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Irritable bowel syndrome and diet: where are we in 2018?

Eirini Dimidi, Megan Rossi, Kevin Whelan

King's College London, Diabetes and Nutritional Sciences Division, London, United Kingdom

Corresponding author:

Professor Kevin Whelan

King's College London

Franklin Wilkins Building

150 Stamford Street, London

United Kingdom

SE1 9NH

kevin.whelan@kcl.ac.uk

tel: +44 (0)20 7848 3858.

ABSTRACT

Purpose of review: The aim is to review the most recent advances in the evidence supporting the use of various dietary interventions for the management of IBS.

Recent findings: There is insufficient evidence of the effect of fibres other than psyllium in IBS, while the recent studies on prebiotics suggest a limited effect in IBS. Recent probiotic trials continue to provide varying results, with some probiotic strains exhibiting beneficial effects, whereas others show no effect. Recent trials have also confirmed the clinical effectiveness of a diet low in fermentable carbohydrates (i.e. low FODMAP diet) in IBS. Although gluten sensitivity has also been recently investigated, its presence cannot be confirmed yet due to the presence of other potential contributing compounds in wheat. Studies also suggest a potential beneficial effect of peppermint oil, which warrants further research.

Summary: It is clear that a low FODMAP diet has a beneficial effect in a majority of patients with IBS. Probiotics also have great potential in the management of IBS, however, it is still unclear which strains and doses are the most beneficial. Further research is needed on the effect of different fibres, or combinations of fibres, in IBS.

Keywords (3-5):

Irritable bowel syndrome, fodmaps, probiotics, prebiotics, gluten

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder with a high prevalence and high patient burden. The definition of IBS has recently been updated in the Rome IV diagnostic criteria as recurrent abdominal pain associated with two or more of: (i) related to defaecation; (ii) associated with a change in frequency of stool; or (iii) associated with a change in form (appearance) of stool [1]. The updated Rome IV diagnostic criteria included four major changes. Firstly it disposed of the term 'discomfort' due to ambiguity and variations in perception; secondly it increased the threshold for frequency of abdominal pain to at least 1 day per week (up from 3 days per month); thirdly 'related to defecation' was used instead of 'improvement with defecation' as many do not experience relief on defecation; and fourthly that the onset of abdominal pain no longer needs to coincide with change in stool frequency or form [1]. In a survey of 5931 people in the United States, Canada and the United Kingdom, these updated criteria resulted in a lowering in prevalence of IBS to 5.7% [2].

Over the past five decades the number of research studies investigating the dietary management of IBS has increased dramatically, and the focus, size and complexity of interventions has also varied. Initially, much research investigated dietary fibre in the management of IBS with at least 14 randomised controlled trials (RCTs) [3]. However since the 1990's probiotics have been increasingly investigated (at least 36 RCTs) [4] and more latterly, the low FODMAP diet (at least 10 RCTs) [5] (Figure 1). The aim is to review the most recent advances in the evidence supporting the use of various dietary interventions for the management of IBS.

FIBRE AND PREBIOTICS

The beneficial effect of psyllium fibre in IBS was described in a meta-analysis, reporting significant improvement IBS symptoms, with a number needed to treat of 7 and with no associated adverse events [3]. More recently, a RCT of 103 children with IBS demonstrated that psyllium resulted in a greater reduction in pain frequency compared to placebo, although it did not significantly reduce

absolute pain frequency or pain severity [6]. However, trials of other fibre types (e.g. bran) have failed to demonstrate consistent effectiveness, with wide variation in effects [3]. This may reflect differential effects in different IBS subtypes, for example, a systematic review of seven RCTs demonstrated that various fibres increased stool frequency and softened stool consistency in constipation [7]. Therefore, research is needed to determine whether other fibres, or combinations of fibres, may be efficacious and which IBS subtype may benefit from such intervention(s).

