy by national guidelines,[19] and has even been proposed as first line dietary therapy to manage IBS.[32] Over half of gastroenterologists in the United States (US) consider dietary therapies as a primary management strategy for IBS.[133]

Implementation of the low FODMAP diet consists of three different phases. The initial phase consists of strict restriction of all FODMAPs, which normally takes 4-8 weeks. This is then followed by FODMAP reintroduction, which can be over a 6-10 weeks, followed finally by personalisation of FODMAPs at long term follow up.[23] Whilst there have been several studies demonstrating the efficacy of the low FODMAP diet, the majority of these studies have assessed the low FODMAP diet in the short term (strict restriction phase).[39,41,43-46,48,57] Recently, there has been emerging evidence for the use of the low FODMAP diet in the long term.[47,50,62,63,65,66] However, studies to date have been small single centre studies, some have been performed in specialist centres, with a relatively short duration of follow up, with the longest follow up period being 18 months.[47,50,62,63,65,66] In addition, only one study has assessed both nutritional and FODMAP intake at long term.[50] As the low FODMAP diet can be restrictive in its initial phase, nutritional concerns of this diet have been raised, with a reduction in nutrient and energy intake noted at short term follow up at 4 weeks.[41,43,69,134] There is little information on the number of individuals who continue to follow the restrictive phase of the low FODMAP diet in the long term, despite not being advocated. In addition, nutritional adequacy at long term follow up of the low FODMAP diet is unclear. A single study from a specialist centre demonstrated nutritional adequacy compared to a habitual diet, which requires replicating.[50] The key components of the low FODMAP diet which lead to symptom relief is also unclear, as well as there being little information in the literature on the effects of the diet on eating out and socialising. As a result of this, the aim of this study was to assess the efficacy of the low FODMAP diet at long term follow up, assess changes to nutritional and FODMAP composition at long term follow up, in addition to assessing the effects on sociability. Sociability was defined as effects on

individuals' social life, as assessed by acceptability of the dietary restriction, as well food related quality of life.

3.3 Materials and Methods

3.3.1 Study Design

Patients with IBS who had received low FODMAP advice for the management of their symptoms in secondary care, were recruited at long term follow up (defined as >6 months after patient had received low FODMAP advice) from six centres across the UK (Royal Hallamshire Hospital, Sheffield; Northern General Hospital, Sheffield; Doncaster Royal Infirmary, Doncaster; University Hospital Lewisham, London; Bradford Royal Infirmary, Bradford; York Hospital, York).

Patients were deemed eligible if they had received low FODMAP advice for the management of IBS (as defined by Rome III criteria) by a gastrointestinal dietitian, having been given advice on the strict reduction of FODMAPs, as well as having received advice on the reintroduction of FODMAPs to tolerance. Patients with co-existing gastrointestinal disease (e.g. CD, IBD, gastrointestinal malignancy, previous abdominal surgery), without internet access, unable to give informed consent and language barriers were deemed ineligible. The study flow of patients is outlined in **Figure 3**. Patients were identified by a dietitian or physician at each centre, with individuals subsequently consented to the study by the lead site (Sheffield) if they wished to participate.

Following recruitment, participants were invited by a dietitian or physician within the lead site (Sheffield) to complete questionnaires assessing gastrointestinal symptoms,

effect on sociability, as well as dietary intake at long term follow up. The primary outcome was symptom response to the low FODMAP diet at long term, with the binary outcome (Yes or No) of whether they had satisfactory relief of gut symptoms.[50,135]

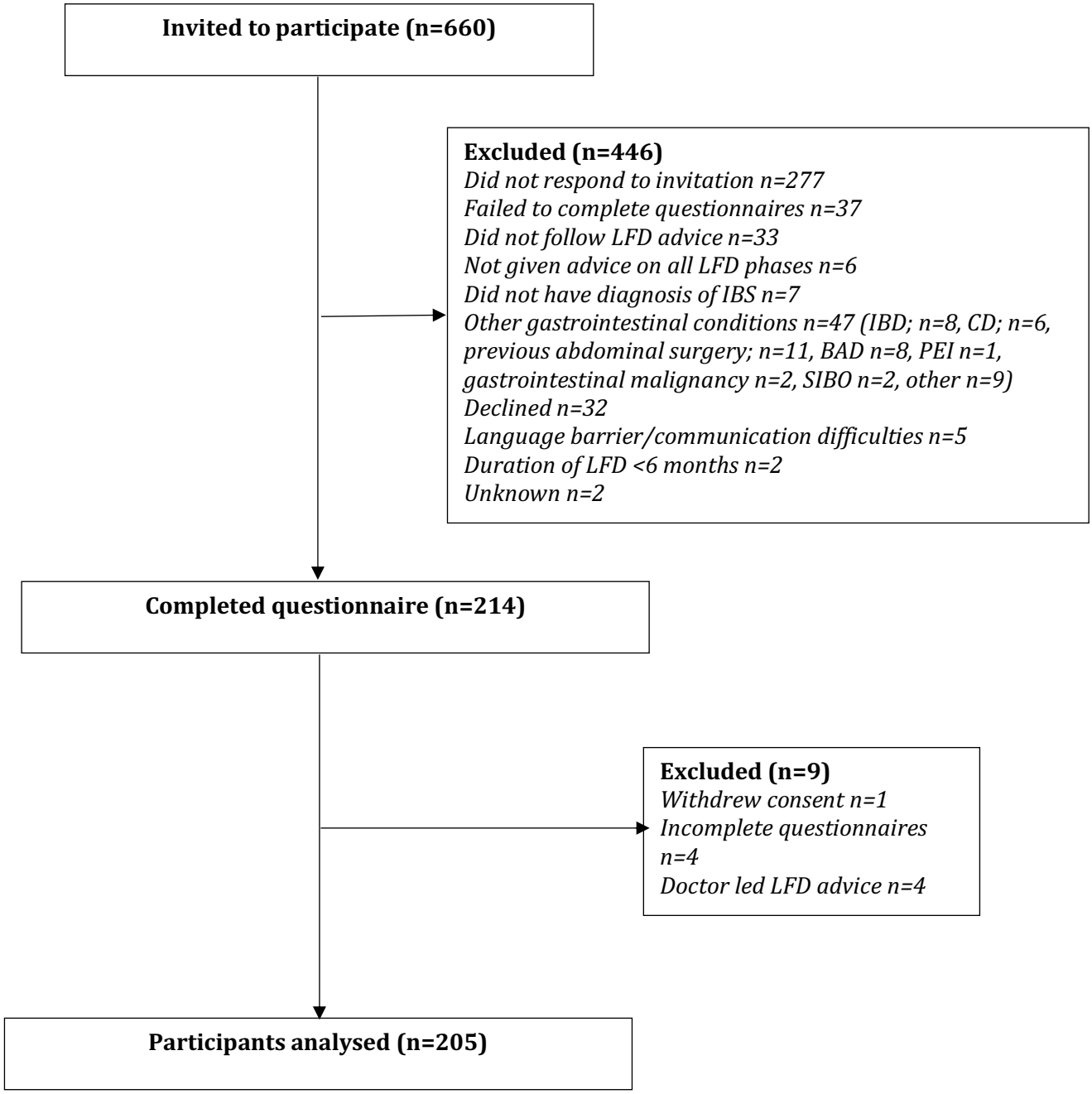


Figure 3 Flow chart for participants during trial

LFD; low FODMAP diet, IBS; irritable bowel syndrome, IBD; inflammatory bowel disease, CD; coeliac disease, BAD; bile acid diarrhoea, PEI; pancreatic exocrine insufficiency, SIBO; small intestinal bacterial overgrowth

3.3.2 Gastrointestinal symptoms

Gastrointestinal symptoms were assessed at long term follow up using the validated gastrointestinal symptom rating scale (GSRS), with symptoms classified on a 4-point Likert scale (0, none; 1, mild; 2, moderate; 3, severe) (**Appendix 1**).[136] Participants recorded stool form, as per Bristol Stool Chart, which was used to classify the subtype of IBS. Individuals with type 1 and 2 stools were classified as having IBS-C; type 6 and 7 stools were classified as IBS-D; type 1 and 2 stools, as well as type 6 and 7 stools were classified as IBS-M; others were classified as IBS-U. Stool frequency was recorded from participants, being reclassified to either normal or abnormal.[126] Participants opening their bowels between once every 3 days to 3 times per day were classified as normal, with those opening their bowels less than once every 3 days or more than 3 times per day as abnormal.[126]

Notes were also reviewed by a dietitian or physician at each site to see whether participants had completed a baseline GSRS as part of routine dietetic care, prior to commencement of the low FODMAP diet. Where this was available, the baseline GSRS was compared to long term GSRS to assess for symptom improvement in this subset of participants.

3.3.3 Sociability

Effects on sociability of the low FODMAP diet was assessed using two questionnaires, an adapted nutrition related QOL (**Appendix 2**) and adapted food related QOL tool (Satisfaction with Food-related Life) (**Appendix 3**).[50,137]

3.3.4 Dietary intake

Dietary intake of participants was assessed at long term follow up using the Comprehensive Nutrition Assessment Questionnaire (CNAQ), a validated semi-quantitative food frequency questionnaire assessing nutrient and FODMAP intake, consisting of 297 questions (**Appendix 4**).[138] This was an online questionnaire which was completed by participants directly via a link provided, or with the aid of the research team who inputted participants' responses onto the online form if completed on paper or via telephone. After all questions were complete, the CNAQ subsequently produced an automated response of FODMAP and nutrient intake for each participant. Participants were also asked additional questions including their diet currently at long term follow up, adherence to their diet, eating out requirements and consumption of specific 'free-from' products. 'Free from' products included lactose free, FODMAP free, gluten or wheat free.

3.3.5 Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki and was approved by the sub-committee of the London-Chelsea Research Ethics Committee (REC reference 18/LO/2234). Written informed consent was obtained from patients.

3.3.6 Statistical analysis

All data was analysed using SPSS version 26 (International Business Machines, Armonk, NY) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, California). Data were summarised using descriptive statistics, including counts and percentages for categorical data and mean±standard deviation (SD) for continuous data. The

independent *t* test was used to compare continuous data between groups. Comparison of categorical data between groups was performed using χ^2 testing. Statistical significance was considered when $p<0.05$.

3.4 Results

A total of 660 patients were invited to participate from six centres (**Figure 3**). From the patients approached, 205 participants completed the study (75%[n=153] female, mean age 50 ± 16 years, mean body mass index 26 ± 5kg/m^2). Participants had received dietetic-led low FODMAP advice between 2010 to 2019, with a mean follow up duration of 44±30 months. A total of 50% had IBS-D (n=101/202), 12% had IBS-M (n=24/202), 15% had IBS-C (n=31/202) and 23% had IBS-U (n=46/202).

3.4.1 Gastrointestinal symptoms at long term follow up

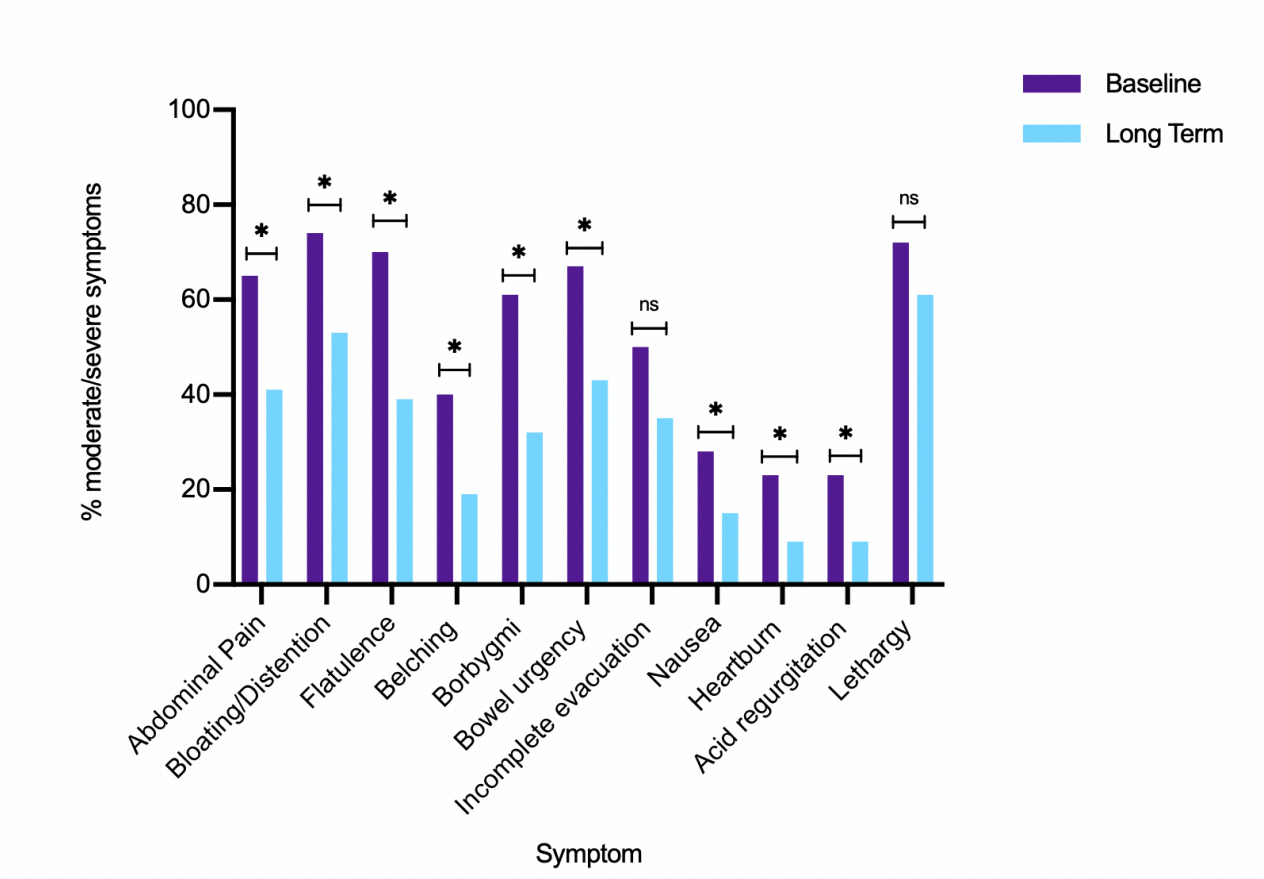
For the primary outcome of overall adequate symptom relief at long term follow up, 60% (n=122/203) of patients had adequate relief of symptoms. There was no significant difference in the proportion of individuals with adequate symptom relief by IBS subtype at long term follow up (63% IBS-D [n=63/100], 46% IBS-M [n=11/24], 61% IBS-C [n=19/31], 63% IBS-U [n=29/46], p=0.47).

3.4.2 Gastrointestinal symptoms – baseline versus long term follow up

Of the 205 participants who completed the study, 74 of these participants (36%) had baseline symptom data available, collected as part of their routine dietetic care. In this

subset of individuals, the proportion with moderate or severe symptoms was significantly lower at long term follow up versus baseline for abdominal pain (65%[n=48] vs 41% [n=30]), p<0.01), bloating/distention (75%[n=55] vs 53%[n=39], p<0.01), flatulence (70%[n=52] vs 39%[n=29], p<0.01), belching (40%[n=29] vs 19%[n=14], p<0.01), borborygmi (61%[n=45] vs 32%[n=24], p<0.01), bowel urgency (67%[n=49] vs 43%[n=32], p<0.01), nausea (28%[n=21] vs 15%[n=11], p=0.05), heartburn (23%[n=17] vs 9%[n=7], p=0.03) and acid regurgitation (23%[n=17] vs 9%[n=7], p=0.03). There was a trend towards an improvement in the proportion with moderate or severe symptoms at long term follow up versus baseline for incomplete evacuation (50%[n=37] vs 35%[n=26], p=0.07) with no difference in lethargy (72%[n=53] vs 61%[n=45], p=0.16). The most frequent moderate/severe symptoms reported by patients at baseline was bloating/distention and lethargy, with the least frequent being heartburn and acid regurgitation (**Figure 4**). The proportion of individuals with abnormal stools was significantly lower at long term follow up compared to baseline (14% [n=10/74] vs 33% [n=24/73], p<0.01).

Figure 4 Symptoms at baseline versus long term follow up as assessed by GSRS



*; statistically significant, ns; not statistically significant

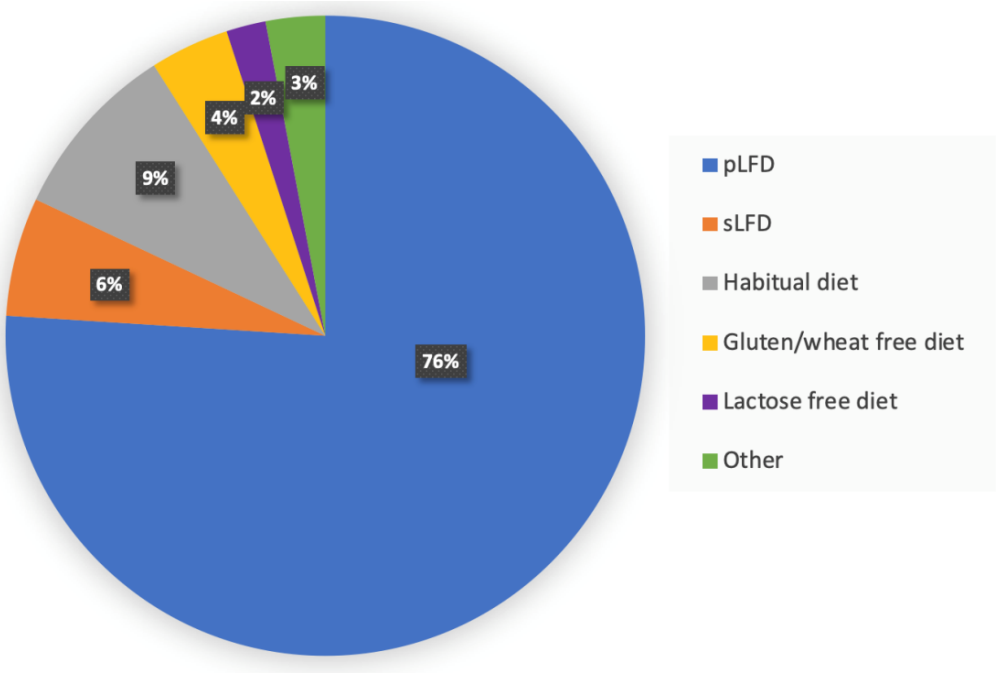
3.4.3 Diet at long term follow up

At long term follow up, 76% (n=155/205) of participants were on the personalisation phase of the low FODMAP diet (pLFD). The remainder of participants were either on the strict reduction phase of the low FODMAP diet (6%, n=12/205), returned to their habitual diet (9%, n=18/205), gluten or wheat free diet (4%, n=9/205), lactose free diet (2%, n=5) or another diet (3%, n=6/205) [**Figure 5**].

The majority of participants on the pLFD at long term had minor lapses (70%, n=107/155), with strict adherence noted in 26% (n=40/155) of individuals, and major

lapses in 5% (n=8/155) of individuals. Overall adequate relief of symptoms differed significantly by adherence ($p<0.01$), with adequate relief of symptoms noted in 68% (n=98/145) of individuals who were strictly adherent or had minor lapses, compared to 13% (n=1/8) of individuals who had major lapses.

Figure 5 Diet at Long Term Follow Up



pLFD; personalisation phase of low FODMAP diet, sLFD; strict reduction phase of low FODMAP diet

3.4.4 Nutritional and FODMAP intake at long term follow up

Compared to dietary reference values (DRVs), the majority of individuals on the pLFD failed to meet total recommended energy intakes. In terms of macronutrient intake, the majority of individuals on a pLFD met recommended protein intake, but the majority failed to meet carbohydrate, fat and dietary fibre intake (**Table 7**). In terms of micronutrient intake, the majority of individuals on a pLFD met recommended

micronutrient intakes (folate, thiamine, riboflavin, vitamin C, sodium, magnesium, calcium, phosphorous, iron and zinc) except for potassium (**Table 7**). There was no difference in total energy intake, macronutrient and micronutrient intake between individuals on a pLFD compared to individuals on a habitual diet, except for a significantly greater proportion of individuals on a pLFD meeting recommended phosphorus intake compared to those on a habitual diet (p<0.01) [**Table 7**].

There was no significant reduction in total FODMAP intake at long term in those on a pLFD, compared to individuals on a habitual diet, with no significant reduction in any specific FODMAP group (**Table 8**).

Table 7 Nutritional intake at long term follow up

Nutritional parameter	**Diet at long term follow up**				**Difference in mean values between groups** *p-value*	**Difference in DRV met between groups** *p-value*
	pLFD (n=155) *mean±SD*	**DRV met** *n (%)*	**Habitual diet (n=18)** *mean±SD*	**DRV met** *n (%)*		
Energy *kcal/d*	1878±635	45 (29)	1889±653	4 (22)	0.95	0.54
Protein *g/d*	83.3±29.5	124 (82)*	87.5±31.5	15 (83)	0.57	0.86
Carbohydrate *g/d*	224±89.1	50 (32)	217±84.1	6 (33)	0.77	0.93
Fat g/d	68.8±26.8	61 (39)	79.1±36.7	11 (61)	0.14	0.08
Dietary fibre *g/d*	29.3±12.3	64 (41)	26.8±9.3	7 (39)	0.40	0.84
Folate *mcg/d*	368±149	141 (91)	337±128	16 (89)	0.40	0.77
Thiamine *mg/d*	1.54±0.95	133 (86)	1.87±0.9	17 (94)	0.16	0.31
Riboflavin *mg/d*	2.32±1.23	141 (91)	2.40±1.22	15 (83)	0.79	0.30
Niacin *mg/d*	20.8±8.8	129 (83)	21.7±7.9	15 (83)	0.69	0.99
Vitamin C *mg/d*	200±126	153 (99)	145±63	17 (94)	0.07	0.19
Sodium *mg/d*	2077±895	105 (68)	2344±974	14 (78)	0.24	0.38
Potassium *mg/d*	3622±1313	77 (50)	3250±1035	8 (44)	0.25	0.67
Magnesium *mg/d*	336±122	106 (68)	306±111	11 (61)	0.33	0.53
Calcium *mg/d*	951±455	109 (70)	918±382	10 (56)	0.77	0.20
Phosphorus *mg/d*	1488±526	153 (99)	1437±509	10 (56)	0.70	<0.01
Iron *mg/d*	12.8±4.7	105 (68)	12.3±4.2	9 (50)	0.64	0.13
Zinc *mg/d*	12.4±4.6	131 (85)	12.6±4.7	13 (72)	0.90	0.19

*missing n=3. DRV; dietary reference values, pLFD; personalisation phase of low FODMAP diet, independent *t* test used to compare difference in mean values between groups, χ^2 test used to compare difference in proportion of DRV met between groups

Table 8 FODMAP intake at long term follow up

FODMAP	Diet at long term follow up		Difference between groups
	pLFD (n=155) *mean±SD*	Habitual diet (n=18) *mean±SD*	*p-value*
Oligosaccharides			
Fructo-oligosaccharides g/d	2.9±2.2	2.9±1.4	0.96
Galacto-oligosaccharides g/d	1.3±1.4	1.0±0.6	0.37
Disaccharides			
Lactose g/d	7.9±10.4	11.3±8.0	0.18
Monosaccharides			
Excess fructose g/d	2.5±3.7	1.8±1.2	0.45
Polyols			
Sorbitol g/d	1.9±2.9	1.5±1.2	0.55
Mannitol g/d	0.6±0.5	0.5±0.3	0.62
Total FODMAPs g/d	17.0±12.5	19.1±9.5	0.51

pLFD; personalisation phase of low FODMAP diet, independent *t* test used to compare difference in mean values between groups

3.4.5 Effect on sociability

The majority of individuals on the pLFD agreed that it took extra time to shop for their diet (57% agreed on pLFD [n=88/155], 11% agreed on habitual diet [n=2/18], p<0.01) and the majority found the cost of the diet to be more expensive (75% agreed on pLFD [n=116/155], 22% agreed on habitual diet [n=4/18], p<0.01). The majority found food labelling to be adequate to confidently choose suitable foods (50% agreed on pLFD [n=78/155], 28% agreed on habitual diet [n=5/18], p<0.01).

