A systematic review of the association between fibromyalgia and functional gastrointestinal disorders

Sharon Erdrich (sharon.erdrich@sydney.edu.au)

Research article

Keywords: fibromyalgia, comorbidity, irritable bowel syndrome, IBS, functional gastrointestinal disorders, FGID, diagnostic criteria

Posted Date: January 28th, 2020

DOI: https://doi.org/10.21203/rs.2.21966/v1

Version of Record: A version of this preprint was published at Therapeutic Advances in Gastroenterology on January 1st, 2020. See the published version at https://doi.org/10.1177/1756284820977402.

Abstract

Background

Fibromyalgia and functional gastrointestinal disorders are frequently encountered in clinical settings. Common to both is significant burden on individuals and health care systems, an elusive aetiology and several comorbid conditions. While a relationship between irritable bowel syndrome and fibromyalgia has been demonstrated, a broader review of the relationship between fibromyalgia and other functional gut disorders has not been undertaken.

Objectives

This paper reports a systematic review of the published literature, identifying the comorbidity of functional gastrointestinal disorders in people with fibromyalgia. We discuss the clinical implications, limitations of current research, and areas of interest for future research Methods A systematic review of the databases Medline, Embase, CINAHL and Web of Science was undertaken in June 2019. Results were screened for original articles meeting strict criteria for identification of functional gastrointestinal disorders in adult subjects with fibromyalgia.

Results

Fourteen articles were included investigating 1340 subjects with fibromyalgia, 363 healthy controls and 441 subjects with other pathologies. Functional gut disorders were matched to Rome II criteria for reporting and comparison. In addition to increased abdominal pain and functional bloating/gas, irritable bowel of mixed-pattern and constipation-types were more prevalent that diarrhoea-predominant irritable bowel in adults with fibromyalgia. One study reported the range of functional gastrointestinal disorders.

Conclusion

Existing research has focused on the relationship between irritable bowel syndrome and fibromyalgia, but sub-typing of irritable bowel syndrome is generally overlooked. A strong association with a range of functional gastrointestinal disorders is suggested. Further investigation is needed to determine the prevalence and relevance of the range of functional gastrointestinal disorders in patients with fibromyalgia.

Background

Both functional gastrointestinal disorders (FGID) and fibromyalgia are poorly understood syndromes significantly impacting quality of life (1) and imposing substantial financial burden (2, 3) with healthcare-associated costs reaching quadruple that of a reference population (4). Both syndromes are considered attributable to sympathetic dysfunction (5) resulting in central sensitisation (6) and were recently categorised as “Central Sensitivity Syndromes” (7, 8). A common aetiology has been proposed (9), but to date no compelling evidence resolves this issue.

Fibromyalgia accounts for about 15% of all referrals to rheumatology clinics (10) and has a global prevalence of around 2% (11) with wide variation (0.2% – 6.6%) depending on the country and assessment tool used (10, 12, 13). Reports consistently concur a higher prevalence for females – up to 10-fold that of males (10, 12, 14, 15), though a recent review by Frederick Wolfe and colleagues suggests this is primarily driven by selection bias and that rates in men and women are similar (11).

The major feature of fibromyalgia is chronic widespread pain (CWP), and is typically accompanied by a range of symptoms including fatigue, headache, sleep and cognitive disturbances, digestive disorders, including irritable bowel syndrome (IBS) (16).

It is estimated that about 50% of all digestive disorders being presented in primary and secondary care are functional in nature (17), with IBS being the most common FGID diagnosed (18). The high comorbidity of IBS with other somatic disorders including fibromyalgia has been established (19) but results of co-prevalence studies vary greatly. This is likely due to study design, including the diagnostic criteria employed, as well as cultural and socioeconomic factors that influence whether a person seeks medical care for either their pain or the accompanying condition.