Prebiotics have recently been redefined as 'substrate that is selectively utilized by host microorganisms conferring a health benefit" [8]. Three recently published studies have investigated the effect of prebiotics in IBS. Firstly, IBS-D patients were randomised to receive either a film-forming reticulated protein with a prebiotic mixture of oligo- and polysaccharides or placebo [9]. At the end of this study, the percentages of patients with abdominal pain and flatulence were significantly lower in the active group than in the placebo group [9]. Similarly, in a second double-blind study in 108 IBS patients, partially hydrolysed guar gum led to a significant improvement in bloating compared with placebo, however no other gut symptoms or stool output measures were improved [10]. Finally, another RCT assessed the effect of 5 g/d short-chain fructo-oligosaccharides (FOS) compared to placebo in 79 IBS patients with rectal hypersensitivity [11]. Although the prebiotic group experienced a significant reduction in anxiety scores compared to placebo, no differences were found for rectal discomfort, IBS symptoms, quality of life or gut microbiota composition between the two groups [11], suggesting that this dose of FOS is not effective for the management of IBS.

To conclude, there is insufficient evidence of the effect of fibres other than psyllium in IBS, primarily due to lack of robust research studies [3], while the recent studies on prebiotics suggest a limited effect in IBS. Indeed, there is controversy regarding the therapeutic potential of prebiotics in IBS. Although prebiotics may partially correct dysbiosis in IBS, there is a growing body of evidence suggesting that at high doses some prebiotic oligosaccharides (e.g. oligofructose, inulin) may worsen

IBS symptoms due to their rapid fermentation and colonic gas generation; and is discussed in detail later in this review.

PROBIOTICS

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host. There has been continued interest in the effect of probiotics in IBS, indeed nine different systematic reviews of probiotics in IBS have been identified , including trials dating back to 1989 [4] (Figure 1). Evidence from those trials indicated that certain species (e.g. *Bifidobacterium*) are more effective on persistence of symptoms or abdominal pain than others (e.g. *Escherichia*). More recently, over 10 studies have been published in this area, including *ex vivo*, animal and human studies.

For example, two recent meta-analyses have investigated the effect of specific probiotic species or strains; the first one examined the efficacy of *B. infantis*, provided either as part of a multispecies probiotic supplement or as single strain *B. infantis 35624* in IBS patients [12]. It was found that multispecies probiotics containing *B. infantis* strains significantly reduced abdominal pain (SMD 0.22; 95% CI, 0.03–0.41) and bloating (SMD 0.30; 95% CI 0.04–0.56), whereas single strain *B. infantis* 35624 did not impact IBS symptoms [12]. Another meta-analysis that included two RCTs on the effect of *Saccharomyces cerevisiae* CNCM I-3856 in 579 IBS patients showed significant improvements in abdominal pain (OR 1.5; 95% CI 1.1-2.2) and stool consistency in the probiotic group compared to placebo; improvements in abdominal pain and stool consistency were also observed in the constipation-predominant IBS subgroup population. However, no sub-analyses for the other IBS subgroups (e.g. diarrhoea-predominant) were performed [13].

As shown in Table 1, three recent RCTs have investigated the effect of other probiotic species and strains in IBS showing conflicting results [14-16]. One RCT showed that *Bifidobacterium longum* NCC3001 improved quality of life, but not symptoms, in IBS and also reduced depression scores, which were associated with changes in brain activation patterns indicative of reduced limbic reactivity [16].

Therefore, taken together, the current evidence suggest a potential beneficial effect of specific probiotic strains in certain IBS symptoms. However, the majority of the studies have considerable limitations, such as the lack of intention-to-treat analyses and the absence of validated assessment tools, and as a result caution is needed with the interpretation of such studies.

THE LOW FODMAP DIET

The low FODMAP diet involves the restriction of short-chain fermentable carbohydrates, including oligosaccharides (inulin-type fructans, galacto-oligosaccharides), disaccharides (lactose), monosaccharides (fructose in excess of glucose) and polyols. The increasing interest in the low FODMAP diet over the past decade has been accompanied by an increase in the number and size of randomised controlled trials and randomised comparative trials of this dietary intervention (Figure 1). Although at least 10 trials have now been published [5], the current review focusses on only the most recent advances in the understanding of the clinical effectiveness of the low FODMAP diet and the mechanisms by which FODMAPs induce symptoms.