The majority of individuals on the pLFD stated that eating out at restaurants made it more difficult to follow the diet (74% agree on pLFD [n=115/155], 22% on habitual diet [n=4/18], p<0.01), as well as eating out at friends and family (71% agree on pLFD

[n=110/155], 17% on habitual diet [n=3/18], p<0.01). Travel overseas also made it more difficult for individuals to follow the pLFD (74% agree on pLFD [n=115/155], 33% on habitual diet [n=6/18], p<0.01). Whilst the majority of individuals were able to easily incorporate the pLFD into their life, this was significantly lower compared to those on a habitual diet (61% agree on pLFD [n=94/153], 89% on habitual diet [n=16/18], p<0.01). No other significant differences in dietary acceptability between the pLFD and habitual diet were noted at long term follow up, as seen in **Table 9**.

With regards to food related QOL, individuals on a habitual diet had greater food and meal satisfaction compared to those on the pLFD (47% agree on pLFD [n=73/155], 78% agree on habitual diet [n=14/18], p=0.03). In addition to this, a minority of individuals on the pLFD saw problems, obstacles and disappointments when thinking of their next meal (22% agree on pLFD [n=34/155], 11% agree on habitual diet [n=2/18], p=0.03). No other significant differences in food related QOL were noted (**Table 10**).

Table 9 Acceptability of personalisation phase of low FODMAP diet

Question	pLFD			Habitual diet			p-value
	Agree *n (%)*	**Neutral** *n (%)*	**Disagree** *n (%)*	**Agree** *n (%)*	**Neutral** *n (%)*	**Disagree** *n (%)*	
I find it easy to buy suitable foods for my current diet at my normal supermarkets or shops	93 (60)	22 (14)	39 (25)*	14 (78)	2 (11)	2 (11)	0.32
I am able to buy foods suitable for my current diet at my normal supermarkets or shops	122 (79)	19 (12)	14 (9)	15 (83)	1 (6)	2 (11)	0.69
I use high street/online specialty shops (e.g. health food shops) to buy food for my current diets	32 (21)	10 (7)	112 (73)*	2 (11)	1 (6)	15 (83)	0.60
It takes extra time to shop for my current diet	88 (57)	12 (8)	55 (36)	2 (11)	1 (6)	15 (83)	<0.01
I find food labelling is adequate to allow me to confidently choose suitable foods	78 (50)	23 (15)	54 (35)	5 (28)	9 (50)	4 (22)	<0.01
The cost of my current diet is more expensive	116 (75)	9 (6)	30 (19)	4 (22)	2 (11)	12 (67)	<0.01
Does eating out at restaurants make it more difficult for you to follow your current diet?	115 (74)	19 (12)	21 (14)	4 (22)	1 (6)	13 (72)	<0.01
Does eating out at friends/families make it more difficult for you to follow your current diet?	110 (71)	18 (12)	27 (17)	3 (17)	1 (6)	14 (78)	<0.01
Does travel (overseas/UK) make it more difficult for you to follow your current diet?	115 (74)	21 (14)	19 (12)	6 (33)	0 (0)	12 (67)	<0.01
Overall, I find my current diet tasty and enjoyable	100 (65)	29 (19)	26 (17)	14 (78)	3 (17)	1 (6)	0.41
I can incorporate my current diet easily into my life	94 (61)	33 (21)	26(17)**	16 (89)	2 (11)	0 (0)	<0.01
My current dietary needs have created stress with my family/friends	61 (39)	28 (18)	66 (43)	3 (17)	2 (11)	13 (72)	0.06

*n=1 missing **n=2 missing. pLFD; personalisation phase of low FODMAP diet

Table 10 Food Related Quality of Life

Question	pLFD			Habitual diet			p-value
	Agree *n (%)*	**Neutral** *n (%)*	**Disagree** *n (%)*	**Agree** *n (%)*	**Neutral** *n (%)*	**Disagree** *n (%)*	
Food and meals are positive elements of my life	87 (56)	35 (23)	33 (21)	14 (78)	0 (0)	4 (22)	0.07
I am generally pleased with my food	98 (63)	32 (21)	25 (16)	12 (67)	4 (22)	2 (11)	0.86
My life in relation to food and meals is close to my ideal	46 (30)	36 (23)	73 (47)	9 (50)	4 (22)	5 (28)	0.18
With regard to food, the conditions of my life are excellent	35 (23)	54 (35)	66 (43)	7 (39)	5 (28)	6 (33)	0.31
Food and meals give me satisfaction in daily life	73 (47)	48 (31)	32 (21)	14 (78)	4 (22)	0 (0)	0.03
I wish my meals were much more pleasant part of my life	79 (51)	26 (17)	50 (32)	8 (44)	1 (6)	9 (50)	0.23
When I think of my next meal, I only see problems, obstacles and disappointments	34 (22)	41 (27)	79 (51)	2 (11)	1 (6)	15 (83)	0.03

pLFD; personalisation phase of low FODMAP diet

3.4.6 Dietary requirements

The majority of individuals on a pLFD at long term follow up had dietary requirements whilst eating out (79%[n=123/155]), with 26% (n=41/155) of individuals describing multiple dietary requirements. The commonest dietary requirement when eating out on the pLFD at long term follow up was a gluten free or wheat free diet (43%[n=67/155]), with 26% requiring a lactose free diet [n=40/155] and 3% requiring a FODMAP free diet [n=5/155], with 10% stating they had other dietary requirements [n=15/155]. 23% of individuals asked for alterations in specific food items rather than a specific diet [n=36/155].

The majority of individuals (80%[n=122/152]) on a pLFD also consumed 'free-from' products at long term follow up, with 29% purchasing a single type of product [n=44/152], 47% purchasing two types [n=72/152] and 4% purchasing three of more products [n=6/152]. The commonest 'free-from' product consumed for individuals on pLFD at long term follow up was a gluten or wheat free product (68%[n=103/152]), with 62% (n=94/152) consuming a lactose free product and 6% (n=9/152) a low FODMAP product.

3.5 Discussion

This is the largest multicentre study demonstrating the efficacy of the low FODMAP diet in the long term for individuals with IBS, with the longest follow up duration to date. The findings highlight that overall symptom response to the low FODMAP diet at long term follow up was 60%. This compares similarly to another long term low FODMAP study in IBS of shorter follow up (between 6-18 months post LFD advice), where symptom

response was reported at 57%.[50] It has been previously suggested that improvement of symptoms with the low FODMAP diet is dependent upon subtype, with lowest symptom improvement noted in individuals with IBS-C, in view of the low fibre content of the low FODMAP diet, with the diet being shown to reduce small intestinal water content.[27,49] However, whilst dietary recommended values for fibre were not met for the majority of those on the pLFD, this was not significantly different to individuals on a habitual diet. Whilst dietary recommended values for fibre were not met for the majority of individuals on the pLFD, it is worth noting that the overall mean values reported for fibre intake in this study were high. Likewise, high overall mean values were reported for vitamin C. This could highlight that individuals may have over-reported their intake of fruits and vegetables, possibly due to the design of the food frequency questionnaire used (CNAQ tool). This study demonstrated the efficacy of the low FODMAP diet independent of subtype, as the low FODMAP diet may not target specific effects on bowel habits.[51]

A key concern of the low FODMAP diet is the restrictiveness of its initial phase, with concerns that individuals remain in this phase without adequate reintroduction of FODMAPs to tolerance. This study demonstrated that the vast majority of individuals at long term follow up were on the personalisation phase of the low FODMAP diet, with only a small minority remaining on the strict reduction phase of the diet. Adherence to the low FODMAP diet appeared to be good at long term follow up, with symptom response better in those with strict adherence or minor lapses compared to those with major lapses.

Individuals on the pLFD failed to meet total energy intake, and failed to meet the majority of macronutrient indices in comparison to DRVs, although the majority of micronutrient indices were met. This may highlight potential nutritional concerns for the low FODMAP

diet at long term, in particular macronutrient intake. However, it is important to note that individuals on the pLFD had a similar nutritional intake to those on a habitual diet at long term follow up, which highlights that this may be a result of dietary behaviours in IBS as a whole, rather than the low FODMAP diet itself. This has been previously shown, with many individuals with IBS having been shown to fail to meet DRVs.[69,134] Whilst a validated food frequency questionnaire was used to assess nutritional and FODMAP intake, and currently the most validated tool available, potential limitations remain, including potential underreporting of total energy intakes using food frequency questionnaires.[139] It is important that individuals are seen by a dietitian to help prevent potential nutritional deficiencies.

Total and specific FODMAP group intake was assessed in this study, with no difference between individuals on a pLFD and habitual diet. Whilst a reduction in fructan intake has been proposed to be one of the key factors to symptom improvement in IBS,[111] no significant reduction was noted in those on a pLFD compared to a habitual diet, similar to previous findings in the literature.[50] This may be as the low FODMAP diet at long term is a personalised diet, and that individuals may have differing FODMAP triggers for symptoms. Currently, it is unclear whether any specific FODMAP components are key for symptom generation in IBS. In addition, currently it is unclear what level of FODMAP restriction is required to derive symptom benefit in IBS, although less than 12g has been suggested, although not validated in the literature.[140] This study demonstrated higher FODMAP intakes on the pLFD at long term follow up, with further studies required to elucidate the optimal FODMAP target intake for symptom management. As there was no difference in total and specific FODMAP intake between individuals on a pLFD and a habitual diet, the symptom benefit seen in this study may be due to other components

rather than FODMAPs. A subset of these individuals may have had gluten-sensitive IBS. The commonest dietary requirement for patients on the pLFD, whilst eating out and 'free-from' products, was gluten or wheat-free in this study. It is likely that the mechanism for symptom improvement is multifactorial, with further studies required to elucidate the pathophysiological mechanisms.

Whilst the low FODMAP diet was shown to be effective at long term follow up in the majority, the diet had an effect on sociability and food related QOL. Some of the issues raised included the low FODMAP diet being a more expensive diet, making it harder to eat out, harder to incorporate the diet into life, as well as lower food and meal related satisfaction. These findings highlight the potential negative effects of the low FODMAP diet on sociability and health related QOL and must be considered prior to implementation. However, this is not unique to this diet alone, having been demonstrated with the gluten free diet also.[128,141] It is also worth noting that the low FODMAP diet has shown greater improvements in health related QOL, anxiety and activity compared to traditional dietary advice at short term follow up.[142]

The commonest dietary requirement for individuals on the pLFD when eating out was gluten or wheat free, with gluten or wheat free from products being the most commonly consumed. This highlights that individuals on the LFD at long term follow up are commonly seeking a gluten or wheat free diet. Individuals maybe employing this, as a gluten or wheat free diet may lead to a reduction in total fructan or FODMAP intake and thereby lead to symptom improvement. However, currently it is unclear which component of wheat leads to symptom improvement in IBS, with FODMAPs, gluten, WGAs and ATIs being suggested as potential triggers for symptom generation in IBS.[24]

Further mechanistic studies are required to assess which wheat components are responsible for symptom generation in IBS. Also, it is possible that individuals may have employed gluten or wheat free products and requested this when eating out as there is huge awareness of this diet, with relatively lower awareness of the low FODMAP diet.[133,143] In addition, a proportion of individuals had multiple dietary requirements whilst eating out, and consumed multiple free from products, highlighting that individuals with IBS may employ multiple dietary alterations. Whilst individuals with IBS may be employing a gluten or wheat free diet to manage symptoms, it is essential that CD is excluded prior to this, as the presentation maybe similar. In view of this, patients with CD were excluded in this study.

The strength of this study was that all participants analysed had received dietetic led low FODMAP advice, which was essential to ensure the diet was implemented correctly as recommended in the literature.[23] In addition, this was a large multicentre study from non-specialist low FODMAP centres, and the findings are likely to be reflective of clinical dietetic practice in most centres. A weakness of this study was that baseline symptom data was not available for all participants. Therefore, individual symptom improvement seen from baseline to long term follow up was seen in a subset of individuals analysed, and may not be representative of the entire cohort. Despite this study, it is unclear whether any specific FODMAP groups are key to symptom improvement, with further research required.

To conclude, the low FODMAP diet appears to be effective at long term follow for adequate relief of symptoms in the majority of individuals with IBS, with no difference in symptom response by subtype. The diet does not appear to effect nutritional intake

compared to a habitual diet at long term follow up. However, it appears that individuals with IBS as a whole fail to meet many nutritional requirements on both a habitual and low FODMAP diet, highlighting the importance of dietetic input. It appears that the majority purchase gluten or wheat free products at long term follow up, with the mechanisms by which wheat inducing symptoms in IBS requiring further research.

3.6 Declaration of Published Work Used

This chapter has been published and been reproduced with minor changes. The following paper was used for this chapter;

1. **Rej A**, Shaw CC, Buckle RL, Trott N, Agrawal A, Mosey K, Sanders K, Allen R, Martin S, Newton A. Robinson K, Elphick D, Chey WD, Aziz I, Sanders DS. The low FODMAP diet for IBS; A multicentre UK study assessing long term follow up. *Dig Liver Dis* 2021; May 31;S1590-8658(21)00247-4

Chapter 4 Effectiveness and Acceptability of Dietary Therapies in Irritable Bowel Syndrome: A Randomised Control Trial of Traditional Dietary Advice, the Low FODMAP Diet and the Gluten Free Diet

4.1 Summary

Background: Various diets are being proposed as first-line therapies for IBS despite insufficient or low-quality evidence. No study has directly compared the effectiveness and acceptability of, as well as the nutritional and stool microbial changes associated with TDA versus the low FODMAP diet (LFD) and GFD in IBS. Moreover, there is sparse data on whether baseline variables predict responsiveness to dietary therapy. We performed a randomised controlled trial to address this issue.

Methods: Patients with Rome IV-defined IBS diarrhoea or mixed subtype were recruited via two centres in the United Kingdom, and block randomised in groups of up to 5 (mean of 3) to receive TDA, LFD or a GFD (the latter allowing for minute gluten cross-contamination). Dietary therapy commenced following face-to-face or virtual dietetic-led education, which was delivered via group sessions. The primary endpoint was clinical response after 4 weeks of dietary intervention, as defined by ≥ 50-point reduction in IBS-SSS. The secondary endpoint was a ≥ 100-point reduction in IBS-SSS, and ≥ 30% reduction in abdominal pain scores. Participants also completed validated questions on cost, convenience, and nutritional intake associated with the diets. Changes in stool dysbiosis from baseline to week 4 were also analysed.

Results: Of the 114 recruited patients with IBS, 101 commenced dietary intervention (TDA=35, LFD=33, GFD=33), with two dropouts over the treatment period. The median age was 34 years, with 70% female, and a mean baseline IBS-SSS of 301. On modified intention-to-treat analysis, the primary endpoint of ≥ 50-point reduction in IBS-SSS was met by 40% of those allocated TDA, 55% for a LFD, and 58% for a GFD; p=0.30. Clinical response rates to diets were similar irrespective of receiving face-to-face or virtual education (p=0.95). A reduction of ≥ 100-points in IBS-SSS was seen in 20% of those taking TDA, 39% with LFD and 33% with GFD; p=0.21. A reduction of ≥ 30% in abdominal pain scores was seen in 34% taking TDA, 58% with a LFD and 39% with a GFD; p=0.13. Individuals found TDA significantly cheaper, tastier, less time-consuming to shop, easier to implement and socially more convenient than the GFD and LFD. Reductions in macro- and micro- nutrient content were similar across the groups. Alterations in stool dysbiosis index did not differ between the diets, with 22-29% showing reduced dysbiosis, 35-39% no change, and 35-40% increased dysbiosis; p=0.99. Finally, clinical characteristics, socioeconomic status and baseline stool dysbiosis index did not predict response to dietary therapy.

Conclusion: TDA, LFD and GFD are effective approaches for individuals with IBS but differ with regards to their cost and convenience. We recommend TDA as the first-choice dietary option due to its widespread availability, relative simplicity, and patient friendliness. A LFD or GFD may be reserved as alternative options based on specific patient preferences and specialist dietetic input.

4.2 Introduction

IBS is a common functional bowel disorder, with a pooled global prevalence of approximately 5%.[3] The cardinal symptoms of IBS are chronic abdominal pain and altered bowel habit, which occur in the absence of organic pathology to explain their presence.[1] IBS remains one of the most common GI disorders seen in primary and secondary care, with patients experiencing substantial health impairment and healthcare utilisation.[5] Amongst the therapeutic armamentarium outlined for the management of IBS, dietary therapies are frequently recommended early within the treatment paradigm given the intrinsic relationship experienced between food and the GI tract on a daily basis.[5] In fact, over 80% of individuals with IBS report food related symptoms,[11,12,132] with almost 63% wanting to know which food(s) they should avoid.[144]

In clinical practice, the last decade has seen a growing interest in the use of three diets for IBS, which are (i) TDA, (ii) a LFD and (iii) GFD.[24] Of these, TDA has historically been considered as the first-line dietary therapy, and is based upon guidance provided NICE and BDA.[19,20] Its principles include adopting healthy and sensible eating patterns, such as having regular meals, maintaining adequate nutrition, limiting alcohol and caffeine intake, adjusting fibre intake, and reducing consumption of fatty and spicy foods, whilst also addressing any perceived food intolerances. The LFD has gained enormous traction in recent times and is now widely considered as a second-line dietary therapy for IBS,[19,20] although some advocate that it should be used as a first-line therapy.[51] FODMAPs are short-chain fermentable carbohydrates that are found in a variety of fruits, vegetables, dairy products, artificial sweeteners, and wheat. They increase small intestinal water volume and colonic gas production that, in those with visceral hypersensitivity, induces gastrointestinal symptoms.[26,29] Finally, the use of a GFD without objective evidence of CD

appears to have become a global phenomenon, with up to 10% of the population reporting gluten-based products to provoke intestinal symptoms compatible with IBS.[145]

However, whilst these three diets are being heavily promoted for the management of IBS they are currently limited in their evidence base.[5,106] The recommendations for TDA are based on a combination of clinical experience and the potential mechanisms by which these foods may induce gastrointestinal symptoms, as opposed to RCTs (except for fibre).[19] With regards to a LFD, a recent systematic review and meta-analysis of RCTs evaluating its efficacy in IBS concluded there to be low quality evidence, mainly to due small sample sizes and significant heterogeneity between studies, the latter attributed to the various control interventions used (e.g. sham diet, high FODMAP diet, habitual diet or TDA).[106] Interestingly, the few studies that compared the LFD with TDA demonstrated the least heterogeneity, but also the smallest magnitude of effect. The use of a GFD in IBS has also come under scrutiny, with the systematic review and meta-analysis identifying only two robust randomised control studies and concluding there to be currently insufficient evidence but welcomed further studies.[106] Additional concerns with many of the aforementioned RCTs are that they have been "feeding studies", in that meals were freshly prepared by research facilities and provided for free to study participants during the treatment period. Whilst controlled feeding studies provide a powerful means for testing proof-of-concept, they are not reflective of real-life clinical practise where, following dietary education, the onus would be left upon patients to shop, purchase and prepare the meal themselves and incorporate into their social and family life. This may be of particular relevance with the conceivably more complex and restrictive diets, such as the LFD and GFD, which require specialist dietetic input prior to implementation and incur substantial pressures on publicly funded healthcare services.[5] Finally, concerns

have been raised that overly restrictive diets may induce potentially detrimental nutritional and stool microbial changes, although the long term implications of the latter are unknown.[24,73,146,147]

In summary, dietary therapies are popular for the management of IBS yet hindered by insufficient or low-quality evidence, and a lack of pragmatic head-to-head trials. There has been no study directly comparing the convenience and effectiveness of TDA against the LFD and GFD. A RCT was performed to address this issue, whilst also investigating the nutritional and stool microbial changes associated with implementing these diets. Finally, factors which may predict a response to dietary intervention were determined, as this could have future implications in providing personalised care.

4.3 Materials and Methods

4.3.1 Ethical Approval

The study was carried out in accordance with the Declaration of Helsinki and was approved by HRA and Health and Care Research Wales [REC reference 19/WM/0069]. Written informed consent was obtained from patients. The study commenced in August 2019 and was completed in May 2021. The clinical trials.gov number is NCT04072991.

4.3.2 Participants and Setting

Patients with IBS were recruited across two secondary care centres in the region of South Yorkshire, United Kingdom (Sheffield Teaching Hospitals, Sheffield and Doncaster Royal Infirmary, Doncaster). The inclusion criteria were adults aged 18 years and over, meeting the Rome IV criteria for IBS-D or IBS-M, and with an IBS-SSS of >75. Additional inclusion

criteria included being English literate, able to travel to hospital, and having telephone or internet access.

Exclusion criteria were those not meeting the above mentioned inclusion criteria or anyone with a history of inflammatory bowel disease, celiac disease, gastrointestinal cancer, previous abdominal surgery, scleroderma, poorly controlled diabetes, severe liver/respiratory/cardiac/psychiatric disease (with "severe" defined as repeated flares, recurrent hospital or general practitioner attendances, numerous medications, clinically appearing unwell due to that disease process), memory impairment, pregnant, current dietary interventions, recurrent or current use of probiotics/antibiotics/narcotics, or currently titrated antidepressants (i.e. not on a stable dose).

4.3.3 Randomisation

This was a parallel group RCT with patients being allocated to TDA, the LFD or a GFD (the latter not being a strict GFD as would be expected for CD, but allowing for cross-contamination e.g. sharing the same household toaster). Individuals were block-randomised, into groups of up to 5 (mean of 3), with diets given in 1:1:1 ratio. The randomisation was performed by an individual not involvement in the recruitment process. Thereafter, participants were seen by specialist dietitians - all accredited in delivering the dietary therapies - where they were only informed of the diet they had been allocated to and blinded to the other dietary interventions. The dietary intervention was delivered via group sessions. Dietary advice was delivered face-to-face via a standardised 45 minute presentation, with subsequent time given for questions, followed by appropriate dietary educational sheets. This was held at Sheffield Medical School,

Sheffield, UK. Delivery of dietary therapies was transferred during the study to a web-based virtual approach (via the Webex by Cisco platform) secondary to the COVID -19 pandemic, with the same information delivered as with face-to-face advice, as well as being delivered via groups like the face-to-face advice. After receiving dietary advice, participants commenced the allocated diet for a 4-week period, with outcomes assessed at 4 weeks and compared with baseline data. After this 4-week period, participants then saw the dietitian once more, where they were provided ongoing standard care, with the trial ending. Standard care was defined as care which would be normally delivered as part of routine NHS care e.g. if the patient had received TDA and not responded in the study, they were offered to undertake the LFD as part of routine NHS care.