Triadafilopoulos et al. (20) reported that 73% of fibromyalgics had altered bowel patterns, and Lubrano and colleagues (21), using Rome Foundation criteria for IBS and ACR 1990 for fibromyalgia, reported fibromyalgia in 20% of patients with IBS (n = 130). A 2002 systematic review of comorbid conditions in IBS conveyed that 28–59% of subjects with fibromyalgia had IBS, and 32–77% of those with IBS have fibromyalgia (19). A more recent systematic review (10) calculated the prevalence of fibromyalgia in those with IBS at 12.9% (95% CI 12.70, 13.10).

Other disorders, not typically related to IBS, such as functional nausea, vomiting and belching, are also commonly reported in patients with fibromyalgia (22), yet no systematic review evaluating the range of FGIDs in patients with fibromyalgia has been undertaken.

This paper presents a summary of the literature reporting the relationship between the spectrum of FGIDs and fibromyalgia in adults. Clinical implications, as well as areas for future research, are discussed.

Methods

Literature Search

This systematic review was registered with PROSPERO (Reg no: CRD42019139878). To identify relevant literature, a search was conducted in Medline, CINAHL, Embase and Web of Science using the search terms in Appendix 1. Citation chaining was undertaken to identify additional studies that may have been relevant to our objectives.

Study Selection Criteria

For inclusion, the following criteria were applied: published in English, available as full-text article, reported co-prevalence of fibromyalgia and any FGID, included adults (≥ 18 years of age), cohort studies, (prospective or retrospective), published since 1978. Searches of the literature took place over June 23–24, 2019. Where diagnostic or demographic data were unclear, attempts were made to contact the authors by email. Where a response was not obtained, the paper in question was removed from the analysis.

Data Extraction

Papers meeting the search criteria were downloaded into EndNote X8 citation software (Clarivate Analytics), and the following data tabulated in a Microsoft Excel spreadsheet: first author, publication year, country in which conducted, study type, age, gender, fibromyalgia diagnostic criteria, FGID criteria used, specific FGID/s identified. For inclusion, fibromyalgia diagnosis based on specifications as outlined by Smythe (1985), Yunus (1981) or ACR criteria (1990, 2010 or 2011) were required. Studies detailing a diagnosis of FGID based on Manning (1978) (23), Drossman (1982) (24), Kruis (25) or any of the Rome criteria (Table 1) were retained.

Table 1
Comparative Classifications of Irritable Bowel Syndrome

Manning (1978) (23)	Drossman (1982) (24)	Rome I (1990) (26)	Rome II (1999) (27)	Rome III (2006) (28)	Rome IV (2016) (29)
2 or more of: - Abdominal distension - Pain improved with passing stool - Frequent stool, with onset of pain - Looser stool, with onset of pain - Passing mucous - Sensation of incomplete evacuation	A. Irregular or varying bowel pattern > 25% of the time B. Abdominal pain: minimum six episodes in the last year AND at least 3 of: - Pain relieved by bowel movement - Loose stools associated with the pain - More frequent stools associated with the pain - Abdominal distension - Mucous in the stool - Sense of incomplete evacuation C. Constipation - Straining at the stools > 25% of the time OR - Two or fewer stools per week D. Diarrhoea: - Loose or watery stools > 25% of the time OR - More than 21 stools per week	A minimum 3 months of: Continuous or recurrent abdominal pain; - Relieved by passing stool OR - Associated with change in frequency or consistency of stool AND at least 3 of: (for at least 25% of days) - Altered stool frequency - Altered stool form - Altered stool passage (straining, urgency, sense of incomplete evacuation) - Passing mucous - Bloating or feeling of abdominal distension	Minimum 12 weeks out of the previous 12 months Abdominal discomfort or pain PLUS 2 of the following: - Relieved by passing stool - Onset associated with a change in frequency of stool - Onset associated with a change in form (appearance) of stool. Supportive symptoms include: - Abnormal stool frequency (> 3/day and < 3/week); - Abnormal stool form (lumpy/hard or loose/ watery stool); - Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation) - Passage of mucous - Bloating or feeling of abdominal distension	Minimum 3 of previous 6 months: Recurrent abdominal pain or discomfort in 3 days/month in the last 3 months, PLUS at least 2 of: - Improvement with defaecation - Onset associated with change in stool frequency - Onset associated with a change in form (appearance) of stool Supportive symptoms as for Rome II	Minimum of last 3 months, onset at least 6 months before diagnosis: Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, PLUS at least 2 of: - Related to defaecation - Associated with a change in stool frequency - Associated with a change in stool form (appearance)

All included papers were assessed by two researchers (SE and JEH) for quality based on Joanna Briggs criteria. Average scores were calculated as percentages and are shown in Table 2.