Clinical effectiveness of the low FODMAP diet

Although nutrient intervention trials are generally easy to control, designing an appropriate placebo control in a whole diet trial is challenging. Solutions include feeding studies, which can be tightly controlled but lack external validity to the clinical setting or sham dietary advice [17]. The first placebo-controlled RCT of low FODMAP dietary advice was recently published comparing outcomes to sham dietary advice. This was delivered together with or without a probiotic in a 2x2 factorial design trial in 104 IBS patients [18]. Adequate symptom relief was reported in 57% of patients in the low FODMAP group compared with 38% in the sham diet group (P=0.051), with an odds of symptom relief of 2.18 (P=0.052), while the low FODMAP diet led to significant reductions in abdominal pain, bloating, flatulence and urgency, and improvements in some components of quality of life [18]. The low FODMAP diet reduced stool Bifidobacterium species, though these were increased in those taking the

probiotic suggesting that probiotic co-administration may negate the impact on these species during the low FODMAP diet [18].

Two further studies have recently been published comparing the effect of a low FODMAP diet to either a high FODMAP diet [19] or a low FODMAP diet plus FOS [20]. First, a single-blind RCT showed that the proportion of responders to the diet was significantly higher in the low FODMAP group (72%) compared to the high FODMAP group (21%, $p<0.009$) [19]. However, this study did not include an intention-to-treat analysis and the use of a high FODMAP diet as a comparator group may actually exacerbate symptoms, therefore inflating the effect size of the low FODMAP diet. The second study compared the effectiveness of a low FODMAP diet plus placebo to a low FODMAP diet plus FOS (i.e. a 'normal FODMAP diet') in a re-supplementation trial [20]. Significantly more patients reported symptom relief in the low FODMAP group (80%) compared to the low FODMAP plus FOS group (30%; $p=0.013$), and nausea, vomiting and flatulence were significantly lower [20].

Another approach to overcoming control groups in dietary intervention trials is to compare to standard treatments. In 2016, a RCT compared the effectiveness of 4 week low FODMAP diet to a standard dietary intervention based on the NICE guidelines in patients with diarrhoea-predominant IBS (IBS-D) [21]. No difference was found in the percentage of patients with adequate relief of symptoms between those in the low FODMAP (52%) and the NICE guidelines groups (41%, $p=0.31$), although there were significantly more abdominal pain responders in the low FODMAP group (51%) compared to the NICE guideline group (23%, $p=0.008$) [21]. Another three-arm RCT compared the clinical effectiveness of a 6 week low FODMAP diet *vs* gut-directed hypnotherapy *vs* a combination of the low FODMAP diet and hypnotherapy in 74 IBS patients, and found high numbers of responders but no differences among the groups [22].

Therefore, the low FODMAP diet has been shown to be effective compared to control and as effective as some other interventions in IBS. However, caution should be exercised in ensuring the restriction phase of the low FODMAP diet is not continued for long periods and that FODMAPs are reintroduced

into the diet to tolerance, in order to mitigate impacts on nutrient intake and gut microbiome. There are as yet no RCT investigating FODMAP reintroduction nor the long term effectiveness of the low FODMAP diet, however in a recent uncontrolled study of 103 patients, 57% reported adequate symptom relief 6-18 months after starting FODMAP reintroduction [23].

Mechanisms of action

Few recent studies have attempted to elucidate the mechanisms by which fermentable carbohydrates may trigger IBS symptoms. A UK study included 29 IBS patients and 29 healthy controls and provided, on 3 separate occasions, 40 g of either glucose, fructose or inulin in a random order, followed by magnetic resonance imaging [24]. Fructose increased small-bowel water content, while inulin increased colonic volume and gas in both patients and controls, but only patients experienced gut symptoms. Importantly, this highlights similar physiological responses to fermentable carbohydrates in health and in IBS, implicating elevated visceral hypersensitivity to gas production in the pathogenesis of IBS symptoms, rather than excess gas production *per se* [24].