4.3.4 Questionnaires

Participants provided baseline demographic data. Their postcode was used to determine socioeconomic status using the Index of Multiple Deprivation (IMD) 2019, a composite of seven different domains representing income, employment, education, skills and training, health deprivation and disability, crime, barriers to housing and services, and living environment. The IMD was used to group individuals into quintiles, with 1 being the most deprived and 5 being least deprived. IMD was evaluated as socioeconomic status may, in part, contribute towards an individual's biopsychosocial model, the presence of IBS, and also how individuals respond to dietary therapies.

The following questionnaires were completed pre- and post- dietary intervention:

a) IBS-symptom severity score (IBS-SSS)[55] – this is a frequently used assessment in clinical studies where responders rate, over the preceding 10 days, abdominal

pain severity, pain frequency, bloating, bowel habit dissatisfaction, and life interferences related to bowel symptoms. The maximum cumulative score available is 500, and subjects can be classified as having no symptoms (<75), to mild (75–175), moderate (175-300), and severe IBS (>300). A reduction of 50 points is considered to confer a clinical improvement and was the primary end-point of this study (**Appendix 5**).

b) Hospital Anxiety and Depression Scale (HADS)[148] - is a psychological screening tool to which there are in total 14 items, seven each for depression and anxiety. Each item is rated from 0 (not present) to 3 (maximum), giving a cumulative score for each subscale to range from 0 to 21. A subscale score of ≥11 is used to indicate a clinically significant level of anxiety or depression (**Appendix 6**).

c) The patient health questionnaire (PHQ)-12 non-GI somatic symptoms scale[149] - The PHQ-12 records bothersome non-GI symptoms over the past month. The twelve symptoms assessed are back pain, limb pain, headaches, chest pain, dizziness, fainting spells, palpitations, breathlessness, menstrual cramps, dyspareunia, insomnia, and lethargy. Subjects were asked to rate how much they had been troubled by these 12 symptoms over the last four weeks as 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot"). Responses were used to calculate the number of sites reporting somatic symptoms (ranging from 0 to 12) and the somatisation severity score (ranging from 0 to 24), which was categorised as minimal (≤3), low (4-7), medium (8-12) and high (≥ 13) (**Appendix 7**).

d) The IBS quality of life (IBS-QOL) questionnaire[150] - this consists of 34 questions which are summed and averaged for a total score, in addition to eight subscale scores (Dysphoria, Interference with Activity, Body Image, Health Worries, Food Avoidance, Social Reaction, Sexuality, Social Relationship). Total and subscale scores are transformed to a 0-100 scale. Higher scores indicate better IBS-specific QOL (**Appendix 8**).

e) The acceptability of dietary restriction questionnaire is based on the adapted nutrition related QOL questionnaire[137] - responses are recorded using a Likert scale, with the responses of agree, neutral and disagree (**Appendix 2**)..

f) The food related QOL questionnaire is a seven-item questionnaire based on the food-related QOL tool (Satisfaction with Food-related Life)[151] - Responses are recorded on Likert scale, as either agree, neutral and disagree (**Appendix 3**)..

g) Comprehensive Nutrition Assessment Questionnaire (CNAQ)[138] - this is a semi-quantitative food frequency questionnaire, consisting of 297 questions, assessing macronutrient and micronutrient intake, as well as FODMAPs, fibre, starch, glycaemic index and glycaemic load (**Appendix 4**)..

4.3.5 Stool Samples

Participants were provided with stool collection kit. They were then invited to complete a stool sample at home, and participants were asked to store samples in their home fridge

one day overnight if needed prior to collection. Stool samples were subsequently collected from participants, both pre- and post- dietary intervention, and were batch stored immediately in a -80 degree freezer until completion of the study. However, during the start of the COVID-19 pandemic and the uncertainties surrounding collection and storage of stool, this process was temporarily suspended and resumed once it was felt safe to do so. Hence, stool samples were collected in around half of cases.

On study completion, samples were shipped on dry ice to Norway for analysis. The GA-map™ Dysbiosis test was used to analyse samples, which is a gut microbiota deoxyribonucleic acid (DNA) analysis tool which can identify and characterize dysbiosis from a faecal sample.[152] The test allows for mapping of select bacteria, and is based on DNA profiling using probes to target variable regions (V3 to V7 regions) of bacteria 16S ribosomal RNA (rRNA) gene to characterize if bacteria are present. Each probe was designed to target a bacterial species or group, based on their 16S rRNA sequence.[152]

Probes were selected on ability to differentiate between healthy individuals, IBS and IBD.[152] The probe set consisted of 48 probes, detecting bacteria within the six phyla; Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria. Tenericutes and Verrucomicrobia. On analysis, bacterial profiles were assigned an overall dysbiosis index (DI), on a scale set from 0 to 5.[152] A DI score of 2 or lower was classified as being within the non dysbiotic region compared to the normobiotic reference cohort. A DI of greater than 2 was considered to be dysbiotic, with a higher DI number indicating greater dysbiosis from the reference range.[152]

Relative bacterial abundance was also supplied for each probe in comparison to the normobiotic reference range, with values ranging from -3 to +3 (dependent upon probe), with -3 being strongly reduced levels of bacteria compared to the reference range, and +3 being strongly elevated levels of bacteria.

In addition, functional bacterial profiles were given, with functional properties deduced from specific bacteria profiles; the bacterial markers of *Anaerobutyricum hallii, [Eubacterium] rectale and Faecalibacterium prausnitzii* were used to assess butyrate producing bacteria, *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* were used to assess gut mucosa protective bacteria, *Faecalibacterium prausnitzii* was used to assess gut intestinal health, *Faecalibacterium prausnitzii, Ruminococcus gnavus, Proteobacteria, Shigella spp. and Escherichia spp.* were used to assess intestinal epithelial barrier, *Proteobacteria, Shigella spp. & Escherichia spp.* were used to assess pro-inflammatory bacteria.

4.3.6 Endpoints

The primary endpoint was clinical response after 4 weeks of dietary intervention, as defined by ≥ 50-point reduction in IBS-SSS. Secondary endpoint included i) a ≥ 100-point reduction in the IBS-SSS, ii) a ≥ 30% reduction in abdominal pain iii) changes in anxiety, depression, somatisation, quality of life, nutritional intake, gut microbiota and iv) convenience of implementing the dietary therapies. An assessment was also made on whether baseline factors (age, gender, IMD, mood, somatisation, stool DI) might be associated with a clinical response to dietary therapy.

4.3.7 Sample Size

The primary end point in this trial was the proportion of responders to the dietary intervention based on the recommended cut-off of a reduction in IBS-SSS ≥50, which is considered to reflect a clinically meaningful improvement.[55] In line with a previous dietary study in IBS using the same endpoint,[43] a power calculation based on the ability to detect a difference between diets in reduction of IBS-SSS of at least 50 points, with 80% power at $\alpha = 0.05$, assuming a standard deviation of 70,[153] indicated that at least 31 patients in each group were required. To anticipate for ~10% attrition rate, the aim was to recruit between 33-35 participants per arm.

4.3.8 Statistical Analysis

Analyses were based on intention-to-treat (ITT) principle, which was a modified ITT (mITT), analysing all participants who were deemed to have commenced the intervention (i.e. provided baseline symptom data prior to intervention, in addition to any data post intervention). To assess whether inclusion of participants who failed to complete the study may have led to bias in the primary outcome, sensitivity analysis was performed using per-protocol analysis for the primary outcome. Stool samples were analysed using per-protocol analysis. All data was analysed using SPSS version 26 (International Business Machines, Armonk, NY) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, California). Statistical significance was considered when $p<0.05$.

Categorical variables were summarised by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using chi-square testing. Normality was assessed for by using the Shapiro-Wilk test. Parametric data were summarized by mean and standard deviation, with difference between multiple groups

performed using one-way analysis of variance, with post-hoc tests (if required) using the Bonferroni correction. Within group comparisons for parametric data were analysed by using paired *t* tests. Non-parametric data were summarised by median and range, with difference between multiple groups being performed by using the Kruskal Wallis test, with post-hoc tests performed if required. Within group comparisons for non-parametric data were performed by using the Wilcoxon test. Missing data was replaced using the last observation carried forward method. Where no baseline outcome data was available, data was excluded from analysis.

Binary logistic regression was used to assess predictors for response to dietary therapies, with univariate analysis used initially, with multivariate analysis if significance was noted.

4.4 Results

A total of 114 participants were recruited, with 101 participants commencing the dietary intervention following randomisation (TDA, n=35; LFD, n=33; GFD, n=33). A total of 99 participants completed the study (see **Figure 6**). There was no difference noted in any baseline variables between groups (see **Table 11**). The median age was 34 years, with 70% female, 89% of white race, 75% IBS-D and 25% IBS-M. The mean baseline IBS-SSS was 301, with 9% having mild IBS, 47% moderate IBS and 45% severe IBS.

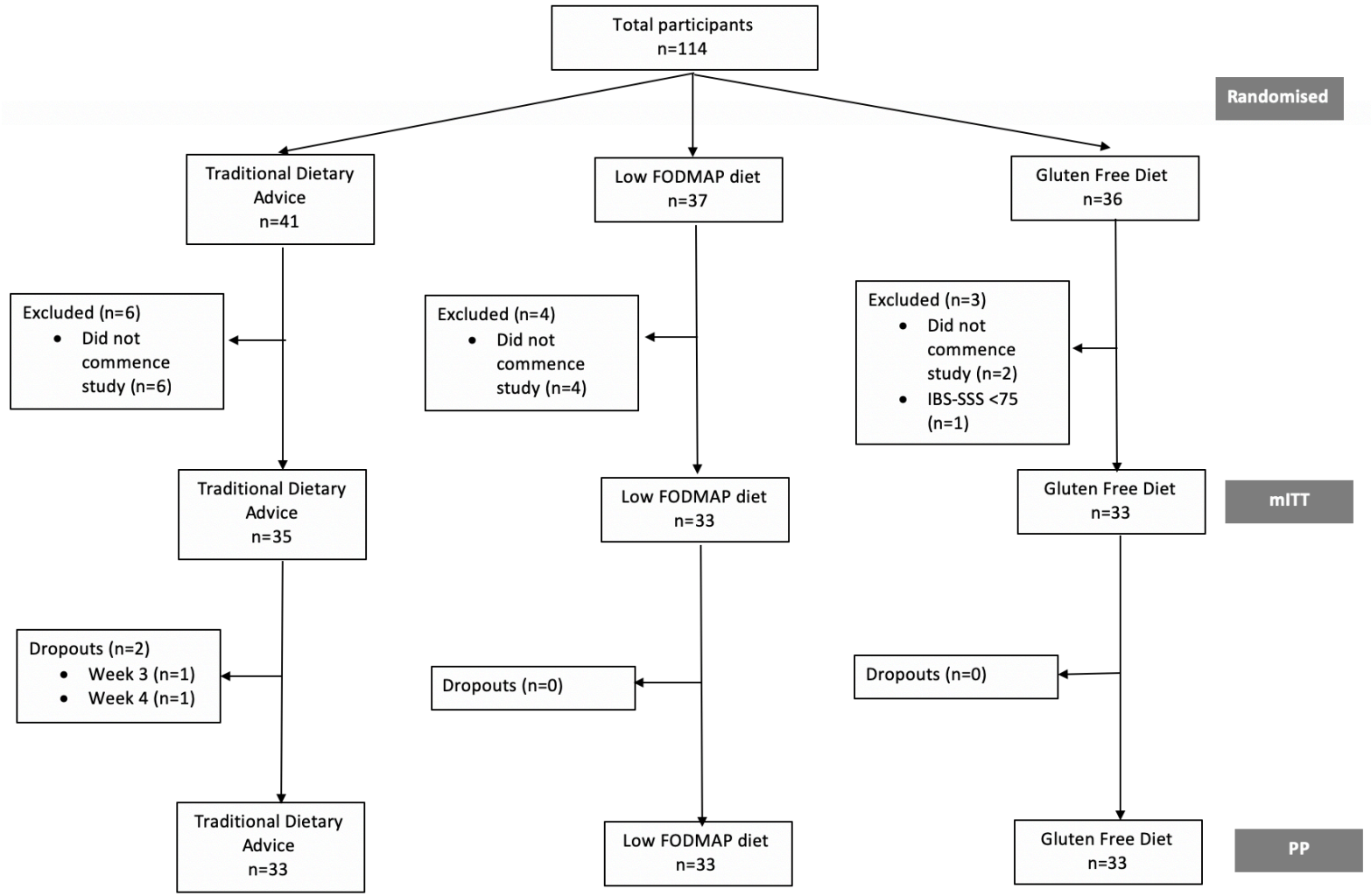


Figure 6: Flow of participants during trial

mITT; modified intention to treat analysis, PP; per protocol analysis

Table 11: Baseline Demographics

Demographics	TDA	LFD[Ψ]	GFD	Overall	Comparison between groups *p-value*
Gender					
Male n (%)	9 (26)	8 (25)	12 (36)	29 (29)	0.52
Female n (%)	26 (74)	24 (75)	21 (64)	71 (70)	
Age (years) *median (IQR)*	38 (25)	31 (16)	35 (22)	34 (22)	0.60
BMI (kg/m^2) *mean ±SD**	27 (10)	26 (11)	24 (8)	25 (10)	0.33
IBS-SSS *mean ±SD*	291 (91)	296 (87)	316 (92)	301 (90)	0.48
IBS-SSS category					
Mild n (%)	4 (11)	3 (9)	2 (6)	9 (9)	
Moderate n (%)	18 (51)	17 (52)	12 (36)	47 (47)	0.47
Severe n (%)	13 (37)	13 (39)	19 (58)	45 (45)	
IMD Quintiles					
Q1 *n (%)*	7 (20)	9 (27)	12 (36)	28 (28)	
Q2 *n (%)*	4 (11)	9 (27)	1 (3)	14 (14)	
Q3 *n (%)*	11 (31)	6 (18)	8 (24)	25 (25)	0.10
Q4 *n (%)*	7 (20)	7 (21)	4 (12)	18 (18)	
Q5 *n (%)*	6 (17)	2 (6)	7 (21)	15 (15)	

TDA; Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet, IMD; Index of Multiple Deprivation, Comparison between groups made using chi squared test [Ψ]n=1 did not wish to declare gender *n=2 missing

4.4.1 Clinical Response

The primary endpoint of ≥ 50-point reduction in IBS-SSS was met by 40% of those allocated TDA, 55% for a LFD, and 58% for a GFD, with no significant difference between the groups; p=0.30 (**Figure 7**). On sensitivity analysis, using per-protocol analysis, findings were confirmed, with no significant difference noted between groups (p=0.43). A reduction of ≥ 100-points in IBS-SSS was seen in 20% of those taking TDA, 39% with LFD and 33% with GFD; p=0.21 (**Figure 7**). A reduction of ≥ 30% in abdominal pain scores was seen in 34% taking TDA, 58% with a LFD and 39% with a GFD; p=0.13.

No significant differences were noted in the change in IBS-SSS, abdominal pain severity, abdominal frequency, abdominal distension severity, bowel satisfaction and interference with life in general between all three groups (see **Table 12)**.

Clinical response rate (≥ 50-point reduction in IBS-SSS) to dietary therapies did not differ between face-to-face (n=30) compared to virtual education (n=71); overall response 50% vs. 51%, p=0.95 [TDA 33% vs. 42%, p=0.64, LFD 60% vs. 52%, p=0.68, GFD 55% vs. 59%, p=0.80].

IBS subtype did not affect clinical response rate (≥ 50-point reduction in IBS-SSS) to dietary therapies; overall response 53% IBS-D vs. 44% IBS-M, p=0.45 [TDA 43% vs. 29%, p=0.49; LFD 63% vs. 33%, p=0.13; GFD 54% vs. 67%, p=0.52].

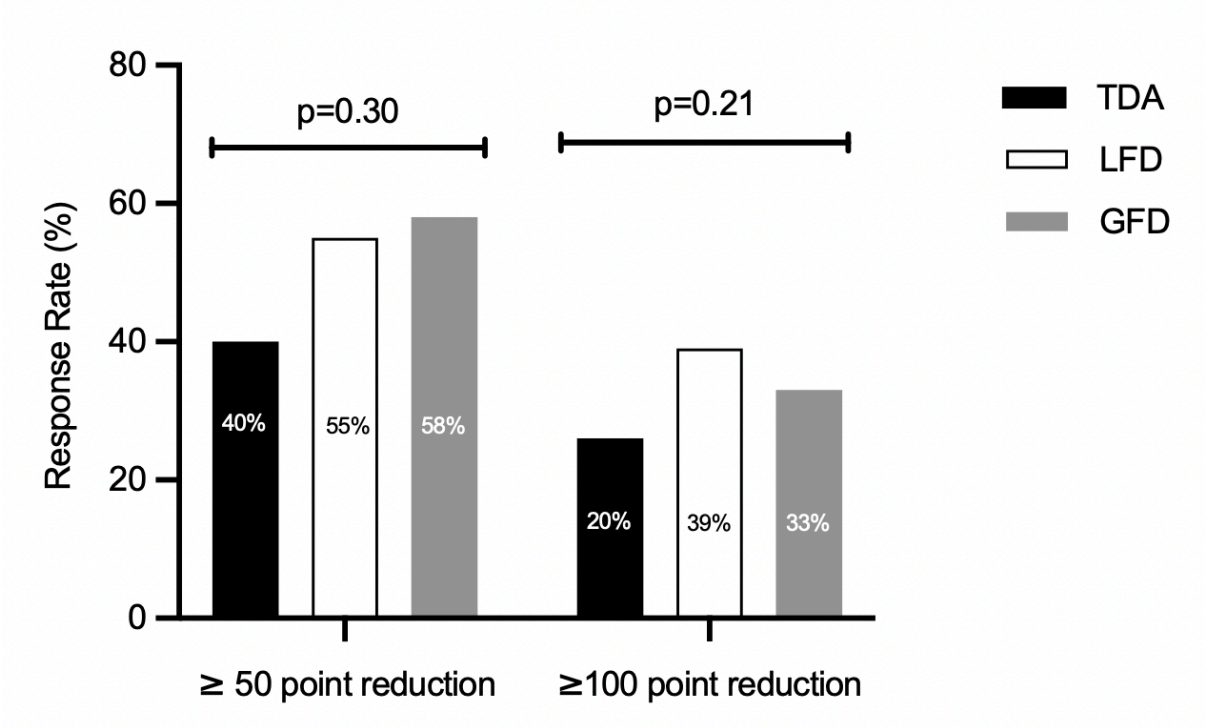


Figure 7: Response rate to dietary therapies

IBS-SSS; Irritable bowel syndrome-symptom severity scale, TDA; traditional dietary advice, GFD; gluten free diet

Table 12: IBS-SSS, HADS, PHQ-12 and IBS-QOL

Symptom Score	Intervention												Comparison of change between groups *p-value*
	TDA				LFD				GFD				
	Baseline	Week 4	Change	Baseline vs Week 4 *p-value*	Baseline	Week 4	Change	Baseline vs Week 4 *p-value*	Baseline	Week 4	Change	Baseline vs Week 4 *p-value*	
IBS-SSS; *mean (SD)*													
Total Score	291 (91)	258 (112)	33 (105)	<0.01	296 (87)	219 (114)	77 (116)	0.04	316 (92)	251 (126)	66 (80)	<0.01	0.10
Abdominal Pain severity	47 (28)	44 (31)	3 (27)	0.50	47 (27)	30 (26)	18 (31)	<0.01	53 (25)	41 (27)	12 (29)	0.03	0.11
Number of days in pain every 10 days	5.9 (2.8)	4.6 (3.2)	1.3 (2.8)	0.01	5.8 (3.1)	4.3 (2.8)	1.5 (3.0)	0.01	6.5 (2.3)	4.9 (3.1)	1.5 (2.6)	<0.01	0.92
Abdominal distention severity	50 (30)	46 (31)	5 (38)	0.47	55 (32)	42 (31)	13 (31)	0.02	55 (29)	39 (34)	16 (20)	<0.01	0.28
Satisfaction with bowel habits	65 (27)	62 (25)	3 (28)	0.55	69 (28)	55 (29)	14 (38)	0.04	76 (22)	63 (28)	13 (18)	<0.01	0.23
Interference with life in general	70 (22)	60 (26)	10 (29)	<0.05	67 (26)	50 (32)	17 (30)	<0.01	67 (21)	58 (32)	9 (20)	0.01	0.19
HADS													
Abnormal HADS-anxiety levels (≥11); *n* (%)	12 (34)	12 (34)	0 (0)	1.00	17 (52)	11 (33)	6 (19)	0.14	17 (52)	13 (39)	4 (13)	0.32	
Abnormal HADS-depression levels (≥11); *n* (%)	4 (11)	5 (14)	-1 (-3)	0.72	7 (21)	10 (30)	-3 (-9)	0.40	7 (21)	6 (18)	1 (3)	0.76	
PHQ-12													
PHQ-12 score; *median (IQR)*	9.0 (7.0)	8.0 (5.0)	1.0 (4.0)	0.05	9.0 (5.0)	8.0 (5.0)	1.0 (4.0)	0.06	8.0 (5.0)	8.0 (7.0)	0.0 (3.0)	0.39	0.63
Number of somatic symptoms; *mean (SD)*	6.7 (2.6)	6.4 (2.2)	0.3 (1.8)	0.32	6.2 (2.5)	5.8 (2.4)	0.4 (1.9)	0.24	6.3 (2.2)	5.8 (2.6)	0.5 (2.0)	0.13	0.88
Level of somatisation severity													
Minimal; *n* (%)	3 (9)	2 (6)			4 (12)	3 (9)			3 (9)	8 (24)			
Low; *n* (%)	12 (34)	13 (37)		0.57	11 (33)	13 (39)		0.69	12 (36)	8 (24)		0.36	
Medium; *n* (%)	11 (31)	15 (43)			12 (36)	14 (42)			13 (39)	13 (39)			
High; *n* (%)	9 (26)	5 (14)			6 (18)	3 (9)			5 (15)	4 (12)			

IBS-QOL													
IBS-QOL score; *mean (SD)*	52 (19)	55 (22)	-3 (15)	0.25	51 (21)	61 (24)	-10 (15)	<0.01	60 (26)	65 (26)	-4 (12)	0.04	0.10
Dysphoria	51 (24)	55 (26)	-3 (20)	0.31	48 (26)	65 (27)	-17 (19)	<0.01	60 (32)	65 (32)	-5 (11)	0.02	<0.01
Interference with activity	49 (21)	54 (25)	-5 (14)	0.06	45 (27)	56 (27)	-12 (20)	<0.01	57 (29)	62 (28)	-5 (15)	0.05	0.19
Body image	53 (24)	55 (21)	-3 (18)	0.38	45 (25)	54 (25)	-9 (20)	0.02	63 (25)	67 (30)	-4 (16)	0.15	0.38
Health worries	57 (21)	55 (26)	2 (19)	0.56	62 (25)	69 (25)	-7 (18)	0.04	62 (27)	69 (24)	-7 (18)	0.04	0.08
Food avoidance	39 (27)	39 (29)	0 (22)	0.95	45 (32)	48 (27)	-3 (33)	0.61	45 (33)	47 (30)	-2 (22)	0.61	0.87
Social Reaction	52 (24)	57 (27)	-5 (22)	0.18	51 (28)	62 (29)	-10 (19)	<0.01	62 (26)	66 (28)	-4 (18)	0.23	0.35
Sexuality	63 (34)	66 (30)	-3 (18)	0.35	70 (30)	70 (28)	-1 (22)	0.85	75 (27)	75 (31)	0 (20)	0.94	0.84
Social relationship	62 (26)	67 (25)	-4 (21)	0.24	64 (29)	68 (29)	-5 (22)	0.25	70 (25)	75 (26)	-5 (16)	0.10	1.00

IBS-SSS; Irritable bowel syndrome symptom severity scale, HADS; Hospital Anxiety and Depression scale, PHQ-12; Patient Health Questionnaire-12, IBS-QOL; Irritable Bowel Syndrome-Quality of Life. TDA; Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet, Within group changes for IBS-SSS analysed using paired *t* test, Change between groups for IBS-SSS analysed using ANOVA. Within group changes for HADS analysed using chi squared test, Within group changes for PHQ-12 analysed using Wilcoxon test, Change between groups for PHQ-12 analysed using Kruskal Wallis test, Within group changes for somatic symptoms analysed using paired *t* test, Change between groups for number of somatic symptoms analysed using ANOVA, Within group changes for level of somatisation severity analysed using chi squared test, Within group changes for IBS-QOL analysed using paired *t* test, Change between groups for IBS-QOL analysed using ANOVA with *post hoc* correction for dysphoria.