Results

5,765 records were retrieved. A diagrammatic representation of the selection process is shown in Fig. 1.

Of 53 studies meeting accepted diagnostic criteria for fibromyalgia, 39 (73.5%) were discarded due to inadequate or unclear criteria for identification of the FGID. The remaining fourteen studies reported data on 1340 subjects with fibromyalgia. Nine used a healthy control population (n = 363). Other comparison populations were variously made up of other rheumatological conditions (n = 166), IBS OR inflammatory bowel disease (IBD) (n = 162) and other diseased control subjects (n = 112). The mean age ranged from 28.6–55.6 years, (SD ± 0.3 to ± 14.9).

Three studies exclusively included women (30–32), one provided age data for males and females separately and is reflected accordingly in Table 2 (33). The pooled population across all studies was 90.7% female; 89.1% when female-only studies are removed.

Table 2 outlines key information from the included studies.

Table 2

Summary of 14 Studies Reporting Functional Gastrointestinal Disorders in Fibromyalgia

		Fibromyalgia cases			Diagnostic Criteria		
Author (Year)	Country	n= (% female)	AGE Mean SD (range)	Controls	FMS	FGID	Quality Score
Triadafilopoulos, 1991 (20)	USA	123 (921.9)	47 (24–64)	46 NC, 54 DJD	ACR1990	Drossman	83%
Veale (1991) (34)	Ireland	20 (75)	(33–36)	20 NC, 20 IBD, 20 IA	Smythe	Manning	83%
Sivri (1996) (35)	Turkey	75 (87)	36.3 ± 11	50 NC	ACR1990	Drossman	83%
Sperber (1999) (32)	Israel	100 (100)	48.6 ± 10.8 - ±14.9	0	ACR1990	Rome I	92%
Yunus (2000) (33)	USA	469 (100)	46.3 ± 13.2	0	ACR1990	Manning	79%
		67 (0)	47.1 ± 13.3	36 NC			
Choudhury (2001) (36)	Bangladesh	30 (90)	28.6 ± 10	30 NC, 30 RA	ACR1990	Manning	75%
Pace (2001) (37)	Italy	27 (92.6)	51(25–73)	25 NC, 32 IBS	ACR1990	Rome I	83%
Pimentel (2004) (38)	USA	42 (86)	46.6 ± 0.3	15 NC, 111 IBS	ACR1990	Rome I	92%
Kurland (2006) (39)	USA	105 (93)	52.9 ± 11.3	62 OR	ACR1990	Rome II	92%
Zoppi (2008) (40)	Italy	67 (97)	55.6 ± 11.01	0	ACR1990	Rome II	50%
Almansa (2009) (41)	Spain	100 (93)	50.5 ± 9.6	100 NC	ACR1990	Rome II	92%
Akkaya (2011) (30)	Turkey	65 (100)	36.21 ± 7.42	41 NC	ACR1990	Rome I#	92%
Okumus (2011) (42)	Turkey	12 (54.8)	40.1 ± 4.4	112 PD	ACR1990	Rome II	75%
Marum (2017) (31)	Portugal	38 (100)	51 (> 18)	0	ACR2011	Rome III#	88%
Total		1340 (90.7)		NC 363, Other 441			

Key: FMS = fibromyalgia; FGID = functional gastrointestinal disorder; ACR = American College of Rheumatology; NC = normal controls; DJD = Degenerative joint disease; IBD = Inflammatory bowel disease; IA = Inflammatory arthritis; RA = Rheumatoid arthritis; OR = other rheumatic diseases; PD = Peritoneal dialysis; *= separated IBS sub-types; #= information provided by email

Table 3

Summary of Functional Gastrointestinal Disease Types and Prevalence Reported in 14 Included Studies