Beyond reducing small intestinal water and colonic gas, numerous preliminary observations from clinical trials indicate additional potential mechanisms of action of the low FODMAP diet. In two of the previously described RCTs, the low FODMAP diet resulted in an eight-fold reduction in urinary histamine [19], and decreased proinflammatory interleukin (IL) 6 and IL-8, suggesting modulation of immune activation by the low FODMAP diet [20].

Alongside an improvement in gut symptoms on the low FODMAP diet, it also exerts a profound impact on the gut microbiota. Recent studies have confirmed previous findings that a diet low in FODMAPs leads to low concentrations of *Bifidobacteria* and higher concentrations of *Roseburia* and *Ruminococcus* [19, 20, 25]. However, the link between such changes in the luminal microenvironment and changes in gut symptoms is still unclear.

The low FODMAP diet is a complex, costly and burdensome diet and therefore predicting responses to the diet would be significant advance in the field. A study of 584 patients with functional bowel disorders showed that chronic diarrhoea and peak breath methane concentrations to a fructose challenge positively predicted symptom relief following the low FODMAP diet in those with fructose intolerance (OR 2.62, *p*=0.007; OR 1.53, *p*=0.042), while chronic nausea negatively predicted symptom relief (OR 0.33, *p*=0.002) [26]. Furthermore, a Swedish study revealed that gut bacterial profiles of IBS patients responding to a low FODMAP diet differed from non-responders at baseline [25]. In particular, bacterial abundance was higher in non-responders compared with responders before and after intervention, while non-responders had higher 'dysbiosis index' scores than responders at baseline. More research is needed until this can be used to select which patients are most likely to respond to the low FODMAP diet in clinical practice.

GLUTEN-FREE DIET

There is a clear and well documented association between gastrointestinal symptoms in IBS and dietary gluten, including wheat, barley and rye [27], driving interest in a gluten-free diet (GFD) for the management of IBS. Recently there have been two randomised double-blind placebo-controlled gluten re-challenge studies in IBS patients with suspected non-coeliac gluten/wheat sensitivity. In both studies participants followed a GFD for three [28] or four weeks [29], resulting in symptom response (defined using different gastrointestinal symptom questionnaires) in 55/77 (71%) [28] and 65/164 (40%) [29], respectively, who then underwent a re-challenge studies.

The re-challenge study undertaken by Ellis et al. involved a seven-day crossover using gluten capsules as the active challenge [28]. Of those completing the study, 18/53 (34%) experienced worsening of symptoms during only the gluten challenge. Nonetheless, following the placebo challenge, symptoms were also induced in a notable number of people suggesting the true gluten challenge effect was likely to be much less than observed. The re-challenge by Zanwar et al. reported that more participants

experienced worsening of symptoms when challenged with wheat bread (active challenge, 55.7%) than with gluten-free bread (placebo challenge, 33.3%, $p<0.05$) [29].

Despite these supportive findings, gluten sensitivity cannot be confirmed in either study due to the presence of other potential candidates in the active challenges. For instance the wheat bread contained several additional components linked with gastrointestinal symptoms including amylase-trypsin inhibitors and fructans [30]. Furthermore, even the gluten-containing capsules used by Ellis et al. contained other non-gluten proteins and therefore an isolated effect of gluten could not be measured [28].

It must also be acknowledge that a GFD may not only present a financial burden but has been linked with a higher risk of nutritional inadequacies. In fact, a recently published epidemiological study in more than 110,000 people without coeliac disease found that those with the lowest intakes of gluten had a higher incidence of coronary heart disease, attributed to their lower intakes of wholegrains [31].