4.4.2 Impact on depression, anxiety, somatisation and quality of life

No differences were noted in the proportion of individuals with clinical anxiety or depression after the TDA, LFD and GFD (see **Table 12)**.

No improvement in PHQ-12 scores, number of somatic symptoms and level of somatisation severity were noted after any of the dietary therapies, with no differences between groups (see **Table 12)**.

There was no significant difference in IBS-QOL change between groups, or any of the subscale measures, except dysphoria scores being significantly greater on the LFD compared to TDA and GFD (see **Table 12**).

4.4.3 Acceptability of dietary restriction and food related QOL

A larger proportion of individuals on the LFD and GFD took longer to shop for their diet compared to those allocated TDA (TDA, 37% agree; LFD, 79% agree; GFD, 70% agree; $p<0.01$). Food labelling was noted to be most adequate on the GFD (TDA, 54% agree; LFD, 61% agree; GFD, 85% agree; $p=0.04$). The GFD and LFD were noted to be the most expensive (TDA, 46% agree; LFD, 82% agree; GFD, 82% agree; $p<0.01$). Eating out with family and friends was harder with the LFD and GFD (TDA, 49% agree; LFD, 67% agree; GFD, 67% agree; $p=0.02$). A larger proportion of individuals on TDA found their diet tasty and enjoyable (TDA, 51% agree; LFD, 42% agree; GFD, 39% agree; $p=0.04$) and easier to incorporate into their life (TDA, 54% agree; LFD, 33% agree; GFD, 46% agree; $p=0.02$) [**Table 13**].

A greater proportion of individuals on the GFD noted food and meals were positive elements of their life compared to those on a LFD and TDA (TDA, 49% agree; LFD, 52% agree; GFD, 67% agree; p=0.04). A larger proportion of individuals on TDA were generally pleased with their food (TDA, 67% agree; LFD, 46% agree; GFD, 52% agree; p<0.05) [**Table 13**].

The proportion of individuals who would consider continuing the diets were 70% (n=23) for TDA, 67% (n=22) for the LFD and 61% (n=20) for the GFD, with no difference between groups (p=0.73).

Table 13: Acceptability of Dietary Restriction and Food Related Quality of Life

	Agree *n (%)*			Neutral *n (%)*			Disagree *n (%)*			Comparison between groups *p-value*
	TDA	**LFD**	**GFD**	**TDA**	**LFD**	**GFD**	**TDA**	**LFD**	**GFD**	
Acceptability of dietary restriction										
I find it easy to buy suitable foods for my current diet at my normal supermarkets or shops	21 (60)	12 (36)	18 (55)	13 (37)	13 (39)	11 (33)	1 (3)	8 (24)	4 (12)	0.08
I am able to buy foods suitable for my current diet at my normal supermarkets or shops	25 (71)	18 (55)	26 (79)	7 (20)	11 (33)	6 (18)	3 (9)	4 (12)	1 (3)	0.27
I use high street/online specialty shops (e.g. health food shops) to buy food for my current diets	13 (37)	3 (9)	9 (27)	7 (20)	7 (21)	7 (21)	15 (43)	23 (70)	17 (52)	0.10
It takes extra time to shop for my current diet	13 (37)	26 (79)	23 (70)	9 (26)	4 (12)	8 (24)	13 (37)	3 (9)	2 (6)	<0.01
I find food labelling is adequate to allow me to confidently choose suitable foods	19 (54)	20 (61)	28 (85)	14 (40)	9 (27)	3 (9)	2 (6)	4 (12)	2 (6)	0.04
The cost of my current diet is more expensive	16 (46)	27 (82)	27 (82)	10 (29)	3 (9)	6 (18)	9 (26)	3 (9)	0 (0)	<0.01
Does eating out at restaurants make it more difficult for you to follow your current diet?	19 (54)	20 (61)	19 (58)	11 (31)	12 (36)	11 (33)	5 (14)	1 (3)	3 (9)	0.62
Does eating out at friends/families make it more difficult for you to follow your current diet?	17 (49)	22 (67)	22 (67)	8 (23)	10 (30)	9 (27)	10 (29)	1 (3)	2 (6)	0.02
Does travel (overseas/UK) make it more difficult for you to follow your current diet?	20 (57)	15 (46)	13 (39)	11 (31)	16 (49)	18 (55)	4 (11)	2 (6)	2 (6)	0.38
Overall, I find my current diet tasty and enjoyable	18 (51)	14 (42)	13 (39)	11 (31)	9 (27)	18 (55)	6 (17)	10 (30)	2 (6)	0.04
I can incorporate my current diet easily into my life	19 (54)	11 (33)	15 (46)	14 (40)	11 (33)	15 (46)	2 (6)	11 (33)	3 (9)	0.02
My current dietary needs have created stress with my family/friends	4 (11)	6 (18)	8 (24)	13 (37)	7 (21)	10 (30)	18 (51)	20 (61)	15 (46)	0.44
Food Related QOL										
Food and meals are positive elements of my life	17 (49)	17 (52)	22 (67)	13 (39)	6 (18)	8 (24)	3 (9)	10 (30)	3 (9)	0.04
I am generally pleased with my food	22 (67)	15 (46)	17 (52)	8 (24)	9 (27)	14 (42)	3 (9)	9 (27)	2 (6)	<0.05
My life in relation to food and meals is close to my ideal	6 (18)	7 (21)	7 (21)	14 (42)	11 (33)	19 (58)	13 (39)	15 (46)	7 (21)	0.26
With regard to food, the conditions of my life are excellent	4 (12)	6 (18)	9 (27)	18 (55)	12 (36)	17 (52)	11 (33)	15 (46)	7 (21)	0.18
Food and meals give me satisfaction in daily life	20 (61)	15 (46)	18 (55)	9 (27)	6 (18)	10 (30)	4 (12)	12 (36)	5 (15)	0.13
I wish my meals were much more pleasant part of my life	11 (33)	20 (61)	13 (39)	11 (33)	7 (21)	13 (39)	11 (33)	6 (18)	7 (21)	0.16
When I think of my next meal, I only see problems, obstacles and disappointments	4 (12)	11 (33)	7 (21)	11 (33)	13 (39)	13 (39)	18 (55)	9 (27)	13 (39)	0.16

UK; United Kingdom, QOL; Quality of Life, TDA; Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet, Comparison between groups made using chi squared test

4.4.4 Nutritional intake and FODMAP composition

The proportion of individuals meeting recommended DRVs for macronutrients following all three diets did not change from pre-intervention. However, a reduction in the proportion of individuals meeting DRVs for potassium and iron was noted with TDA. A reduction in the proportion of individuals meeting DRVs for thiamine and magnesium was noted both on the LFD and GFD. The majority of individuals across all three diets failed to meet DRVs for total energy intake both pre- and post-intervention [see **Table 14**].

There were no significant differences in both macronutrient and micronutrient change between all three diets, although there was a trend towards a greater reduction in fibre intake on the LFD compared to the GFD and TDA (p=0.06) [**Table 15**].

In terms of FODMAP intake, individuals taking TDA had a significant reduction in fructo-oligosaccharides, lactose, mannitol and total FODMAP intake (24.9g/day pre-intervention to 15.2g/day on TDA; p<0.01). The LFD led to a reduction in all FODMAPs (27.7g/day pre-intervention to 7.6g/day on LFD; p<0.01). Individuals on a GFD had a reduction in fructo-oligosaccharides, galacto-oligosaccharides and total FODMAP intake (27.4g/day pre-intervention to 22.4g/day on a GFD; p=0.03). In terms of change in FODMAP intake between groups, individuals on a LFD had a significantly greater reduction in total FODMAP intake compared to the GFD (p<0.01) and TDA (p=0.04). Individuals on a LFD had a significantly greater reduction in fructo-oligosaccharides (p<0.01), galacto-oligosaccharides (p<0.01) and mannitol (p=0.03) compared to TDA.

Individuals on a LFD also had a significantly greater reduction in lactose ($p=0.02$), excess fructose ($p<0.01$) and mannitol ($p<0.01$) compared to the GFD [**Table 16**].

Table 14: Proportion of individuals meeting dietary reference values

Nutritional parameter	Intervention								
	TDA[Ψ]			LFD[*]			GFD		
	Baseline DRV met *n (%)*	**Week 4 DRV met** *n (%)*	**Baseline vs Week 4** *p-value*	**Baseline DRV met** *n (%)*	**Week 4 DRV met** *n (%)*	**Baseline vs Week 4** *p-value*	**Baseline DRV met** *n (%)*	**Week 4 DRV met** *n (%)*	**Baseline vs Week 4** *p-value*
Energy *kcal/d*	14 (41)	10 (29)	0.31	14 (45)	8 (26)	0.11	18 (55)	14 (42)	0.32
Protein *g/d*	31 (91)	25 (74)	0.06	26 (81)	23 (72)	0.38	29 (88)	27 (82)	0.49
Carbohydrate *g/d*	15 (44)	14 (41)	0.81	17 (53)	12 (38)	0.21	14 (42)	14 (42)	1.00
Fat g/d	25 (74)	26 (76)	0.78	17 (53)	16 (50)	0.80	20 (61)	20 (61)	1.00
Dietary fibre *g/d*	21 (62)	13 (38)	0.05	12 (38)	9 (28)	0.42	18 (55)	13 (39)	0.22
Folate *mcg/d*	33 (97)	29 (85)	0.09	28 (88)	23 (72)	0.12	33 (100)	31 (94)	0.55
Thiamine *mg/d*	32 (94)	30 (88)	0.39	30 (94)	20 (63)	<0.01	32 (97)	26 (79)	0.02
Riboflavin *mg/d*	29 (85)	30 (88)	0.72	27 (84)	25 (78)	0.52	30 (91)	30 (91)	1.00
Niacin *mg/d*	30 (88)	29 (85)	0.72	25 (81)	18 (58)	0.05	30 (91)	28 (85)	0.45
Vitamin C *mg/d*	34 (100)	34 (100)	1.00	31 (97)	29 (91)	0.30	33 (100)	33 (100)	1.00
Sodium *mg/d*	27 (79)	24 (71)	0.40	25 (78)	22 (69)	0.40	22 (67)	17 (52)	0.21
Potassium *mg/d*	27 (79)	24 (53)	0.02	18 (56)	11 (34)	0.08	22 (67)	17 (52)	0.21
Magnesium *mg/d*	27 (79)	21 (62)	0.11	20 (63)	12 (38)	<0.05	26 (79)	18 (55)	0.04
Calcium *mg/d*	28 (82)	23 (68)	0.16	24 (75)	19 (59)	0.18	28 (85)	23 (70)	0.14
Phosphorus *mg/d*	34 (100)	33 (97)	0.31	32 (100)	31 (97)	0.31	33 (100)	33 (100)	1.00
Iron *mg/d*	24 (71)	16 (47)	<0.05	19 (61)	16 (52)	0.44	20 (61)	17 (52)	0.46
Zinc *mg/d*	27 (79)	27 (79)	1.00	25 (81)	22 (69)	0.37	30 (91)	26 (79)	0.17

DRV; Dietary Reference Value, TDA; Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet

[Ψ]Missing baseline data for n=1 for all variables

*Missing baseline data for n=1 for all variables, except for variables energy intake, niacin, iron and zinc, where n=2 missing

Table 15: Nutritional Intake

Nutritional parameter	Intervention									Difference in reduction between groups *p-value*
	TDA[Ψ]			LFD[Ψ]			GFD			
	Baseline *Median (IQR)*	**Week 4** *Median (IQR)*	**Reduction** *Median (IQR)*	**Baseline** *Median (IQR)*	**Week 4** *Median (IQR)*	**Reduction** *Median (IQR)*	**Baseline** *Median (IQR)*	**Week 4** *Median (IQR)*	**Reduction** *Median (IQR)*	
Energy *kcal/d*	2373 (1149)	1861 (832)	475 (811)	2338 (1191)	1738 (1021)	519 (1207)	2366 (889)	1958 (1364)	298 (756)	0.63
Protein *g/d*	104.2 (78.9)	90.9 (43.1)	8.3 (31.9)	97.1 (44.5)	80.4 (44.1)	17.3 (51.2)	99.7 (58.2)	79.1 (43.8)	10.7 (31.4)	0.52
Carbohydrate *g/d*	268 (118)	223 (117)	45 (116)	277 (146)	223 (136)	74 (170)	307 (144)	227 (132)	45 (95)	0.55
Fat g/d	86.8 (54.3)	65.3 (43.3)	10.4 (41.3)	82.3 (58.0)	64.6 (51.7)	15.9 (40.5)	86.1 (44.9)	77.9 (63.7)	14.8 (32.1)	0.66
Dietary fibre *g/d*	32.6 (13.2)	28.5 (14.0)	1.8 (8.5)	23.5 (27.3)	18.7 (17.4)	7.2 (18.9)	32.7 (16.0)	25.9 (13.9)	3.1 (12.6)	0.06
Folate *mcg/d*	449 (232)	353 (223)	82 (159)	362 (374)	291 (232)	79 (273)	392 (213)	335 (242)	54 (122)	0.22
Thiamine *mg/d*	1.70 (1.35)	1.40 (0.63)	0.2 (0.6)	1.40 (1.40)	1.00 (0.85)	0.6 (1.3)	1.50 (1.25)	1.10 (0.90)	0.4 (0.8)	0.13
Riboflavin *mg/d*	2.50 (2.55)	2.00 (1.43)	0.0 (1.3)	1.90 (1.85)	1.65 (1.40)	0.6 (1.3)	2.10 (1.90)	2.00 (1.60)	0.2 (0.8)	0.12
Niacin *mg/d*	24.0 (14.3)	19.6 (7.3)	1.0 (8.3)	19.1 (12.0)	14.8 (9.4)	3.0 (11.4)	20.2 (9.1)	17.7 (8.2)	2.2 (6.5)	0.72
Vitamin C *mg/d*	185 (137)	172 (135)	0 (74)	111 (174)	94 (140)	19 (50)	163 (120)	150 (87)	0 (51)	0.16
Sodium *mg/d*	2772 (1509)	1947 (969)	273 (1037)	2220 (1275)	1761 (1270)	219 (1442)	2424 (1237)	1910 (1456)	469 (979)	0.97
Potassium *mg/d*	4394 (1881)	3704 (1841)	704 (1675)	4042 (2258)	3119 (1716)	879 (2162)	4039 (1901)	3518 (1995)	614 (1060)	0.50
Magnesium *mg/d*	377 (230)	315 (172)	45 (138)	324 (201)	247 (164)	69 (169)	347 (134)	298 (146)	57 (83)	0.36
Calcium *mg/d*	1122 (1113)	896 (732)	107 (557)	991 (1354)	888 (809)	366 (543)	1057 (907)	1049 (905)	144 (489)	0.14
Phosphorus *mg/d*	1771 (1145)	1476 (547)	296 (514)	1472 (964)	1365 (940)	289 (788)	1606 (1182)	1435 (889)	169 (467)	0.41
Iron *mg/d*	13.4 (6.2)	11.5 (4.9)	1.2 (4.7)	11.7 (7.2)	10.4 (7.6)	1.6 (7.3)	12.7 (6.0)	10.6 (5.3)	1.1 (3.2)	0.70
Zinc *mg/d*	11.8 (6.2)	10.7 (5.0)	0.0 (4.5)	11.0 (4.6)	11.1 (6.6)	0.4 (4.6)	11.2 (6.4)	10.9 (7.5)	0.6 (3.1)	0.70

Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet
[Ψ]Missing baseline data for n=1 for all variables

Table 16: FODMAP Intake

FODMAP	Intervention									Difference in change between groups *p-value*
	TDA[Ψ]			LFD[Ψ]			GFD			
	Baseline *Median (IQR)*	**Week 4** *Median (IQR)*	**Baseline vs Week 4** *p-value*	**Baseline** *Median (IQR)*	**Week 4** *Median (IQR)*	**Baseline vs Week 4** *p-value*	**Baseline** *Median (IQR)*	**Week 4** *Median (IQR)*	**Baseline vs Week 4** *p-value*	
Oligosaccharides										
Fructo-oligosaccharides g/d	3.8 (2.1)	2.9 (1.5)	<0.01	3.3 (4.4)	1.6 (1.8)	<0.01	3.9 (1.5)	2.4 (2.4)	<0.01	<0.01
Galacto-oligosaccharides g/d	1.1 (0.7)	1.1 (0.6)	0.05(1)	1.2 (1.6)	0.6 (0.8)	<0.01	1.2 (1.3)	0.9 (0.9)	0.02	<0.01
Disaccharides										
Lactose g/d	11.7 (22.1)	4.9 (14.0)	<0.01	12.5 (20.7)	1.9 (6.0)	<0.01	14.3 (19.1)	13.0 (17.3)	0.22	0.02
Monosaccharides										
*Excess fructose g/d**	5.2 (4.4)	2.8 (5.1)	0.31	3.5 (8.4)	1.5 (2.7)	<0.01	4.0 (4.3)	4.0 (4.2)	0.95	<0.01
Polyols										
Sorbitol g/d	1.9 (2.4)	1.4 (2.4)	0.18	1.3 (1.6)	0.3 (0.9)	<0.01	2.1 (2.1)	1.9 (2.5)	0.84	<0.05
Mannitol g/d	0.8 (0.6)	0.6 (0.6)	<0.01	0.6 (0.5)	0.1 (0.3)	<0.01	0.7 (0.7)	0.6 (0.9)	0.70	<0.01
Total FODMAPs g/d	24.9	15.2	<0.01	27.7	7.6	<0.01	27.4	22.4	0.03	<0.01

FODMAPs; fermentable oligo-, di-, mono- saccharides and polyps, Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet
[Ψ]Missing baseline data for n=1 for all variables except excess fructose
*Missing baseline for n=10 in BDA, n=6 in LFD, n=4 GFD

4.4.5 Stool Analysis

A total of 55 paired stool samples were analysed (TDA, n=18; LFD, n=17; GFD, n=20). The change in dysbiosis index following TDA, LFD and GFD did not differ (p=0.99), with 22-29% having an improvement, 35-39% having no change, and 35-40% having worsening dysbiosis index (**Figure 8** and **Table 17**).

No significant changes in functional bacterial profiles were noted between the diets (**Table 18).** Individuals on TDA had a reduction in the abundance of *Dorea* spp. On the LFD, individuals had a reduction in the abundance of *Actinobacteria* and *Bacteroides fragilis*, with an increase in abundance of *Alistipes, Parabacteroides johnsonii, Clostridium methylpentosum* and *Lachnospiraceae*. On the GFD, individuals had a reduction in abundance of *Actinobacteria, Parabacteroides johnsonii, Eubacteriumrectale*, as well as *Ruminococcusalbus* and *R. bromii* (See **Tables 18-20**).

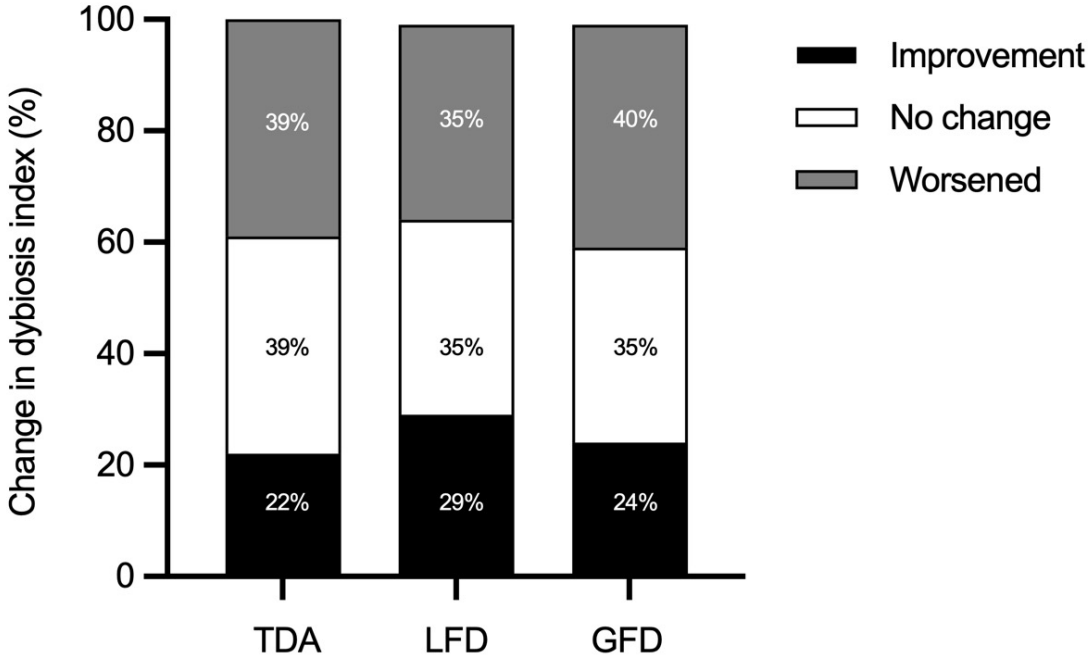


Figure 8: Change in Dysbiosis Index

TDA; traditional dietary advice, LFD; low FODMAP diet, GFD; gluten free diet

Table 17: Change in Dysbiosis Index by Intervention and Responders

	Change in Dysbiosis Index			Comparison of responders vs non-responders *p-value*
	Improved *n(%)*	No change *n(%)*	Worsened *n(%)*	
TDA				
Responders	3 (33)	2 (22)	4 (44)	0.30
Non-responders	1 (11)	5 (56)	3 (33)	
LFD				
Responders	2 (29)	2 (29)	3 (43)	0.84
Non-responders	3 (30)	4 (40)	3 (30)	
GFD				
Responders	2 (18)	4 (36)	5(46)	0.72
Non-responders	3 (33)	3 (33)	3 (33)	
Overall				
Responders	7 (26)	8 (30)	12 (44)	0.55
Non-responders	7 (25)	12 (43)	9 (32)	

Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet

Table 18: Functional bacterial profiles between interventions

	TDA			LFD			GFD		
	Baseline *n (%)*	Follow Up *n (%)*	*p-value*	Baseline *n (%)*	Follow Up *n (%)*	*p-value*	Baseline *n (%)*	Follow Up *n (%)*	*p-value*
Low levels of butyrate producing bacteria	5 (28)	2 (22)	0.70	4 (24)	2 (12)	0.37	3 (15)	5 (25)	0.43
Low levels of gut mucosa protective bacteria	3 (17)	3 (17)	1.00	3 (18)	4 (24)	0.67	4 (20)	6 (30)	0.47
Low levels of F.prausnitzii	0 (0)	3 (17)	0.07	3 (18)	2 (12)	0.63	2 (10)	4 (20)	0.38
Imbalance between selected gut barrier protective and potentially harmful bacteria	2 (11)	2 (11)	1.00	4 (24)	5 (29)	0.70	6 (30)	3 (15)	0.26
High levels of pro-inflammatory bacteria	1 (6)	1(6)	1.00	4 (24)	4 (18)	0.67	0 (0)	1 (5)	0.31

TDA; Traditional Dietary Advice, LFD; Low FODMAP diet, GFD; Gluten Free Diet

Table 19: Bacterial abundance following TDA diet

Genus/Species	Class	Phylum	DI at Follow up vs Baseline	*p-value*
Actinobacteria	Actinobacteria	Actinobacteria	No difference	0.67
Actinomycetales	Actinobacteria	Actinobacteria	No difference	0.18
Bifidobacterium spp.	Actinobacteria	Actinobacteria	No difference	1.00
Alistipes	Alistipes	Bacteroidetes	No difference	0.32
Alistipes onderdonkii	Alistipes	Bacteroidetes	No difference	0.66
Bacteroides fragilis	Bacteroides	Bacteroidetes	No difference	0.56
Bacteroides pectinophilus	Bacteroides	Bacteroidetes	No difference	0.08
Bacteroides spp.	Bacteroides	Bacteroidetes	No difference	0.26
Bacteroides spp. & Prevotella spp.	Bacteroides	Bacteroidetes	No difference	0.33
Bacteroides stercoris	Bacteroides	Bacteroidetes	No difference	0.71
Bacteroides zoogleoformans	Bacteroides	Bacteroidetes	No difference	0.26
Parabacteroides johnsonii	Parabacterioides	Bacteroidetes	No difference	1.00
Parabacteroides spp.	Parabacterioides	Bacteroidetes	No difference	0.32
Firmicutes	Negativicutes/ Clostridia	Firmicutes	No difference	0.19
Bacilli	Bacilli	Firmicutes	No difference	0.60
Catenibacterium	Erysipelotrichia	Firmicutes	No difference	1.00
Clostridia	Clostridia	Firmicutes	No difference	0.72
Clostridium methylpentosum	Ruminiclostridium	Firmicutes	No difference	1.00
Clostridium sp.	Clostridia	Firmicutes	No difference	1.00
Coprobacillus cateniformis	Erysipelotrichia	Firmicutes	No difference	1.00
Dialister invisus	Negativicutes	Firmicutes	No difference	1.00
Dialister invisus & Megasphaera micronuciformis	Negativicutes	Firmicutes	No difference	0.32
Dorea spp.	Clostridia	Firmicutes	Decreased	<0.05
Eubacterium biforme	Clostridia	Firmicutes	No difference	0.26
Eubacterium hallii	Clostridia	Firmicutes	No difference	0.56
Eubacterium rectale	Clostridia	Firmicutes	No difference	1.00
Eubacterium siraeum	Clostridia	Firmicutes	No difference	0.41
Faecalibacterium prausnitzii	Clostridia	Firmicutes	No difference	0.53
Lachnospiraceae	Clostridia	Firmicutes	No difference	0.71
Lactobacillus ruminis & Pediococcus acidilactici	Bacilli	Firmicutes	No difference	0.16
Lactobacillus spp.	Bacilli	Firmicutes	No difference	0.76
Lactobacillus spp. 2	Bacilli	Firmicutes	No difference	0.71
Phascolarctobacterium sp.	Negativicutes	Firmicutes	No difference	0.32
Ruminococcus albus & R. bromii	Clostridia	Firmicutes	No difference	0.78
Ruminococcus gnavus	Clostridia	Firmicutes	No difference	0.56
Streptococcus agalactiae & Eubacterium rectale	Bacilli	Firmicutes	No difference	0.56

Streptococcus salivarius ssp. thermophilus & S. sanguinis	Bacilli	Firmicutes	No difference	0.71
Streptococcus salivarius ssp. Thermophilus	Bacilli	Firmicutes	No difference	1.00
Streptococcus spp.	Bacilli	Firmicutes	No difference	0.78
Streptococcus spp. 2	Bacilli	Firmicutes	No difference	0.85
Veillonella spp.	Negativicutes	Firmicutes	No difference	0.60
Firmicutes (various)	-	Firmicutes/ Tenericutes/ Bacteroidetes species	No difference	1.00
Proteobacteria	-	Proteobacteria	No difference	0.41
Acinetobacter junii	Gammaproteobacteria	Proteobacteria	No difference	1.00
Enterobacteriaceae	Gammaproteobacteria	Proteobacteria	No difference	0.16
Shigella spp. & Escherichia spp	Gammaproteobacteria	Proteobacteria	No difference	1.00
Mycoplasma hominis	Mollicutes	Tenericutes	No difference	1.00
Akkermansia muciniphila	Verrumicrobiae	Verrucomicrobia	No difference	0.41

TDA; Traditional Dietary Advice, DI; Dysbiosis Index

Table 20: Bacterial abundance following LFD diet

Genus/Species	Class	Phylum	Abundance at Follow up vs Baseline	*p-value*
Actinobacteria	Actinobacteria	Actinobacteria	Decreased	<0.05
Actinomycetales	Actinobacteria	Actinobacteria	No difference	0.56
Bifidobacterium spp.	Actinobacteria	Actinobacteria	No difference	0.16
Alistipes	Alistipes	Bacteroidetes	Increased	0.02
Alistipes onderdonkii	Alistipes	Bacteroidetes	No difference	0.18
Bacteroides fragilis	Bacteroides	Bacteroidetes	Decreased	0.02
Bacteroides pectinophilus	Bacteroides	Bacteroidetes	No difference	0.71
Bacteroides spp.	Bacteroides	Bacteroidetes	No difference	0.38
Bacteroides spp. & Prevotella spp.	Bacteroides	Bacteroidetes	No difference	0.18
Bacteroides stercoris	Bacteroides	Bacteroidetes	No difference	1.00
Bacteroides zoogleoformans	Bacteroides	Bacteroidetes	No difference	0.53
Parabacteroides johnsonii	Parabacterioides	Bacteroidetes	Increased	<0.05
Parabacteroides spp.	Parabacterioides	Bacteroidetes	No difference	0.13
Firmicutes	Negativicutes/ Clostridia	Firmicutes	No difference	0.18
Bacilli	Bacilli	Firmicutes	No difference	0.16
Catenibacterium	Erysipelotrichia	Firmicutes	No difference	0.32
Clostridia	Clostridia	Firmicutes	No difference	0.38
Clostridium methylpentosum	Ruminiclostridium	Firmicutes	Increased	0.03
Clostridium sp.	Clostridia	Firmicutes	No difference	0.32
Coprobacillus cateniformis	Erysipelotrichia	Firmicutes	No difference	0.32
Dialister invisus	Negativicutes	Firmicutes	No difference	0.32
Dialister invisus & Megasphaera micronuciformis	Negativicutes	Firmicutes	No difference	0.66
Dorea spp.	Clostridia	Firmicutes	No difference	0.48
Eubacterium biforme	Clostridia	Firmicutes	No difference	0.16
Eubacterium hallii	Clostridia	Firmicutes	No difference	0.48
Eubacterium rectale	Clostridia	Firmicutes	No difference	0.76
Eubacterium siraeum	Clostridia	Firmicutes	No difference	1.00
Faecalibacterium prausnitzii	Clostridia	Firmicutes	No difference	0.74
Lachnospiraceae	Clostridia	Firmicutes	Increased	0.01
Lactobacillus ruminis & Pediococcus acidilactici	Bacilli	Firmicutes	No difference	0.32
Lactobacillus spp.	Bacilli	Firmicutes	No difference	0.32
Lactobacillus spp. 2	Bacilli	Firmicutes	No difference	0.26
Phascolarctobacterium sp.	Negativicutes	Firmicutes	No difference	0.16
Ruminococcus albus & R. bromii	Clostridia	Firmicutes	No difference	0.71
Ruminococcus gnavus	Clostridia	Firmicutes	No difference	0.89
Streptococcus agalactiae & Eubacterium rectale	Bacilli	Firmicutes	No difference	0.48

Streptococcus salivarius ssp. thermophilus & S. sanguinis	Bacilli	Firmicutes	No difference	0.48
Streptococcus salivarius ssp. Thermophilus	Bacilli	Firmicutes	No difference	0.32
Streptococcus spp.	Bacilli	Firmicutes	No difference	0.06
Streptococcus spp. 2	Bacilli	Firmicutes	No difference	0.19
Veillonella spp.	Negativicutes	Firmicutes	No difference	0.21
Firmicutes (various)	-	Firmicutes/ Tenericutes/ Bacteroidetes species	No difference	0.66
Proteobacteria	-	Proteobacteria	No difference	0.23
Acinetobacter junii	Gammaproteobacteria	Proteobacteria	No difference	1.00
Enterobacteriaceae	Gammaproteobacteria	Proteobacteria	No difference	0.66
Shigella spp. & Escherichia spp	Gammaproteobacteria	Proteobacteria	No difference	0.16
Mycoplasma hominis	Mollicutes	Tenericutes	No difference	1.00
Akkermansia muciniphila	Verrumicrobiae	Verrucomicrobia	No difference	0.20

LFD; Low FODMAP diet, DI; Dysbiosis Index

Table 21: Bacterial abundance following GFD diet

Genus/Species	Class	Phylum	Abundance at Follow up vs Baseline	*p-value*
Actinobacteria	Actinobacteria	Actinobacteria	Reduced	0.03
Actinomycetales	Actinobacteria	Actinobacteria	No difference	0.41
Bifidobacterium spp.	Actinobacteria	Actinobacteria	No difference	0.08
Alistipes	Alistipes	Bacteroidetes	No difference	0.37
Alistipes onderdonkii	Alistipes	Bacteroidetes	No difference	1.00
Bacteroides fragilis	Bacteroides	Bacteroidetes	No difference	0.32
Bacteroides pectinophilus	Bacteroides	Bacteroidetes	No difference	0.48
Bacteroides spp.	Bacteroides	Bacteroidetes	No difference	0.74
Bacteroides spp. & Prevotella spp.	Bacteroides	Bacteroidetes	No difference	1.00
Bacteroides stercoris	Bacteroides	Bacteroidetes	No difference	0.16
Bacteroides zoogleoformans	Bacteroides	Bacteroidetes	No difference	1.00
Parabacteroides johnsonii	Parabacterioides	Bacteroidetes	Reduced	0.01
Parabacteroides spp.	Parabacterioides	Bacteroidetes	No difference	0.26
Firmicutes	Negativicutes/ Clostridia	Firmicutes	No difference	1.00
Bacilli	Bacilli	Firmicutes	No difference	0.21
Catenibacterium mitsuokai	Erysipelotrichia	Firmicutes	No difference	1.00
Clostridia	Clostridia	Firmicutes	No difference	0.78
Clostridium methylpentosum	Ruminiclostridium	Firmicutes	No difference	0.26
Clostridium sp.	Clostridia	Firmicutes	No difference	1.00
Coprobacillus cateniformis	Erysipelotrichia	Firmicutes	No difference	1.00
Dialister invisus	Negativicutes	Firmicutes	No difference	0.32
Dialister invisus & Megasphaera micronuciformis	Negativicutes	Firmicutes	No difference	0.05
Dorea spp.	Clostridia	Firmicutes	No difference	1.00
Eubacterium biforme	Clostridia	Firmicutes	No difference	0.08
Eubacterium hallii	Clostridia	Firmicutes	No difference	0.27
Eubacterium rectale	Clostridia	Firmicutes	Reduced	0.02
Eubacterium siraeum	Clostridia	Firmicutes	No difference	0.52
Faecalibacterium prausnitzii	Clostridia	Firmicutes	No difference	0.21
Lachnospiraceae	Clostridia	Firmicutes	No difference	0.32
Lactobacillus ruminis & Pediococcus acidilactici	Bacilli	Firmicutes	No difference	0.56
Lactobacillus spp.	Bacilli	Firmicutes	No difference	0.56
Lactobacillus spp. 2	Bacilli	Firmicutes	No difference	0.33
Phascolarctobacterium sp.	Negativicutes	Firmicutes	No difference	0.08
Ruminococcus albus & R. bromii	Clostridia	Firmicutes	Reduced	0.04
Ruminococcus gnavus	Clostridia	Firmicutes	No difference	0.17
Streptococcus agalactiae & Eubacterium rectale	Bacilli	Firmicutes	No difference	0.16

Streptococcus salivarius ssp. thermophilus & S. sanguinis	Bacilli	Firmicutes	No difference	0.06
Streptococcus salivarius ssp. Thermophilus	Bacilli	Firmicutes	No difference	0.10
Streptococcus spp.	Bacilli	Firmicutes	No difference	0.59
Streptococcus spp. 2	Bacilli	Firmicutes	No difference	0.42
Veillonella spp.	Negativicutes	Firmicutes	No difference	0.77
Firmicutes (various)	-	Firmicutes/ Tenericutes/ Bacteroidetes species	No difference	0.10
Proteobacteria	-	Proteobacteria	No difference	0.41
Acinetobacter junii	Gammaproteobacteria	Proteobacteria	No difference	1.00
Enterobacteriaceae	Gammaproteobacteria	Proteobacteria	No difference	1.00
Shigella spp. & Escherichia spp	Gammaproteobacteria	Proteobacteria	No difference	0.32
Mycoplasma hominis	Mollicutes	Tenericutes	No difference	1.00
Akkermansia muciniphila	Verrumicrobiae	Verrucomicrobia	No difference	0.10

GFD; Gluten Free Diet, DI; Dysbiosis Index

4.4.6 Factors associated with clinical response to dietary therapies

Age, gender, IBS-subtype, IMD quintiles, somatisation severity, clinical HADS anxiety and depression levels did not predict clinical response to dietary therapies (**Table 22**), and nor did baseline stool dysbiosis index (**Figure 9**).

Table 22: Binary logistic regression analysis of patient baseline variables on response to dietary therapies

Variable	Intervention			
	TDA	**LFD**	**GFD**	**Overall**
	OR (CI)	*OR (CI)*	*OR (CI)*	*OR (CI)*
Age (years)	1.06 (1.00-1.12)	0.99 (0.94-1.05)	0.98 (0.92-1.03)	1.01 (0.98-1.04)
Gender				
Male	1	1	1	1
Female	0.68 (0.14-3.34)	1.67 (0.32-8.59)	0.62 (0.15-2.58)	0.91 (0.38-2.15)
IBS-subtype				
IBS-D	1	1	1	1
IBS-M	0.53 (0.09-3.24)	0.30 (0.06-1.51)	1.69 (0.34-8.40)	0.71 (0.29-1.76)
IMD Quintiles				
Q1-3	1	1	1	1
Q4-5	2.50 (0.61-10.26)	4.14 (0.71-24.16)	0.29 (0.06-1.32)	1.31 (0.57-3.03)
Somatisation Severity				
Minimal	1	1	1	1
Low	1.00 (0.07-14.64)	1.50 (0.10-23.07)	4.00 (0.27-58.56)	1.50 (0.37-6.16)
Medium	1.14 (0.08-16.95)	0.11 (0.01-1.52)	4.50 (0.31-65.23)	0.80 (0.20-3.25)
High	2.50 (0.16-38.60)	0.33 (0.02-5.33)	0.50 (0.02-12.90)	0.82 (0.18-3.74)
HADS-anxiety levels (clinical)				
Normal	1	1	1	1
Abnormal	0.65 (0.15-2.79)	0.53 (0.13-2.14)	0.40 (0.10-1.68)	0.60 (0.27-1.31)
HADS-depression levels (clinical)				
Normal	1	1	1	1
Abnormal	1.58 (0.20-12.79)	0.25 (0.04-1.54)	0.21 (0.03-1.32)	0.42 (0.15-1.23)

TDA; Traditional dietary advice, LFD; low FODMAP diet, GFD; Gluten Free Diet, OR; odds ratio, CI; confidence interval; IBS; Irritable Bowel Syndrome, IMD; Index of Multiple Deprivation, HADS; Hospital Anxiety and Depression Scale

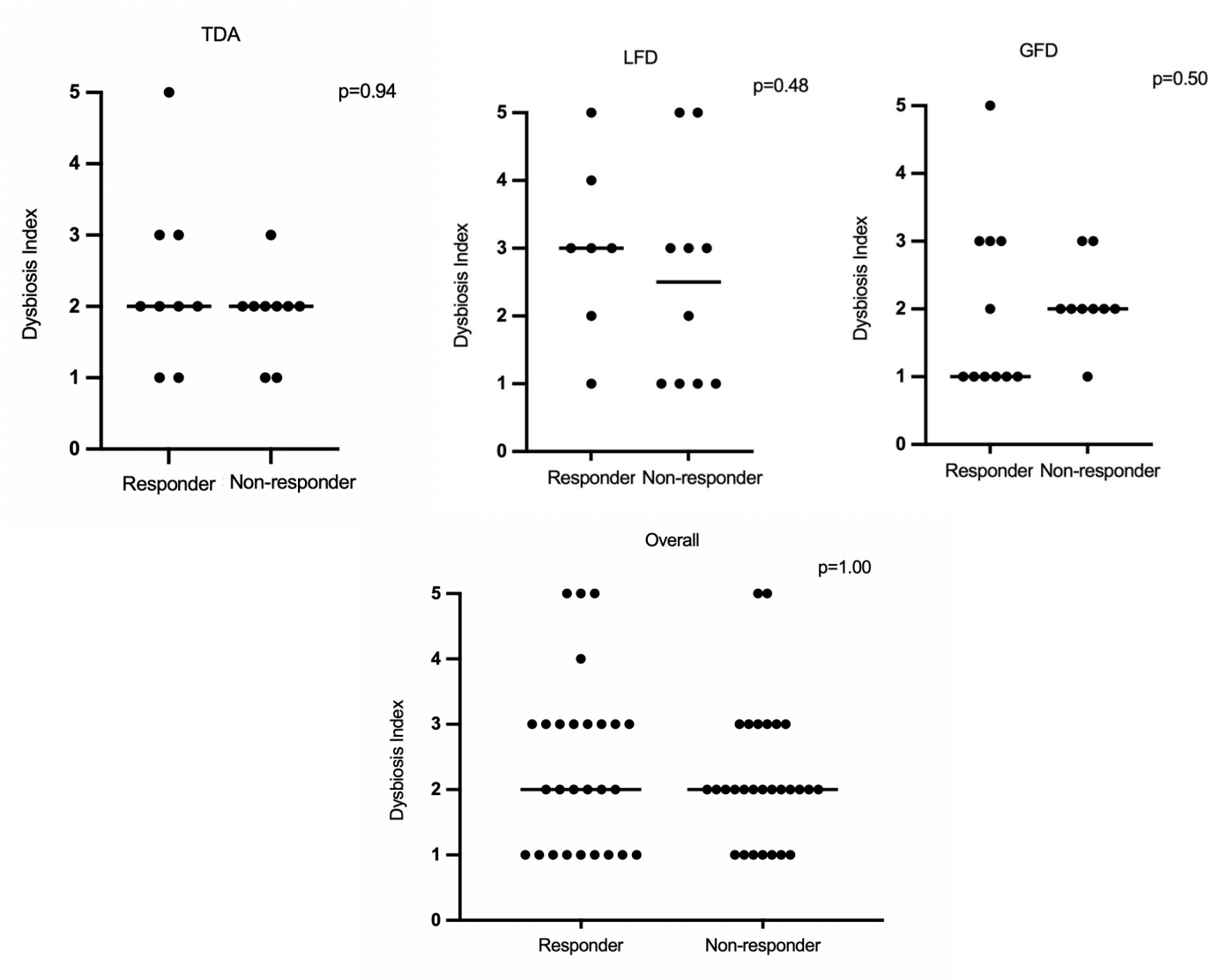


Figure 9: Dysbiosis Index between responders and non-responders at baseline

TDA; traditional dietary advice, LFD; low FODMAP diet, GFD; gluten free diet

4.5 Discussion

This is the first randomised control trial directly comparing the effectiveness and convenience of TDA, LFD and GFD for the management of IBS. The main findings are that, on both modified intention-to-treat and per protocol analysis, the diets have a similar level of clinical efficacy, with approximately a 50% response rate with regards to the primary end-point of ≥ 50-point reduction in IBS-SSS. However, individuals found TDA significantly cheaper, tastier, less time-consuming to shop, easier to implement and socially more convenient than the GFD and LFD. Clinical characteristics, socioeconomic status and baseline stool DI did not predict response to dietary therapy. Finally, the mode of dietary education, either face-to-face or virtual, did not affect clinical response to dietary therapy.

The chief strength of this study, which adds important value to the literature, is that it is a "real-life pragmatic' study as opposed to being a feeding study. By leaving the responsibility upon the patient to undertake the dietary intervention following appropriate education, as one would expect in routine clinical care, we provide a clearer picture of its efficacy and social convenience; hence, these findings can be generalised to daily clinical practise. This data is line with recent RCTs showing TDA to have a similar level of clinical efficacy to a LFD, and supports British guidelines recommending TDA as the first-line dietary therapy for IBS.[5,19] In contrast to suggestions by some investigators,[51] a degree of caution should be urged against early deployment of complex, restrictive diets (i.e. the LFD and GFD), as not only do patients find them more inconvenient and costly, but they also require extensive dietetic input and incur a substantial burden on the healthcare service. Indeed, even within a highly established

health care system like the United Kingdom (UK), there is inequity of GI dietetic services, with regional differences in the level of provision and extent of specialist care available (see **Chapter 5**).

With this is mind, the current position of a LFD as outlined by the BSG for the management of IBS should be questioned, where, despite acknowledging its low quality evidence base, it is placed within the initial top tier of therapy should TDA not suffice.[5] In fact, it is highlighted as an option before widely available over-the-counter therapies such as peppermint oil or antispasmodics, which have a similar number needed to treat as a LFD (~4), but arguably may be easier and cheaper for patients and healthcare providers to implement, and without interfering on other household members during meal time.[5,154] On a similar theme, the Canadian Association of Gastroenterology Clinical Practise Guidelines for the management of IBS has a LFD placed after antispasmodics but before probiotics,[155] whereas the American College of Gastroenterology recommends a limited trial of a LFD but without clearly stating when.[5,155,156] In all, this highlights the uncertainty amongst international guidelines as to where the LFD belongs within the treatment algorithm. With regards to a GFD, current guidelines do not recommend its use in IBS due to insufficient evidence,[5,155,156] but this study adds to the literature base, and alongside other recent publications suggests that it warrants re-evaluation.[24] In the meantime, restrictive diets should be placed lower down the treatment algorithm for IBS although a caveat to this suggestion, and indeed one overlooked by current guidelines, is the lack of data on whether a LFD or GFD are effective second line dietary therapies in those who fail to respond to TDA. This deserves further study, as does a RCT evaluating the clinical efficacy and convenience of the LFD or GFD versus medical therapies such as antispasmodics, peppermint oil or probiotics.