Taken together, sensitivity to wheat may affect a subgroup of IBS, although identifying the specific wheat component (fructans, gluten, amylase-trypsin inhibitors), the level of sensitivity and whether transient or lifelong exclusion is needed warrants further research.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

The variable efficacy of conventional therapies in managing IBS symptoms has drawn attention from some patients and clinicians to complimentary alternative medicine (CAM). CAMs cover a wide range of therapies, although few have been tested in robust clinical trials.

In IBS the most convincing evidence for CAM lays with peppermint oil and its active ingredient L-menthol. The benefits of peppermint oil are mainly attributed to its antispasmodic properties, although it has been linked with several other actions including anti-infective and anti-inflammatory [32]. A review of a meta-analysis suggests an overall benefit of peppermint oil compared to placebo for global relief of IBS symptoms (RR 2.23, 95% confidence interval (CI) 1.78-2.81) and for improving

abdominal pain (RR 2.14, 95% CI 1.64-2.79) [33]. Nonetheless, the overall quality of studies was acknowledged in the weak-graded clinical guideline recommendations [32].

More recently a four-week, randomised, double-blind, placebo-controlled trial demonstrated a 40% reduction in Total IBS Symptom Score with peppermint oil compared with 24% in the placebo group (p=0.03) [33]. Although promising, the generalisability of these results are restricted to a select population who did not take common medications and supplements.

There is also growing evidence to support combination CAMs. Recent RCTs have reported greater reductions in IBS Symptom Severity Scale from curcumin and fennel oil compared with placebo (mean relative: 50.1 ± 28.9% vs 26.1 ± 30.6%, P<0.001) [34] and between a proprietary mixture of curcuminoids and essential oils from different Curcuma species, fish oil, peppermint oil, caraway oil and vitamins B1, B9 and D3 (point change: -113.0 ± 64.9 vs -38.7 ± 64.5, P<0.001) [35].

Although these studies were small and had short durations compared to more rigorously designed trials needed for Food and Drug Administration approval, the role of CAM in IBS deserves greater attention in high quality clinical trials.

FUTURE DIRECTIONS AND CONCLUSION

The growing understanding of the pathophysiology of IBS supports the mechanistic potential of a wide range of dietary therapies although these largely focus on managing symptoms as opposed to treating the underlying cause. Nonetheless it is becoming increasingly clear that IBS is a heterogeneous condition and therefore it is unlikely that one nutrition therapy will benefit all. Currently the most convincing evidence for management of IBS symptoms is psyllium fibre, probiotics and a low FODMAP diet, although these have varying effect sizes. In order to progress dietary management of IBS, research needs to investigate the role of nutrition in targeting the

underlying cause of IBS. Given the role of the gut microbiota in the pathogenesis of IBS and the pivotal role diet plays in influencing this, the gut microbiota appears to be an attract target.

WORD COUNT (max 2500 words): 2,950

KEY POINTS (3-5 key points/sentences summarising the paper)

- Many RCTs have been undertaken confirming that certain probiotics improve symptoms and quality of life in patients with IBS. However, effect sizes may be relatively small, effects are strain-specific, and the optimal strain, dose, and administration period remains unclear.
- An increasing number of RCTs have been recently published confirming the clinical effectiveness of a low FODMAP diet for the management of IBS.
- A landmark mechanistic study revealed fructose increased small-bowel water content and inulin increased colonic gas in both patients and controls, but only patients experienced gut symptoms, revealing that visceral hypersensitivity to colonic gas is involved in symptom induction, rather than excess gas production *per se.*
- Wheat sensitivity appears to affect a subgroup of IBS, although identifying the specific wheat component (fructans, gluten, amylase-trypsin inhibitors) and the level of sensitivity warrants further research.