All three diets led to a reduction in total FODMAP intake which, as expected, was greatest in the LFD group compared to TDA and the GFD. At week 4, the FODMAP intake in the LFD was 7.6g/day compared with 15.2 g/day for TDA and 22.4g/day for the GFD. This suggests a degree of overlap to exist between diets albeit along a spectrum. To help restore adequate FODMAP intake on a LFD, it is important to emphasise that it is altogether a 3-stage process, and that after its strict elimination phase there are further steps of re-introduction and personalisation, which should be all done under the supervision and guidance of a dietitian.[5,19,155,156] However, "real world" experience from a Canadian healthcare system suggests that of those referred for a LFD, 70% go through the LFD process without dietetic supervision, and demonstrate diminishing adherence with the diet along its phases (71% elimination, 39% re-introduction, and 29% personalisation).[140] Whilst adherence is better in the 30% seen by a dietitian, it still drops off over the phases (96% elimination, 70% re-introduction and 65% personalisation).[140] As a whole, only 40% of those referred for a LFD satisfactorily completed all 3-phases of the programme which, in turn, might imply that a substantial proportion of the rest remain within the strict elimination phase, are at risk of developing overly restrictive eating patterns and nutritional inadequacies.[24,140] To counteract this concern, there has been suggestions that a 'bottom-up' or a "more personalised" approach to the LFD may overcome its extensive and complex 3-phase programme.[33,157] For example, it has been shown that in the long term many patients on a personalised LFD are reducing fructan intake to manage their symptoms, and facilitate this by purchasing gluten or wheat free products.[50,158] This raises the hypothesis that maybe a GFD should be considered as an option before enrolling onto the complete LFD programme.[158] The pathophysiological mechanism by which symptoms improve on a GFD are extensively debated but appear, in the main, not to be via the removal of gluten *per se*, but rather due to a reduction in

dietary fructan content (a FODMAP) due to wheat exclusion.[95,111] It has been previously postulated that a GFD is a dietary cousin of a LFD, and may be the express route to reducing fructan and galacto-oligosaccharide content.[159,160] Other reasons to consider using a GFD in IBS is in those who are positive for antigliadin antibodies without evidence of CD, as well as those who present with self-reported non-coeliac gluten/wheat sensitivity.[101,145] This study, amongst another recent publication, shows that a GFD in IBS does not need to be strict (as one would require in CD) and that clinical benefit can be achieved whilst allowing for gluten cross-contamination.[101] Future studies assessing the level of gluten restriction required to derive symptom benefit are required.

Nutritional inadequacy has been highlighted as a concern with the use of dietary therapies in IBS.[24] This study found that reductions in macro- and micro- nutrient content were similar across the groups, except for the LFD showing a trend towards more fibre reduction. Moreover, whilst the proportion of individuals meeting the DRVs for macronutrients did not change from pre-intervention for all three diets, there were reductions in the proportion of individuals meeting DRVs for specific micronutrients on all three diets (potassium and iron on TDA, thiamine and magnesium on both LFD and GFD). Interestingly, the majority of individuals failed to meet DRVs for total energy intake even pre-intervention. This may be a result of eating patterns in IBS itself, rather than the dietary interventions employed, with it being previously demonstrated that individuals with IBS fail to meet dietary recommended values for multiple nutrients.[134] Whilst the most validated food frequency tool available currently (CNAQ tool) was used, it is possible that using a food frequency tool may have led to under-reporting of total energy intake.[139] Nevertheless, it does highlight that implementation of dietary therapies should not be taken lightly, and that nutritional parameters be monitored.

Diet is thought to be key environmental component in the composition of the gut microbiome,[161] with the LFD having previously been shown in short term studies to reduce the proportion of luminal *Bifidobacterium*, as well as total bacterial abundance.[41,72,73] On the GFD, reduction in *Bifidobacterium* has also been noted, as well as *faecalibacterium prausnitzii* proportions.[119] Whilst changes in bacterial abundance following all three interventions were noted, the clinical significance of this is unclear, with no significant difference in functional bacterial profiles noted. A previous study, using the same method of stool analysis, demonstrated that response to a LFD, but not TDA, could be determined from baseline faecal bacterial profiles.[72] However, we were unable to replicate these findings, highlighting the uncertainty in this area.

This study does have other notable strengths. Due to the impact of COVID-19, dietary education moved away from face-to-face to virtual consults. There was a similar level of efficacy to dietary therapy irrespective of the mode of educational delivery. Moreover, dietary therapy was provided in a group setting, with a clinical response rate similar to studies where patients have been seen individually.[43,44] Moving forward, this suggests that dietary education can be delivered successfully virtually and in small group settings, which will have cost saving implications for public healthcare services, and alleviate any ongoing concerns that patients may have travelling to hospitals in the current climate.

A limitation of this study was that the food frequency questionnaire used (CNAQ tool) was based on the Australian diet. Whilst this tool is the most objective tool currently available in the literature, and has been used in previous UK studies,[50] the nutritional and FODMAP assessments may have been under- or over- estimated. However, in this study,

the CNAQ tool was used both pre- and post-intervention to assess change between all three groups, to ensure consistency. In addition, dietary recommended values were based on UK reference values, adjusting for age and gender. Another limitation was that the stool samples assessed changes in the gut bacteriome, rather than the virome and mycobiome, and therefore may not be representative of the entire microbiota.

In conclusion, the TDA, GFD and LFD are effective approaches for individuals with IBS. We recommend TDA as the first-choice dietary option due to its widespread availability, relative simplicity, and patient friendliness. The LFD or GFD may be used as an alternative option based on specific patient preference and with specialist dietetic counselling.

4.6 Declaration of Published Work Used

This chapter has been submitted for consideration of publication.

Chapter 5 Provision of Gastroenterology Dietetic Services in England

5.1 Summary

Background: Whilst there has been an increasing demand for dietitians, little is known on the provision of GI dietetic services in England. There have been no studies assessing the provision of gastroenterology dietetic services as a whole in England to date. The aim of the study was to assess the provision of dietetic services for CD, IBS and IBD.

Methods: Hospitals within all National Health Service (NHS) trusts in England were approached (n=209). A custom-designed web-based questionnaire was circulated via contact methods of e-mail, post or telephone. Individuals/teams with knowledge of GI dietetic services within their trust were invited to complete.

Results: 76% of trusts (n=158) provided GI dietetic services, with responses received from 78% of these trusts (n=123). The median number of dietitians per 100,000 population was 3.64 (range 0.15-16.60), which differed significantly between regions (p=0.03). The commonest individual consultation time for patients with CD, IBS and IBD was 15-30 mins (43%, 44% and 54% respectively). GI dietetic services were delivered both via individual and group counselling, with individual counselling being the more frequent delivery method available (93% individual vs 34% group). A significant proportion of trusts did not deliver any specialist dietetic clinics for CD, IBS and IBD (49% [n=60], 50% [n=61] and 72% [n=88] respectively).

Conclusion: There is an inequity of GI dietetic services across England, with regional differences in the level of provision and extent of specialist care. Allocated time for clinics

appears to be insufficient compared to time advocated in the literature. Group clinics are becoming a more common method of dietetic service delivery for CD and IBS. National guidance on GI dietetic service delivery is required to ensure equity of dietetic services across England.

5.2 Introduction

Since the inception of the NHS in the UK in 1948, there have been huge changes in population demographics, with an increase in chronic long term conditions. [162] The role of the dietitian has become established over time, with a growing recognition on nutritional interventions on health outcomes.[162]

Whilst there has been an increasing demand for dietitians, little is known on the provision of GI dietetic services in England. The last survey assessing the provision of dietetic services was in 2007, where dietetic provision was only one third of what was recommended by the BSG guidelines for CD.[163]

Dietetic input is essential in GI services. In CD, dietetic input can help educate individuals on a GFD, monitor adherence, identify hidden sources of gluten, healthy gluten free grains and ensure adequate fibre and nutrient intake.[164] There has been a rapid expansion in the role of dietary therapies in IBS, with dietitians required at the forefront to deliver these therapies effectively.[56] Current diets being implemented by dietitians for IBS include general dietary advice and the LFD, as advised by the BDA.[19] Nutritional input from dietitians is also essential in IBD, with dietitians required to prevent and treat malnutrition and micronutrient deficiencies, as well as the prevention of osteoporosis.[165]

There have been no studies assessing the provision of gastroenterology dietetic services as a whole in England to date. In view of this, the aim of the study was to assess the current provision of dietetic services in CD, IBS and IBD.

5.3 Methods

5.3.1 Study Design

Hospitals within all England NHS trusts were approached between February 2019 to June 2019, with all NHS trusts within England being identified from the NHS England website (https://www.england.nhs.uk/). Following this, dietetic departments within all England NHS trusts were approached, either via telephone, letter or e-mail. Individuals/teams of dietitians with knowledge of GI services within their trusts were invited to complete a custom-designed web-based questionnaire, or a paper version if unable to complete electronically. Trusts which did not provide any gastroenterology dietetic services were excluded (**Figure 10**).

Questions asked included time allocated to GI services, grade of dietitian responsible for GI services, setting in which patients are seen, waiting times, average consultation time and teaching methods used.

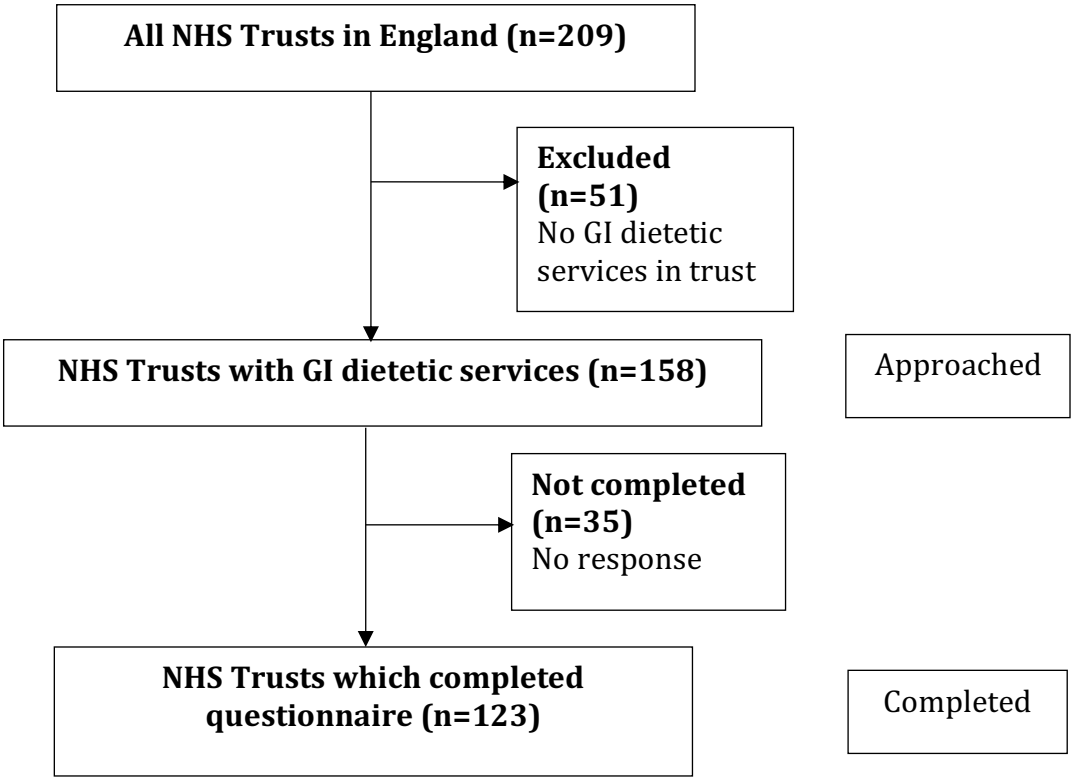


Figure 10 Flow chart for participants during trial

5.3.2 Statistical Analysis

All data collected was maintained confidentially, with data being analysed using SPSS version 24 (International Business Machines, Armonk, NY). Data was summarised using descriptive statistics, including counts and percentages for categorical data and median and range for non-normally distributed data. The Shapiro-Wilk test was used to assess normality of data. The Kruskal Wallis test was used to assess multiple non-parametric groups. Comparison between categorical data between both groups was performed using χ^2 testing. Statistical significance was considered when $p<0.05$.

5.4 Results

Hospitals within all NHS trusts were contacted (n=209). There were 51 trusts which did not provide any GI dietetic services (e.g. mental health trust, ambulance trust). Surveys were completed from 123 out of 158 trusts (78%) with GI dietetic services. The majority of hospitals which responded were from district general hospitals (51%), followed by central teaching hospitals (28%) and the community (21%). The completion rate by region is shown in **Table 23**, with no statistically significant difference in response rate by region (p=0.12).

Table 23 Responses to Dietetic Survey by Region

Region	Number of Trusts	Number of Trust responses	Percentage of Trusts Responded (%)
East of England	19	11	58
North East and Yorkshire	24	19	79
London	24	19	79
Midlands	24	18	75
North West	23	22	96
South East	24	17	71
South West	20	17	85
Total	158	123	78

5.4.1 Overall Service Delivery

The Full Time Equivalent (FTE) per head of populations was 3.64 per 100,000 (range 0.15-16.60) across England. There was a statistically significant difference (p=0.03) between regions, with the highest being noted in North East and Yorkshire (5.86 FTE per 100,000 [range 0.20-9.19]) and lowest being noted in North West region (2.16 FTE per 100,000 [range 0.36-14.00]), as seen in **Table 24**.

Across England, the vast majority of trusts saw adults in their service (95.1% [n=117], 95.9% [n=118] and 94.3% [n=116] for CD, IBS and IBD respectively). 63.4% (n=78) of trusts saw children with CD and 49.6% (n=61) saw children with IBD.

Table 24 Full Time Equivalent (FTE) Dietitians by Region

Region	FTE Dietitians/100,000
East of England	2.38 (0.48-16.60)
North East and Yorkshire	5.86 (0.20-9.19)
London	3.25 (1.06-14.40)
Midlands	3.68 (0.15-8.50)
North West	2.16 (0.36-14.00)
South East	4.09 (0.92-8.33)
South West	3.40 (0.70-8.33)
Total	3.64 (0.15-16.60)

*Data presented as median (range)

5.4.2 Time Allocation to Services

Hours allocated monthly varied between conditions ($p<0.01$), with median hours allocated to IBS being the highest at 15 [range 0-175] hours/month, whereas median time allocated to CD was 6 [range 0-40] hours/month and IBD was 7 [range 0-100] hours/month.

The most frequent waiting time for individuals to be seen was <2 months for individuals with CD and IBD, whereas it was longer for IBS at 2-4 months. In terms of consultation length, the most frequent consultation length was 15-30 minutes for patients with IBS, CD, and IBD (**Table 25**).

Approximately half of all trusts had a dietitian responsible for the delivery of CD (54% n=66), IBS (49%, n=60) and IBD (59%, n=72) services. The majority of individuals with the main responsibility of delivering this service were Band 6 dietitians (pay band, scaled from 1 to 9) for all GI services (**Table 25**).

Out of those trusts who had a dietitian responsible for GI dietetic service delivery, 52% (n=34) had received post registration training in CD, 92% (n=55) had received post registration training in IBS and 57% (n=41) had received post registration training in IBD. The commonest professional membership for dietitians responsible for the delivery of CD was the BDA (97%, n=64) followed by Coeliac UK (82%, n=54). Likewise, the commonest professional membership for dietitians responsible for the delivery of IBS was the BDA (98%, n=65) followed by Coeliac UK (58%, n=35). Also, the commonest professional membership for dietitians responsible for the delivery of IBD was the BDA (96%, n=69) followed by Coeliac UK (40%, n=29).

Table 25 Provision of Dietetic Services for Coeliac Disease, Irritable Bowel Syndrome and Inflammatory Bowel Disease

	CD	IBS	IBD
	n (%)	**n (%)**	**n (%)**
Band of Dietitian with Main Responsibility of Service			
5	6 (8)	4 (6)	1 (1)
6	40 (53)	41 (61)	44 (56)
7	28 (37)	22 (33)	33 (42)
8a or above	2 (3)	0 (0)	0 (0)
Specialist Clinic Frequency			
Weekly	21 (33)	27 (44)	18 (51)
Fortnightly	13 (21)	10 (16)	6 (17)
Monthly	20 (32)	24 (39)	10 (29)
Less than monthly	9 (14)	1 (2)	1 (3)
Policy for Management of Condition			
Yes	58 (47)	66 (54)	30 (24)
No	65 (53)	57 (46)	93 (76)
Waiting time			
<2 months	84 (72)	46 (39)	65 (57)
2-4 months	32 (27)	58 (50)	42 (37)
4-6 months	0 (0)	11 (9)	7 (6)
>6 months	1 (1)	2 (2)	0 (0)
Consultation Length			
<15 minutes	3 (3)	0 (0)	0 (0)
15-30 minutes	51 (43)	51 (44)	64 (54)
30-45 minutes	48 (41)	49 (42)	44 (37)
45-60 minutes	16 (14)	16 (14)	10 (9)
Teaching method used			
Individual	116 (94)	115 (94)	117 (95)
Group	39 (32)	42 (34)	1 (1)

CD; coeliac disease, IBS; irritable bowel syndrome, IBD; inflammatory bowel disease

5.4.3 Specialist Service Delivery

Specialist clinics were defined as dietetic clinics designated for the management of one condition, rather than general dietetic clinics where patients with a wide variety of conditions were seen. A large proportion of trusts did not deliver any specialist clinics for CD, IBS and IBD (49% [n=60], 50% [n=61] and 72% [n=88] respectively). Out of those who had specialist clinics, the frequency of clinics is outlined in **Table 25**, with weekly clinics being the most frequent.

47% of trusts had policies for the dietetic management of CD, 54% of trusts had policies for the dietetic management of IBS, whereas only 24% had policies for the dietetic management of IBD.

The large majority of trusts delivered teaching on dietetic therapies on a one-to-one basis (**Table 25**). A large number of trusts also delivered teaching through group therapies, particularly for CD (32%, n=39) and IBS (34%, n=42) rather than IBD (1%, n=1).

5.5 Discussion

This is the first study since 2007 assessing the provision of gastroenterology dietetic services in England, and the first to assess the provision of IBS and IBD services in addition to CD. This study had a high response rate (78%), which compares favourably to the previous study looking at the provision of dietetic services in CD, which had a response rate of 38%.[163] There was no statistically significant difference in response rates between regions, with these findings likely to be an accurate representation of the provision of services across England.

There was a significant difference in the number of FTE dietitians per population by region, highlighting the variation in dietetic GI service delivery across England, similar to the previous study assessing the provision of CD in the UK.[163] This may in part be due to variation in funding of GI dietetic services across England, although funding was not assessed.

It appears that a large proportion of trusts do not have a dietitian responsible for the delivery of specialist gastroenterology services, which were CD, IBS and IBD. Adherence to dietary therapies have been demonstrated to be improved by patients having regular access and follow up in clinic.[166] This highlights that individuals requiring dietary therapies are failing to receive specialist advice, despite this being advocated in the literature.[56,125,159] CD is common, with a prevalence of 1%, with diet being the mainstay of treatment. Without access to specialist services, these individuals are likely to be at an increased risk of nutritional deficiencies, such as deficiencies of folate, calcium, magnesium, iron, zinc and fibre intake.[80,112,115] The prevalence of IBS is also high, reported at approximately 10 percent, with diet being reported as a trigger in up to 84% of patients.[4,11,12,132] Dietary therapies for IBS can be complex to implement such as the LFD, with specialist dietetic input being essential in the implementation of these diets.[125] In view of this, it is likely that many patients with IBS are not receiving dietary interventions or are self-implementing these diets. A large study of 1500 gastroenterologists demonstrated that a common mode to provide nutritional advice to IBS patients by gastroenterologists was educational handouts (81%), highlighting the suboptimal care patients are currently receiving.[133]

A greater proportion of individuals are receiving post registration training in IBS versus CD and IBD. This may in part be due to an increase in knowledge of the role of dietary therapies in IBS, as well as the emerging evidence for the role of dietitians in the delivery of these dietary therapies.[19,125] It is also worth noting that dietetic training for IBS in England is commonly delivered through paid courses, and arguably this should be embedded within their teaching curriculum in view of the high prevalence of IBS.

There seems to be disparity between recommended consultation time in the literature and true clinical practice. In the literature, it is recommended that 45-60 minutes is required for a new patient to educate them on a LFD,[23] whereas the most frequent consultation length was 15-30 minutes in this study. This highlights the challenges to dietetic services to deliver these therapies effectively. The commonest mode of dietetic review was on a one-to-one basis. Of note, there were an increasing number of individuals who were seen in group clinics, mainly for CD and IBS. There appears to be an emerging role for the use of group clinics within and outside the field of gastroenterology, with group clinics being a potential way to increase efficacy of seeing patients.[126,167-170] This method could potentially bridge capacity issues in delivering these dietetic therapies effectively, although further studies are required.

A large proportion of trusts did not have policies for the dietetic management of either CD, IBS or IBD. This suggests that the delivery of care within trusts maybe heterogenous, although it is worth noting that national guidelines are available such as NICE and BDA guidelines.[19,20]

There are potential limitations with this study. Firstly, this study assessed the provision of GI services in England only. Whilst this study is likely to be representative of the provision of dietetic services across England, this may not be representative of the entire NHS which encompasses the UK. Also, as this is the first study assessing the dietetic provision of CD, IBS and IBD together, there is little data outlining previous provision to compare. Also, there is little guidance on the required level of GI dietetic services to deliver an effective service in England.

To conclude, there appears to be an inequity of GI dietetic services across England, with regional differences in the level of provision and the extent of specialist care. A large proportion of patients are failing to receive specialist dietetic care, likely leading to patients self-implementing or not implementing dietary interventions, despite evidence of their efficacy. National guidance is required to guide the level of GI dietetic services required to deliver an effective service.

5.6 Declaration of Published Work Used

This chapter have been published and been reproduced with minor changes. The following paper was used for this chapter;

1. **Rej A**, Buckle RL, Shaw CC, Trott N, Urwin H, McGough N, Aziz I, Sanders DS. National Survey evaluating the provision of gastroenterology dietetic services in England. *Frontline Gastroenterology* 2020; doi: 10.1136/flgastro-2020-101493

Chapter 6: Summary of Key Findings and Recommendations for Future Research

The aim of this body of work was to assess the role of nutritional therapies in IBS, as well as assessing the provision of dietetic services to facilitate delivery of these therapies.

In Chapter 3, the aim of the study was the assess the role of the LFD at long term follow up. Whilst there have been studies assessing the efficacy of the LFD, the majority of studies have assessed its efficacy at short term follow up,[39,41,43-46,48,57] there have been few studies assessing long term follow up.[47,50,62,63,65,66] It is essential that the long term phase of the LFD is assessed, as there are multiple phases of this diet, with the strict reduction phase initially, followed by FODMAP reintroduction and finally personalisation at long term follow up.[23]

The study performed in Chapter 3 demonstrated efficacy of the low FODMAP diet at long term follow up, with adequate relief of symptoms reported at 60%, which was similar to a previous study which had shorter follow up.[50] Reassuringly, the majority, reported at 76%, were on the personalisation phase of the LFD, rather than the restrictive phase. This was an important finding, as there are concerns of nutritional intake at short term with the LFD,[41,43] and this has been attributed to the initial strict reduction of FODMAPs at short term follow up. In this study, no difference in mean nutritional intake was noted between individuals on the personalisation phase of the low FODMAP diet, compared to those who had returned to a habitual diet. Whilst the majority of individuals on the personalisation phase of the low FODMAP diet met the majority of micronutrient indices, the majority of macronutrient indices were not met, as well as failing to meet total energy

intakes. This study highlighted that many individuals may fail to meet nutritional requirements as a result of eating patterns themselves, rather than specifically the low FODMAP diet, with it being shown previously that individuals with IBS fail to meet dietary recommended values.[69,134] However, it is worth noting that this study compared energy intakes against estimated average requirements rather than calculated total energy requirements of individual patients (i.e. from prediction equations). Therefore, results should be interpreted with caution.

The findings of many individuals with IBS failing to meet DRVs for nutritional intake highlights the need for dietetic-led therapy, in order to prevent nutritional inadequacy, and prevent obsessive behaviours such as orthorexia nervosa.[147] Whilst a survey demonstrated that large proportion of gastroenterologists in the US recommended a low FODMAP diet, interestingly only a minority were referred to a dietitian for nutritional counselling.[133] It is likely that the LFD is being implemented without dietitians in the majority of individuals. This study was performed in the US, arguably with high level of infrastructure within its healthcare system, and it is likely that the LFD is being implemented without a dietitian in a large proportion of individuals globally, especially in lower income countries, where resources are more sparse.[24] Future studies comparing dietetic-led to other modalities of delivery, such as physician-led or information sheets alone may be useful to inform the efficacy of the LFD when implemented without a dietitian, and any potential nutritional consequences. A recent case-series in patients with functional gastrointestinal symptoms demonstrated that a significantly greater proportion of individuals were able to follow all three phases of the low FODMAP diet when this was dietetic-led compared to other modes of delivery.[140]

An interesting finding from Chapter 3 was that many individuals on the LFD at long term follow up either requested the GFD or WFD whilst eating out, or purchased gluten-free or wheat 'free-from' products. Individuals maybe employing these diets in order to reduce fructan intake, one of the FODMAPs, as a major dietary source of fructans is bread.[171] Some of the symptom improvement seen in the long term low FODMAP diet maybe as a result of fructan reduction through consuming gluten or wheat free foods. It is worth noting, as mentioned previously, that several components of wheat may be key to the pathophysiology of symptom generation. In addition to fructans, WGAs, ATIs and gluten maybe key components to symptom improvement.[81] Whilst there has been a study demonstrating that fructan, rather than gluten, maybe key to symptom induction,[111] further studies are required in patients with IBS to elucidate the pathophysiological mechanisms. In addition, the optimal FODMAP threshold to lead to symptom relief is yet to be determined, although a threshold of 12g daily has been proposed.[140] Chapter 3 demonstrated that individuals on the long term phase of the low FODMAP diet had a total FODMAP intake of 17g daily, with other long term FODMAP studies demonstrating intakes of 9.0g and 20.6g daily respectively, highlighting the need for studies to assess the optimal threshold.[50,140] However, it is worth noting that there may not be an optimal threshold per se, as individuals with IBS may have differing FODMAP thresholds dependent upon their level of visceral hypersensitivity, with the prevalence of visceral hypersensitivity in IBS being reported variably in the literature.[172]

Whilst Chapter 3 has demonstrated benefits of the LFD at long term follow up, building upon the evidence for its use in IBS, data is currently conflicting with regards to the comparative efficacy of this diet in comparison to other dietary therapies. A study in Sweden demonstrated no difference between the LFD and TDA and a study in the US also

showed no difference in adequate symptom relief between the LFD and modified NICE diet.[43,44] However, individuals on the LFD were shown to have a higher proportion of abdominal pain responders, compared to the modified NICE diet.[44] In contrast to the previous two studies,[43,44] a study more recently in Iran demonstrated superiority of the LFD in comparison to traditional dietary advice,[57] highlighting the uncertainty in this area. In this study of 110 patients with IBS-D, both generalised dietary advice (Baseline IBS-SSS 253 vs Week 6 IBS-SSS 150, $p<0.001$), as well as the LFD (Baseline IBS-SSS 264 vs Week 6 IBS-SSS 108, $p<0.001$), led to the adequate improvement of GI symptoms at 6 weeks.[57] However, the magnitude of response was greater for individuals following the LFD compared to generalised dietary advice ($p=0.002$). Of note, the proportion of clinical responders (defined as a drop of 50 points on IBS-SSS) was not used as an endpoint, and therefore the clinical significance of the magnitude of improvement is unclear.[57]

As highlighted in Chapter 1, there is growing evidence of the benefits of a GFD in IBS,[82,94,96,97] with Chapter 3 highlighting that many individuals are using gluten or wheat free products as part of the LFD. However, a systematic review and meta-analysis evaluating the GFD and LFD suggested there was insufficient evidence to recommend a GFD to reduce IBS symptoms, with low quality evidence for the use of the low FODMAP diet.[106] As a result of this, there was a clear need to evaluate the efficacy of TDA, the LFD and GFD head to head in IBS for the first time in the literature. This led to Chapter 4, where the response rate to traditional dietary advice, LFD and GFD was noted to be 40%, 55% and 58% respectively. Interestingly, there was no statistically significant difference in response rates between all three diets, despite the study being adequately powered. Whilst similar efficacy was noted between all three diets, differences were noted in the acceptability of the dietary restriction as well as food related QOL. Individuals on the GFD

and LFD took longer to shop for their diet, the diets were more expensive and eating out was harder with family and friends, in comparison to TDA. In addition, individuals receiving TDA found their diet tasty and enjoyable. As can be seen from this study, whilst the three diets were of equal efficacy, patients may prefer TDA from a quality of life perspective. The challenges of the LFD were also highlighted at long term follow up in Chapter 3, where similar themes were also noted, with the LFD being noted to be more expensive, more difficult to eat out at restaurants and harder to follow the diet whilst overseas in comparison to a habitual diet. The study findings seen in both Chapter 3 and 4 highlight the need to consider the impact of quality of life when evaluating dietary therapies. Despite the differences noted in quality of life, Chapter 4 demonstrated that the majority of individuals would consider continuing all three diets, with no differences between groups. Current guidelines propose the use of TDA, with the LFD being proposed as second line therapy, with the GFD not included in guidelines as a therapy option currently.[5,19] However, the findings in Chapter 4 challenge this notion, with the GFD being shown to be as effective as both TDA and the low FODMAP diet at short term follow up of 4 weeks.

Whilst the GFD was shown to be as effective as TDA and the LFD, this RCT was assessing response over 4 weeks. A previous study in Sheffield demonstrated that 72% of patients with IBS-D who had an initial clinical response planned to continue a GFD at long follow up, with a mean follow up of 18 months, reporting ongoing symptom remission.[92] However, as data is currently limited, further studies are required to assess the efficacy of the GFD at long term follow up, to assess whether findings are sustained.

A recent study in individuals with IBS, as well as healthy subjects, demonstrated symptom improvement in individuals with IBS, particularly in those with antigliadin IgG and IgA antibodies (AGAs).[100,101] The findings suggest that AGA positivity may be potentially used as a biomarker to assess individuals with IBS who may respond to a GFD.[100] However, whilst this may be a potential future biomarker, it is worth noting that the prevalence of AGA positivity was high in the study, reported at 50%,[101] similar to that in individuals with NCGS, with there being a significant overlap between NCGS and IBS.[173] However, in the validation cohort, 21% were noted to be AGA positive,[101] with variable AGA positivity being reported in the literature previously, between 7 to 18%.[102,103] Further studies are required to confirm whether AGAs are a potential biomarker for response to a GFD in IBS. Whilst AGAs may be potential biomarkers to evaluate those who may respond to a GFD, a more pragmatic approach may be to assess if individuals with IBS have symptoms triggered by wheat. Wheat is noted to trigger symptoms in up to 30% of individuals with IBS, [77] and these individuals may potentially respond to a GFD or LFD, as wheat contains both gluten and fructans.

In terms of assessing predictors for response to dietary therapies, the role of stool samples in predicting responsiveness to dietary therapies was explored in Chapter 4. A previous study, using the same method of stool analysis, demonstrated that responders could be discriminated from non-responders on the LFD using faecal bacterial profiles, but not with the TDA diet.[72] These findings were not replicated in Chapter 4, as responders could not be discriminated from non-responders following TDA, LFD and GFD. However, it is worth noting that the sample size for the stool analysis was small, and may have been underpowered, secondary to temporary suspension of stool sample collection during the COVID-19 pandemic. Currently, there is uncertainty with the role of

the microbiome in dietary therapies and IBS. Whilst a reduction in Bifidobacterium has been demonstrated in previous studies with the LFD and GFD,[41,119] it is unclear whether changes seen at short term are sustained at long term follow up. In Chapter 4, alterations in bacterial abundance were noted, but the clinical significance of this was unclear. In addition, assessment of dysbiosis was based upon a Nordic normobiotic reference cohort.[152] The diets consumed by the reference cohort was also unknown, which may have altered the baseline reference cohort range.[72,152] The faecal flora may have an unequal distribution within stool samples, as well as individuals having a unique gut microbiota profile.[105,121,159] This highlights the challenge of assessment of the gut microbiota, with further research in this area required, including the optimal sampling method. Changes in the gut microbiome were assessed, but it is important to note that the virome and mycobiome may play a role in the assessment of dietary therapies. In terms of other predictors, there were no other signals from Chapter 4 that predicted responsiveness to dietary therapies. Further research is required to assess predictors to dietary therapies in IBS, to enable targeted therapies.

In terms of nutritional intake, no significant differences in macronutrient and micronutrient change were noted between all three diets, in Chapter 4. The majority of individuals failed to meet DRVs for total energy intake both pre- and post- intervention following all three diets at short term follow up. Similar to the long term low FODMAP data presented in Chapter 3, from the RCT, it appears that many individuals with IBS may fail to meet nutritional requirements as a result of eating patterns themselves, rather than specific diets. Orthorexia nervosa is now a well-established term, being a disorder associated with the focus on 'healthy eating'.[174] A single-centre prospective study in 233 IBS patients who had commenced a LFD group programme, using the SCOFF eating

disorder questionnaire, demonstrated that 23% (n=54) were at risk of eating disorder behaviour, highlighting this maybe prevalent in IBS.[175] However, like Chapter 3, estimated average requirements for energy were used, rather than individually calculated total energy requirements, and therefore these findings should be interpreted with caution. In addition, further research is required in exploring the prevalence of disordered eating in IBS. It is worth noting at short term follow up, that there were significant changes in specific micronutrients demonstrated, with changes in potassium and iron with the TDA diet, and thiamine and magnesium on both the LFD and GFD. Further research is required to fully explore both macro- and micro – nutrient changes in individuals with IBS, both with and without specific dietary interventions.

Whilst efficacy of the TDA diet, LFD and GFD was demonstrated in Chapter 4, it is possible that these effects may be overestimated. The placebo response has been noted to be as high as 40% in patients with IBS,[176] and this may in part be contributed by patients entering trials when their symptoms of IBS are most severe,[177] with 45% of participants having severe IBS (IBS-SSS >300) in this RCT. In addition, IBS is characterised by a fluctuating course, with a 10-year study demonstrating that less than 40% of individuals originally who met the criteria for IBS, using the Rome III criteria, still met the criteria.[178,179] However, it is worth noting that the low FODMAP diet has shown superior adequate of relief of symptoms compared to a habitual diet.[41] In addition, the LFD has been shown to have a significantly lower reduction in IBS-SSS compared to a sham diet[46], and a high FODMAP diet,[45] as well as lower gastrointestinal symptom scores compared to an Australian diet.[39] Whilst these studies suggest superiority of a LFD compared to conventional diets, and it may be extrapolated that the GFD and TDA are more effective

than conventional diets on the basis of equal efficacy shown in Chapter 4, studies are required to confirm this.

It is worth noting that individuals with IBS-D and IBS-M were recruited in Chapter 4, with patients with IBS-C not recruited. It has been suggested that symptom improvement on a LFD is dependent upon subtype, with the diet has been suggested to be less effective in patients with IBS-C due to the low fibre content of the low FODMAP diet. [49] In the study in Chapter 4, there was a trend towards greater fibre reduction, which may be expected. However, in Chapter 3, it was shown that the response rate to the LFD was independent of subtype, including those with IBS-C. It has also been suggested that FODMAP intake does not alter faecal water, and is not targeted towards specific effects on bowel habit.[39,51] In view of this uncertainty, further studies are required assessing the role of the LFD in individuals with IBS-C. In addition, the majority of studies on a GFD have not focussed on patients with IBS-C either, with further research required.

Study design is therefore key in dietary trials of IBS, but this remains challenging. Whilst there have been a growing number of RCTs in IBS, including the study performed in Chapter 4, study design has been heterogenous.[106] Whilst participants should ideally be blinded to their intervention, this has been increasingly challenging with the increasing awareness of both the LFD and GFD.[24,107] In Chapter 4, participants were aware of the diet they were randomly allocated to, but unaware of the other interventions until completion of the study. Dietary advice was given, rather than the RCT being a feeding study. Whilst dietary intake may have been more strictly controlled and achieved on a feeding study,[95] this may not be representative of 'real-life' intake.[24] It has also been suggested that several different ways may be used to assess dietary therapies, such as comparing against

extremes of intakes, comparing diets against placebo, as well as comparing diets head-to-head, as seen in Chapter 4.[147]

Whilst TDA, LFD and GFD have been explored as dietary therapies for IBS in this thesis, it is feasible that other dietary approaches may also be potential therapeutic options for IBS that need further exploration. A tailored 'bottom-up' approach has been suggested for the LFD, with the reduction of a few specific foods thought to trigger symptoms in patients, dependent upon patient reported symptoms.[33] A study comparing the 'bottom-up' approach such as a fructan free diet, in comparison to other dietary therapies such as the low FODMAP diet, GFD and first TDA may help better understand whether this approach may be effective in IBS. Of note, as mentioned previously, one study did demonstrate that fructans may potentially be the cause for symptoms rather than gluten.[111]

Whilst the focus of this thesis has been on the role of dietary therapies in IBS, it is also important to explore the efficacy of dietary therapies in comparison to other available modalities. It is worth noting that psychological therapies may be an effective management option for IBS, such as cognitive behavioural therapy.[180] It is worth noting that gut-directed hypnotherapy has been shown to be as effective as the LFD, which was sustained at 6 months.[62] In addition, similar symptom improvement has been shown comparing yoga and the low FODMAP diet head-to-head.[61] Little is known on the comparative efficacy of medical treatments to dietary therapies in IBS. Studies comparing traditional medical treatments, such as antispasmodic drugs, peppermint oil and gut-brain neuromodulators (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors) to dietary therapies are required.[181] It has been suggested that less stringent

criteria should be used in the evaluation of dietary therapies, in comparison to medical trials.[110] In pharmaceutical trials, the Food and Drug Administration and European Medicines Agency require symptom benefit over a prolonged time period as well as a good safety profile.[24] It could be argued that dietary therapies should be held to the same level of scrutiny as medical therapies, as they are not without potential risk.[24] However, funding of dietary trials may be more challenging in comparison to medical trials. Larger dietary studies are required in order to increase the strength of evidence for their use, and a cost effective way to deliver larger studies could be through remote delivery such as webinars.[182]

In Chapter 3 and 4, outcomes of dietary therapies were assessed from dietetic-led advice, which is in line with the literature, with the evidence base for these therapies being derived from dietetic-led advice.[24] In view of this, it was important to establish whether there was infrastructure to deliver these therapies in clinical practice. Chapter 5 explored the provision of GI dietetic services in England. The provision of dietetic services varied throughout the country, which was similar to a previous study performed in 2007.[163] A key finding was that a significant proportion of trusts did not deliver specialist clinics for IBS. Currently, it is unclear whether dietitians who delivery specialist clinics to IBS patients leads to a greater clinical response, in comparison to those seen in a general clinic. Studies assessing the impact of grade of dietitian and specialist interest may help better inform this.

In addition, the commonest consultation length for patients with IBS was between 15-30 minutes. This appears to be an inadequate consultation length, as it has been suggested in the literature that between 45 to 60 minutes is required to educate a new patient on

the LFD.[31] However, there are no national guidelines currently in terms of the level of GI dietetic services to deliver these dietary therapies effectively. In addition, this study highlighted similar deficiencies in provision across other GI conditions, with IBD and CD having similar findings.

Another important finding was that individual consultations were the most frequent consultation method, although a significant proportion were seen in group clinics. There has been an increase in interest of delivering dietetic therapies via group clinics, with this been shown to be as effective as one-to-one therapy when evaluated with the LFD in IBS, as well as being potentially more cost-effective.[126] This approach has also been shown to be effective with the GFD in patients with CD.[170] In addition, in Chapter 4, the response rate seen to dietary therapies, where diets were delivered via group clinics, was similar to studies where patients were seen individually.[43,44] This may be a cost-effective approach in delivering these therapies going forward, and help to deliver these therapies where resources are limited. As a result of the COVID-19 pandemic, dietetic delivery of therapies was switched from face-to-face to online remote delivery. Chapter 4 demonstrated no difference in the efficacy of these therapies when delivered either face-to-face or remotely, using the same dietitians and delivery content. This highlights the efficacy of a remote approach, which may be potentially more cost-effective, with research required to analyse this.

To conclude, this thesis has demonstrated the efficacy of dietary therapies in IBS. The long-term efficacy of the LFD has been demonstrated, highlighting that many individuals use the GFD or WFD to manage their symptoms, although the mechanistic reasons are unclear. TDA, GFD and LFD appear to have equal efficacy in IBS at short term follow up,

although TDA may be more preferable to patients. Further research is required to assess the role of the microbiome in IBS. Whilst dietary therapies are effective to manage IBS, there is an inequity of services across England, with a likely need for a shift in delivery methods of dietetic therapies to meet needs.

Declaration of Published Work Used

Ideas from sections of this chapter have been published. The following papers have been used for this chapter;

1. **Rej A**, Aziz I, Tornblom H, Sanders DS, Simren M. The Role of Diet in Irritable Bowel Syndrome: Implications for Dietary Advice. *J Intern Med* 2019; 286(5): 490-502
2. **Rej A**, Aziz I, Sanders DS. Personalising dietary therapies for irritable bowel syndrome – what is gluten's role. *Clin Gastroenterol Hepatol* 2020; doi: 10.1016/j.cgh.2020.10.024
3. **Rej A,** Sanders DS, Buckle RL, Trott N, Aziz I, Shaw CC. What is the optimal FODMAP threshold in IBS? *J Gastroenterol Hepatol* 2021; doi: 10.1111/jgh.15470

Appendices

Appendix 1 GSRS questionnaire

1. Please rate your symptoms during the last week by placing a tick in the box that best describes each symptom
(please tick none if you do not have this symptom)

	No symptoms or very rarely None	Occasional or mild symptoms Mild	Frequent symptoms that affect some social activities Moderate	Continuous symptoms that affect most social activities Severe
Abdominal pain/discomfort	☐	☐	☐	☐
Abdominal bloating/distension	☐	☐	☐	☐
Increased flatulence/wind	☐	☐	☐	☐
Belching or burping	☐	☐	☐	☐
Stomach/abdominal gurgling	☐	☐	☐	☐
Urgency to open bowels	☐	☐	☐	☐
Incomplete evacuation (feeling of inability to pass all stool)	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Heartburn	☐	☐	☐	☐
Acid regurgitation	☐	☐	☐	☐
Tiredness/lethargy	☐	☐	☐	☐

2. Currently, how often do you pass a bowel action? (please tick one box)

Once a week	☐
Once every 4-6 days	☐
Once every 2-3 days	☐
Once a day	☐
2-3 times a day	☐
4-6 times a day	☐
7 or more times a day	☐

3. Do you currently have satisfactory relief of your gut symptoms? (circle one)

Yes No

4. Please tick the box that best describes your current stool:

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Appendix 2 Acceptability of Dietary Restriction Questionnaire

	Agree	Neutral	Disagree
I find it easy to buy suitable foods for my current diet at my normal supermarkets or shops			
I am able to buy foods suitable for my current diet at my normal supermarkets or shops			
I use high street/online speciality shops (eg, health food shops) to buy food for my current diets			
It takes extra time to shop for my current diet			
I find food labelling is adequate to allow me to confidently choose suitable foods			
The cost of my current diet is more expensive			
Does eating out at restaurants make it more difficult for you to follow your current diet?			
Does eating out at friends/families make it more difficult for you to follow your current diet?			
Does travel (overseas/UK) make it more difficult for you to follow your current diet?			
Overall, I find my current diet tasty and enjoyable			
I can incorporate my current diet easily into my life			
My current dietary needs have created stress with my family/friends			

Appendix 3 Food Related QOL Questionnaire

	Agree	Neutral	Disagree
Food and meals are positive elements of my life			
I am generally pleased with my food			
My life in relation to food and meals is close to my ideal			
With regard to food, the conditions of my life are excellent			
Food and meals give me satisfaction in daily life			
I wish my meals were much more pleasant part of my life			
When I think of my next meal, I only see problems, obstacles and disappointments			

Appendix 4 CNAQ Questionnaire

FRUIT – INCLUDE FRESH AND CANNED (exclude dried fruit and juices).