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446 **Table 1: Recent original randomised, placebo-controlled trials of probiotics in IBS**

Study	n	Diagnosis	Dose, genus, species, and strain	Form	Duration	Main findings
Hod et al, 2017 [14]	107	IBS-D	6×10^9 CFU/d *L. rhamnosus* LR5; 4×10^9 CFU/d *L. casei* LC5; 2×10^9 CFU/d *L. paracasei* LPC5; 2×10^9 CFU/d *L. plantarum* LP3; 10^{10} CFU/d *L. acidophilus* LA1; 8×10^9 CFU/d *B. bifidum* BF3; 2×10^9 CFU/d *B. longum* BG7; 4×10^9 CFU/d *B. breve* BR3; 2×10^9 CFU/d *B. infantis* BT1; 4×10^9 CFU/d *S. Thermophiles* ST3; *L. bulgaricus* LG1, dose unknown; 6×10^9 CFU/d *Lactococcus lactis* SL6.	Capsule	8 weeks	No difference between the probiotic and the placebo groups in pain intensity (27.8% *vs* 46.0% *p*=0.068), stool consistency (42.6% *vs* 34.0% *p*=0.423) or overall responder rates (20.4% *vs* 24.0%, *p*=0.814). No difference was found in high sensitivity C reactive protein concentrations between the probiotic (median 1.39; IQR 0.39-2.66 mg/L) and the placebo group (median 1.48 mg/L; IQR 0.59-2.86 mg/L, p=0.177). No difference was found in faecal calprotectin concentrations between the probiotic (median 12.0 µg/g; IQR 7.0-25.8 µg/g) and placebo groups (median 23.0 µg/g; IQR 12.0- 74.0 µg/g; *p*=0.817).
Pinto-Sanchez et al, 2017 [16]	44	IBS-D & IBS-M with mild to moderate anxiety or depression.	*B. longum* NCC3001; dose is unclear	Powder	6 weeks	Significantly more patients in the probiotic group had reduced depression scores that in the placebo group (RR 1.98; 95% CI 1.16-3.38; *p*=0.04). No differences in anxiety were found. *B. longum* reduced responses to negative emotional stimuli in multiple brain areas, including amygdala and fronto–limbic regions, compared with placebo. In the probiotic group, reduced engagement of the amygdala was more likely to occur in patients with adequate relief of IBS symptoms than in those without it (RR 3.07; 95% CI 0.89-10.59; *p*=0.03).
Mezzasalma et al, 2016 [15]	150	IBS-C	**Group 1:** 5×10^9 CFU/d *L. acidophilus* PBS066; 5×10^9 CFU/d *L. reuteri* PBS072; **Group 2:** 5×10^9 CFU/d *L. plantarum* PBS067; 5×10^9 CFU/d *L. rhamnosus* LRH020; 5×10^9 CFU/d *B. lactis* BL050.	Capsule	8 weeks	The percentage of responders (a decrease of symptoms of at least 30% compared for at least 50% of the intervention period) for abdominal pain, bloating, constipation and flatulence was higher in both probiotic groups compared to placebo. At the end of the intervention, quality of life was significantly improved in both probiotic groups (Group 1: 22.2 ± 1.0; Group 2: 22.0 ± 0.8) compared to placebo (28.7 ± 1.8; *p*<0.001).

447 IBS: irritable bowel syndrome; IBS-D: diarrhoea-predominant IBS; IBS-C: constipation-predominant IBS; IBS-M: mixed-type IBS; IQR: interquartile range; RR: relative risk; B.: *Bifidobacterium*; L.:
448 *Lactobacillus*; S.: *Streptoc*