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Apple									
Apricot									
Banana									
Blackberries (1/2 cup)									
Blueberries (1/2 cup)									
Boysenberries (1/2 cup)									
Cantaloupe melon (1 slice)									
Carambola, star fruit									
Cherries (1/2 cup)									
Cranberries (1/2 cup)									
Cumquat									
Currants (1/3 cup)									
Figs (1)									
Grapefruit (1/2)									
Grapes (1/2 cup)									
Guava									
Honeydew melon (1 slice)									
Jackfruit (1/2 cup)									
Kiwifruit									
Lemon juice (1 tablespoon)									
Lime juice (1 tablespoon)									
Longan (3)									
Lychee (3)									
Mandarin/Satsuma/tangerine / clementine									
Mango (1/2)									
Nashi pear									
Nectarine									
Orange									
Passionfruit									

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Paw paw (1 slice)									
Peach									
Pear									
Persimmon/Sharon fruit									
Pineapple (1 slice)									
Plum									
Pomegranate (1/2)									
Quince									
Raspberries (1/2 cup)									
Rhubarb (1/2 cup)									
Strawberries (1/2 cup)									
Tamarillo									
Tangelo									
Watermelon (1 slice)									

DRIED FRUIT

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Apple (6 pieces)									
Apricots (8 halves)									
Banana (1/2 whole or 6 chips)									
Currants (1 tb)									
Cranberry (1 tb)									
Dates (4 medium)									
Figs (2 medium)									
Mango (3 pieces)									
Paw paw (3 pieces)									
Pear (6 pieces)									
Pineapple (2 pieces)									
Prunes (4 pieces)									
Raisins (3 tablespoons)									
Sultanas (3 tablespoons)									

VEGETABLES

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Alfalfa (1/2 cup)									
Artichoke, canned/jarred (1 heart)									
Artichoke, globe (1 heart)									
Artichoke, Jerusalem (1)									
Asparagus (4 spears)									
Avocado (1/2)									
Bamboo shoots (1/2 cup)									
Bean sprouts (1/2 cup)									
Beans, green (1/2 cup)									
Beetroot (2 slices or 1 small)									
Bok Choy (1/2 cup)									
Broccoli (1/2 cup)									
Brussels sprouts (3)									
Cabbage (1/2 cup)									
Capsicum (1/4 whole)									
Carrot (1/2 cup)									
Cauliflower (1/2 cup)									
Celeriac (1/2 cup)									
Celery (1/2 cup)									
Chicory (1/2 cup)									
Chilli (1/4 fresh chilli)									
Chives (1 tablespoon)									
Choko (1/2 cup)									
Cucumber (6 slices)									
Eggplant/Aubergine (1/4 whole)									
Endive (1/2 cup)									
Fennel (1/4 cup)									
Garlic (1 clove)									
Horseradish (1 tablespoon)									
Kohlrabi (1/2 cup)									

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Leek (1/4 cup)									
Lettuce, all types (1/2 cup)									
Marrow (1/2 cup)									
Mushrooms (1/2 cup)									
Okra (2)									
Olives (4)									
Onion, brown/white (1/4 cup)									
Onion, Spring – long white stem with green leaves (1/4 cup)									
Onion, Spanish (1/4 cup)									
Onion, Shallot – small brown onion (1)									
Parsnip (1/2 cup)									
Peas (1/2 cup)									
Potato (1 medium)									
Potato, fries (1/2 cup)									
Potato, mashed (1/2 cup)									
Pumpkin, butternut (1/2 cup)									
Pumpkin, all others (1/2 cup)									
Radicchio lettuce (1/2 cup)									
Radish (1)									
Rocket (1/2 cup)									
Silverbeet (1/2 cup)									
Snow peas/Mangetout (1/2 cup)									
Spinach (1/2 cup)									
Squash (1/2 cup)									
Sugar snap peas (1/2 cup)									
Swede (1/2 cup)									
Sweet corn (1 cob or ½ cup kernels)									
Sweet potato (1/2 cup)									

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Taro (1/2 cup)									
Tomato (1 medium)									
Tomato, sundried (6 pieces)									
Tomato, canned/puree (1/2 cup)									
Turnip (1/2 cup)									
Waterchestnut (1/2 cup)									
Watercress (1/2 cup)									
Witlof (1/2 cup)									
Zucchini/Courgette (1/2 cup)									

LEGUMES - Serving size is ½ cup cooked

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Baked beans									
Borlotti beans									
Broad beans									
Butter beans									
Cannellini beans									
Chickpeas									
Haricot beans									
Kidney beans									
Lentils									
Lima beans									
Soya beans									
Split peas									
Canned bean mix									

EGG, MEAT, FISH AND EQUIVALENTS

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Eggs (1)									
Beef/lamb/pork/veal FAT-TRIMMED e.g.steak/chop/cutlet (100g = 1 chop)									
Beef/lamb/pork/veal INCLUDING FAT e.g. steak/chop/cutlet (100g)									
Minced meat, e.g. in hamburger, lasagne (100g)									
Chicken/turkey NO skin e.g. breast, leg, thigh (100g = 1 thigh)									
Chicken/turkey WITH skin e.g. breast, leg, thigh (100g = 1 thigh)									
Bacon (2 slices)									
Deli meats: Lean meats, e.g. ham, chicken/turkey breast (2 slices)									
Deli meats high fat, e.g. luncheon meat, chicken loaf, salami (2 slices)									
Processed meat products, e.g. hot dog (1), chicken nuggets (6)									
Offal, e.g. liver, kidney (100g)									
Tofu (50g)									
Canned fish (90g small tin)									
Fresh white fish (100g = small fillet)									
Salmon/tuna (100g = small fillet)									
Shellfish e.g. mussels, oysters, prawns (6 large pieces)									

DAIRY

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Skim or low fat milk (250ml)									
Full cream milk (250ml)									
Ice cream (1/2 cup)									
Custard (1/2 cup)									
Yoghurt full cream (small tub)									
Yoghurt low fat (small tub)									
Cream (1 tablespoon)									
Sour cream (1 tablespoon)									
Evaporated milk, Regular fat (1/2 cup)									
Low fat Evaporated milk (1/2 cup)									
Condensed milk (1/2 cup)									
Cream cheese, Regular fat (1 tablespoon)									
Low fat Cream cheese, (1 Tbs)									
Hard cheese e.g. cheddar, parmesan (30g slice)									
Low fat hard cheese, e.g. reduced fat cheddar (30g slice)									
	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Cheese, Aged, e.g. brie, camembert 30g slice									
Cottage/Ricotta cheese (1 tablespoon)									
Rice milk (250 ml)									
Soy milk (250ml)									

Milk, cow, lactose free (250ml)									
Yoghurt, reduced fat, reduced lactose (200g tub)									
Yoghurt, soy, vanilla, low fat (small tub)									
Sorbet/Gelati (1/2 cup)									

BREAKFAST CEREALS

		Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
All bran (1/2 cup)										
Cooked cereal, e.g. porridge (1 cup										
Muesli (1/3 cup)	Fruit									
	Fruit + Nut									
	Nut + grains									
	Wheat free									
Mixed cereal with fruit and grains (1 cup)	Wheat based									
	Wheat free									
Plain wheat-based cereal, e.g. Weet- bix, mini wheats, Branflakes (1 cup)										
Plain corn/rice cereal, e.g. cornflakes, rice bubbles/krispies (1 cup)										
Cereal snack bar (1 bar)										

BREADS

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Multigrain (1 slice, ½ roll)									
White (1 slice, ½ roll)									
Wholemeal (1 slice, ½ roll)									
High fibre white (1 slice)									
Sourdough bread (1 slice, ½ roll)									
Bread, flat (1 whole)									
Bread, pita (1 whole)									
Roti/Naan (1 slice)									
Turkish bread (1 slice)									
Crumpet, bagel, English muffin (1 whole)									
Spelt bread (1 slice)									
Raisin/fruit bread (1 slice)									
Rye bread, light rye (1 slice, ½ roll)									
Rye bread, dark rye (1 slice, ½ roll)									
Pumpernickel (1 slice)									
Bread, oat (1 slice)									
Gluten-free bread (1 slice)									
Gluten free bread, fruit loaf (1 slice)									
Corn tortillas (1 piece)									

CARBOHYDRATE FOODS - Serving size is 1 cup, cooked

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Wheat pasta									
Gluten-free pasta									
Wheat noodles – Hokkein, Udon, Two Minute, Super noodles									
Noodles – rice									
Rice, white									
Rice, basmati/doongara									
Rice, brown									
Barley									
Burghul/Bulgar, e.g.in Tabouli									
Cous cous									
Gnocchi									
Polenta									
Sago									
Semolina									
Buckwheat									
Millet									
Sorghum									
Quinoa									
Amaranth									
Sugars and Spreads	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Sugar (1 teaspoon)									
Artificial sweeteners, e.g. Nutrasweet, Equal, Splenda, Silverspoon (1 teaspoon)									
Syrup, e.g. Golden, Maple, Treacle (1 tablespoon)									
Honey (1 tablespoon)									
Jam (1 tablespoon)									
Peanut butter (1 tablespoon)									
Vegemite/Marmite/Aussie Mite etc (1 tablespoon)									

FATS AND OILS

Include use as a spread and in cooking:

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Butter (1 tsp)									
Butter, salt reduced (1tsp)									
Margarine (1 tsp)									
Margarine, fat reduced (1 tsp)									
Margarine, milk free (1 tsp)									
Oil, Vegetable/ Sunflower (1 tbls)									
Oil, Olive/canola (1 tbsp)									
Oil, Peanut, Sesame (1 tbsp)									
Lard (1 tbsp)									

CONDIMENTS AND SAUCES

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Mayonnaise, regular (1 Tbsp)									
Mayonnaise, low fat (1 Tbsp)									
Salad Dressing (1 Tbs)									
Salad dressing, low fat (1 Tbs)									
Mustard (1 Tbsp)									
Chutney, pickles, relishes (1 tablespoon)									
Tomato sauce (1 tablespoon)									
Tomato paste (1 tablespoon)									
Barbecue sauce (1 tbsp)									
Plum sauce (1 tablespoon)									
Soy sauce (1 tablespoon)									
Oyster sauce (1 tablespoon)									
Coconut cream (1/2 cup)									
Coconut milk, canned (1/2 cup)									
Pasta sauce, ready made e.g. Dolmio (1/2 cup)									
Stir fry sauce, ready made, e.g. Sweet & Sour, Blackbean (1/2 cup)									

DRINKS

		Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Fruit juice, orange, pineapple (200ml)										
Fruit juice, apple/tropical/mix (200ml)										
Vegetable juice (200ml)										
Soft drink/fizzy (1 can, 375ml)										
Diet/Sugar free soft drink/Fizzy (1 can, 375ml)										
Cordial/Squash (1 cup, 250ml)										
Diet/Sugar free cordial/Squash (1 cup, 250ml)										
Flavoured milk drinks (1 small carton 300ml)										
Flavoured milk drinks, low fat (1 small carton, 300ml)										
Dandelion Tea										
Ecco/Caro coffee substitute drinks										
Beer, regular (1 pot or ½ pint)										
Beer, light (1 pot or ½ pint)										
Wine (120ml glass)	Dry white									
	Sweet white									
	Sparkling									
	Red									
	Dessert wine/Sticky									
Spirit (30ml)										

MISCELLANEOUS

	Never or <1/month	1-3/ month	1/ week	2-4/ week	5-6/ week	1/ day	2-3/ day	4-5/ day	6+/ day
Wheat crackers, e.g. salada, vita wheat, Carrs (1 cracker)									
Rye Crispbreads, e.g. ryvita (1 crispbread)									
Rice crackers, plain (5)									
Rice crackers, flavoured (5)									
Rice cakes or corn cakes (2)									
Pretzels (5)									
Plain sweet biscuit (1)									
Chocolate biscuit (1)									
Fruit biscuit (1)									
Gluten-free cake (1 slice)									
Gluten-free sweet biscuit (1)									
Plain Cake/muffin, (1 piece)									
Fruit cake (1 piece)									
Muesli bar (1)									
Dried fruit bar (1)									
Chocolate (50g bar)									
Lollies/Sweets (1 handful)									
Chewing gum, reg sugar (1)									
Chewing gum, sugar free (1)									
Nuts (1 handful)									
Potato crisps (1 small packet)									
Sweet pastry, e.g. apple pie, custard tart, croissant (1 serve)									
Savoury pastries, e.g. pie, sausage roll (1)									
Pizza (1 slice)									
Rice paper roll (1)									
Sushi (1 hand roll)									
Other take away meals, e.g. Burger, fries (1 average serve)									

Appendix 5 IBS-SSS Questionnaire

IBS SEVERITY SCORE

Office use only

1. a) Do you currently suffer from abdominal (tummy) pain? YES NO

Circle appropriate box

b) If yes, how severe is your abdominal (tummy) pain?

c) Please enter the number of days that you get pain in every 10 days. *For example if you enter 4 it means you get pain 4 out of 10 days. If you get pain everyday enter 10.*

Number of days with pain ☐ x10

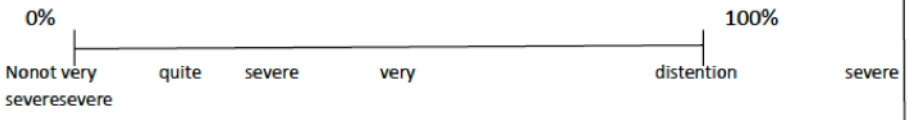
2 a) Do you currently suffer from abdominal distention?* YES NO

(bloating, swollen or tight tummy)

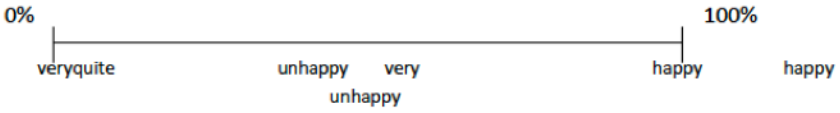
Circle appropriate box

*(*women, please ignore distention related to your periods)*

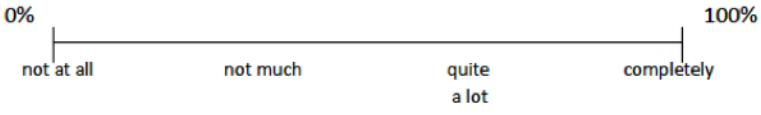
b) If yes, how severe is your abdominal distention/tightness?



3. How satisfied are you with your bowel habit?



4. Please indicate with a cross on the line below how much your irritable bowel syndrome is affecting or interfering with your life in general



IBS Severity Score ☐

Appendix 6 HADS Questionnaire

(HADS): This questionnaire tells us how you are feeling. Read every sentence. Place a circle around the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time (occasionally)	1
	Not at all	0
D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	**I can enjoy a good book or radio/TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Appendix 7 PHQ 12 Somatisation Questionnaire

Part 4: PHQ12 somatisation questionnaire week 0

In the past 4 weeks how much have you been bothered by the following problems?

1. **Back pain**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

2. **Arm/leg/Joint (knee, hip etc) pain**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

3. **Headaches**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

4. **Chest pain**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

5. **Dizziness**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

6. **Fainting spells**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

7. **Palpitations (Feeling of the heart thumping or racing)**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

8. **Breathlessness**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

9. **Insomnia (difficulty sleeping)**

   Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

10. **Lethargy (tiredness)**

    Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

11. **Period pain (only answer if this question applies to you)**

    Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

12. **Pain during sexual intercourse (only answer question applies to you)**

    Not bothered at all ☐, Bothered a little ☐, Bothered a lot ☐

Appendix 8 IBS-QOL Questionnaire

Please think about your life over the **past month (30 days),** and look at the statements below. Each statement has five possible responses. For each statement, please circle the response that best describes your feelings..

Q1. I feel helpless because of my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q2. I am embarrassed by the smell caused by my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q3. I am bothered by how much time I spend on the toilet. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q4. I feel vulnerable to other illnesses because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q5. I feel fat because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q6. I feel like I'm losing control of my life because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q7. I feel my life is less enjoyable because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q8. I feel uncomfortable when I talk about my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q9. I feel depressed about my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q10. I feel isolated from others because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q11. I have to watch the amount of food I eat because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q12. Because of my bowel problems, sexual activity is difficult for me. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q13. I feel angry that I have bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q14. I feel like I irritate others because of my bowel problems . *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q15. I worry that my bowel problems will get worse. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q16. I feel irritable because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q17. I worry that people think I exaggerate my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q18. I feel I get less done because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q19. I have to avoid stressful situations because of my bowel problems. *(Please circle one number*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q20. My bowel problems reduce my sexual desire. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q21. My bowel problems limit what I can wear. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q22. I have to avoid strenuous activity because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q23. I have to watch the kind of food I eat because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q24. Because of my bowel problems, I have difficulty being around people I do not know well. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q25. I feel sluggish because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q26. I feel unclean because of my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q27. Long trips are difficult for me because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q28. I feel frustrated that I cannot eat when I want because of my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q29. It is important to be near a toilet because of my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Q30. My life revolves around my bowel problems. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q31. I worry about losing control of my bowels. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q32. I fear that I won't be able to have a bowel movement. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q33. My bowel problems are affecting my closest relationships. *(Please circle one number)*

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 A GREAT DEAL

Q34. I feel that no one understands my bowel problems. (*Please circle one number*)

1 NOT AT ALL
2 SLIGHTLY
3 MODERATELY
4 QUITE A BIT
5 EXTREMELY

Publications During Research Period

Related to Thesis

Medline Publications:

1. **Rej A**, Avery A, Ford AC, Holdoway A, Kurien M, McKenzie Y, Thompson J, Trott N. Whelan K, Williams M, Sanders DS. Clinical Application of Dietary Therapies in Irritable Bowel Syndrome. *J Gastrointestin Liver Dis* 2018; 27(3): 307-16
2. **Rej A**, Aziz I, Sanders DS. Breaking bread! *Proc Nutr Soc* 2018; Oct 16: 1-8
3. **Rej A**, Sanders DS. Gluten-Free Diet and Its 'Cousins' in Irritable Bowel Syndrome. *Nutrients* 2018; 10: 1727
4. **Rej A**, Trott N, Sanders DS, Aziz I. Letter: the low FODMAP diet is not the only diet for IBS. *Aliment Pharmacol Ther* 2019; 49(8); 1108-1109
5. **Rej A**, Trott N, Aziz I, Sanders DS. A Gluten Free Diet: The Express Route to Fructan Reduction. *Am J Gastroenterol* 2019; 114(9): 1553
6. **Rej A**, Aziz I, Tornblom H, Sanders DS, Simren M. The Role of Diet in Irritable Bowel Syndrome: Implications for Dietary Advice. *J Intern Med* 2019; 286(5): 490-502
7. **Rej A,** Buckle RL, Shaw CC, Trott N, Aziz I, Sanders DS. Letter: the gluten-free diet as a bottom-up approach for irritable bowel syndrome. *Aliment Pharmacol Ther* 2020; 51(1):184-185
8. Shaw CC, Buckle RL, **Rej A**, Trott N, Aziz I, Sanders DS . A Gluten Reduction Is the Patients' Choice for a Dietary 'Bottom Up' Approach in IBS. *Nutrients*. 2020; 12(1): 137
9. **Rej A**, Buckle RL, Shaw CC, Trott N, Aziz I, Sanders DS. Is CBT the dominant non-drug IBS treatment? The rise of dietary therapies. *Gut* 2021; 70(2):432-433

10. **Rej A**, Shaw CC, Buckle RL, Trott N, Agrawal A, Mosey K, Sanders K, Allen R, Martin S, Newton A. Robinson K, Elphick D, Chey WD, Aziz I, Sanders DS. The low FODMAP diet for IBS; A multicentre UK study assessing long term follow up. *Dig Liver Dis* 2021; May 31;S1590-8658(21)00247-4
11. **Rej A**, Tai FWD, Green PHR, Lebwohl B, Sanders DS. The Growing Global Interest in the Gluten Free Diet as Reflected by Google Searches. *Dig Liver Dis* 2020; 52(9): 1061-1062
12. **Rej A**, Aziz A, Sanders DS. Personalising dietary therapies for irritable bowel syndrome – what is gluten's role. *Clin Gastroenterol Hepatol* 2020; doi: 10.1016/j.cgh.2020.10.024
13. **Rej A,** Sanders DS, Buckle RL, Trott N, Aziz I, Shaw CC. What is the optimal FODMAP threshold in IBS? *J Gastroenterol Hepatol* 2021; 36(6):1723-1725
14. **Rej A**, Shaw CC, Buckle RL, Trott N, Agrawal A, Mosey K, Sanders K, Allen R, Martin S, Newton A. Robinson K, Elphick D, Chey WD, Aziz I, Sanders DS. The low FODMAP diet for IBS; A multicentre UK study assessing long term follow up. *Dig Liver Dis* 2021; May 31;S1590-8658(21)00247-4

Non-Medline Publications:

15. **Rej A**, Trott N, Sanders DS. Self-Reported Wheat Sensitivity and Chronic Gastrointestinal Symptoms: Recent advances in understanding. *Clinical Nutrition*; 11(1): 13-15

Unrelated to Thesis

Medline Publications:

16. **Rej A**, Menic N, Nyamali I *et al*. Open access publishing in gastroenterology: good for the researcher and good for the public! *Front Gastroenterol* 2019; 11(2):170-171
17. **Rej A**, Sanders DS. The overlap of Irritable Bowel Syndrome and noncoeliac gluten sensitivity. *Curr Opin Gastroenterol* 2019; 35(3):199-205
18. Croall ID, Trott N, **Rej A**, Aziz I, O'Brien DJ, George HA, Hossain MY, Marks LJS, Richardson JI, Rigby R, Hadjivassiliou M, Hoggard N, Sanders DS . A Population Survey of Dietary Attitudes towards Gluten. *Nutrients* 2019; 11(6): 1276
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27. Coleman SH, **Rej A**, Baggus EMR, Lau MS, Marks LJ, Hadjivassiliou M, Cross SS, Leffler DA, Elli L, Sanders DS. What is the Optimal Method Assessing for Persisting Villous Atrophy in Adult Coeliac Disease? *J Gastrointestin Liver Dis* 2021; doi: 10.15403/jgld-3370

Medline Publications (accepted for publication):

28. Trott N, **Rej A**, Coleman S, Sanders DS. The Role of a Low FODMAP Diet in Patients with Celiac Disease, IBS Symptoms and a Histologically Normal Duodenal Remission Biopsy – *accepted for publication in Gastroenterology and Hepatology From Bed to Bench Journal*

Book Chapters:

1. **Rej A**, Sanders DS. Chapter: Weight Loss. For publication in Yamada's Textbook of Gastroenterology
2. **Rej A**, Sanders DS. Chapter: Irritable Bowel Syndrome. For publication in Coeliac

Disease and Gluten-Related Disorders

3. **Rej A**, Sanders DS. Chapter: Pathomechanism of Gluten Related Disorders. For publication in Gluten Related Disorders: Diagnostic approaches, Treatment Pathways and Future Perspectives
4. **Rej A**, Chew J, Sanders DS. Chapter: Gastroenterology. For publication in Davidson's Principles and Practice of Medicine 24th edition

Presentations at Regional/National Conferences Relevant to Thesis

Chapter 3

- **British Society of Gastroenterology National Conference 2020**; Is the low FODMAP diet effective in the long term? The largest multicentre prospective study

This was a 10-minute oral presentation which was presented virtually at this national conference in January 2021

Chapter 4

- **United European Gastroenterology Week Conference 2021**; Dietary Therapies in Irritable Bowel Syndrome: A Multicentre Randomised Control Trial.

This will be a 10-minute oral virtual presentation at this international conference – it is due to be presented in October 2021

- **5th National Patient Reported Outcome Measures Research Conference 2021**; Dietary Therapies in Irritable Bowel Syndrome: A Multicentre Randomised Control Trial.

This was a poster presentation which was presented virtually at this national conference in June 2021

- **Yorkshire and Humber Academic Presentation Day 2021**; Dietary Therapies in Irritable Bowel Syndrome: A Multicentre Randomised Control Trial.

This was a poster presentation which was presented virtually at this regional conference in June 2021

- **Bardhan Fellowship 2021**; Dietary Therapies in Irritable Bowel Syndrome: A Multicentre Randomised Control Trial.

This was a 10-minute oral presentation at this regional conference in March 2021– this presentation was the winning presentation, with £500 awarded

Chapter 5

- **British Society of Gastroenterology National Conference 2020**; National survey evaluating the provision of gastroenterology dietetic services in England

This was a poster presentation which was presented virtually at this national conference in January 2021

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