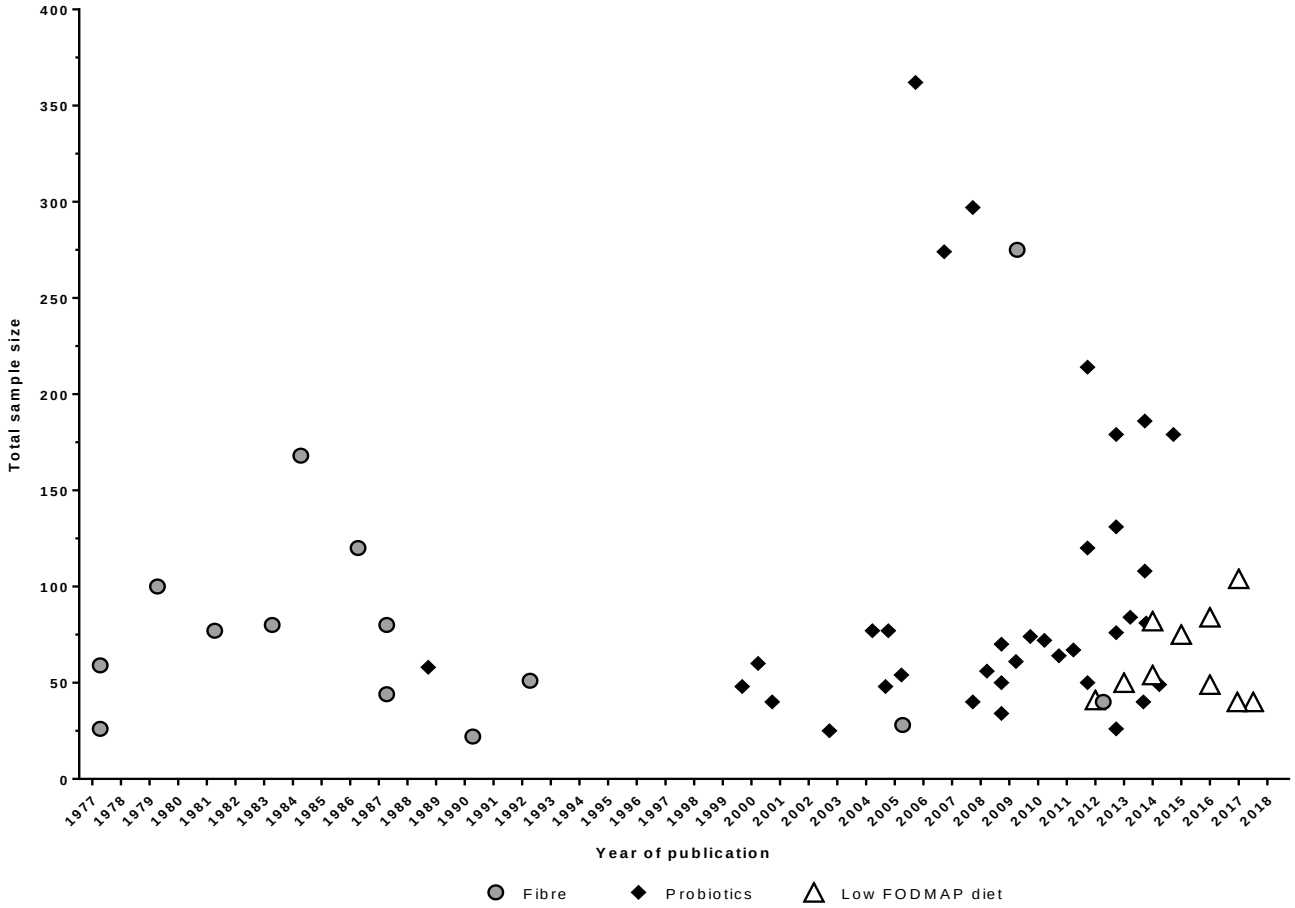

Figure 1: Trends in dietary intervention trials in irritable bowel syndrome. A scatter plot of the year of publication and sample size of randomised controlled/comparative trials of fibre, probiotics and the low FODMAP diet over the past four decades.

This figure indicates a primary focus on dietary fibre during the last millennium, which has now very much declined, and has been replaced by a greater focus on probiotic research in the 2000's and by trials of the low FODMAP diet in the 2010's. In general, the increase in trials of a specific dietary intervention has been accompanied by a steady increase in sample sizes of these trials. The individual studies depicted in this scatter plot are obtained from recent reviews and systematic reviews on fibre [3], probiotics [4] and the low FODMAP diet [5], and the sample size of cross-over trials is doubled for comparability.