Author	FGID Type	Fibromyalgia		Normal Controls		Other Controls	
	(Rome II)	FGID %	IBS%	IBS %	p-value	IBS %	p-value
Triadafilopoulos (20)	C1, C2, C3, C4, D1	74.0	60.0	0	nr	DJD 13	nr
Veale (34)	C1	70.0	70.0	10	nr	IBD 5 IA 15	nr nr
Sivri (35)	C1, C*, C2, C3, C4, D1	41.8	41.8	16	< 0.05	-	-
Sperber (32)	C1	32.0	32.0	-	-	-	-
Yunus (33)	C1	≥38.9	38.9	0	< 0.03	-	-
		≤13.8	13.8	-	-	-	-
Choudhury (36)	C1	30.0	30.0	7	0.02	RA 3	< 0.02
Pace (37)	C1	66.7	66.7	0	nr	-	-
Pimentel (38)	C1	52.4	52.4	nr	-	-	-
Kurland (39)	C1, C*, C3, C4	81.0	81.0	-	-	OR 24	< 0.001
Zoppi (40)	C1	14.9	14.9	-	-	-	-
Almansa (41)	A1, A2, A3, A4, A5, B1, B2, B3, C1, C2, C3, C4, D1, D2, E1, E2, F2a, F2b, F3	98.0	39.0	3	< 0.001	-	-
Akkaya (30)	C1	61.5	61.5	nr	-	-	-
Okumus (42)	C1	16.7	16.7	-	-	PD 7	0.25
Marum (31)	C1, C*, C3, C4	95.0	95.0	-	-	-	-
Pooled data		50.8	46.2	4.9		11.7	

Key: FGID = functional gastrointestinal disorder; IBS = irritable bowel syndrome; Fx = Functional

A1 = Globus; A2 = Rumination syndrome; A3 = Fx chest pain; A4 = Fx heartburn; A5 = Fx dysphagia; B1 = Fx dyspepsia; B2 = Aerophagia; B3 = Fx vomiting; C1 = IBS; C*=Alternating constipation & diarrhoea; C2 = Fx bloating; C3 = Fx constipation; C4 = Fx diarrhoea; D1 = Abdominal pain; D2 = Unspecified functional pain; E1 = Gallbladder dysfunction; E2 = Sphincter of Oddi dysfunction; F1 = Fx incontinence; F2a = Levator ani syndrome; F2b = Proctalgia fugax; F3 = Pelvic floor dysfunction

NC = normal controls; DJD = Degenerative joint disease; IBD = Inflammatory bowel disease; IA = Inflammatory arthritis; RA = Rheumatoid arthritis; OR = other rheumatic diseases; PD = Peritoneal dialysis; nr = not reported

The prevalence of FGIDs varied widely, from 13.8% in an all-male cohort, to 98% in a primarily female cohort. All studies reported IBS in subjects, which varied from 13.8–95%, and all except one (31) utilised diagnostic criteria according to Rome II, or earlier. Table 3 details the classification reported, as matched to Rome II criteria. Pooled data from all 14 studies reveals an overall prevalence of FGID in subjects of 50.8%, and 46.2% for IBS. It should be noted that 12 of the 14 studies only reported IBS, hence FGID and IBS prevalence in these does not differ.

One study set out to examine the prevalence of the range of FGIDs in fibromyalgia (41), five (20, 32, 34, 35, 39) focused on IBS. In four studies (31, 33, 36, 40) IBS was recorded as part of a bigger research question and in the remaining four studies (30, 37, 38, 42) IBS data was reported as a secondary not primary outcome measure. Four studies (32, 34, 37, 38) included additional cohorts of patients with IBS; these subjects are excluded from control data presented in Table 2. Appendix B contains information related to the aim of each of the included studies.

Two studies included controls with non-rheumatic diseases: IBD (34) and chronic kidney failure (42). Separation of control groups revealed that IBS occurred in those with other pathologies at more than double the rate of healthy controls.

While not detailed, it appears the control group in the study by Pimentel et al. (38) was selected based on absence of both fibromyalgia and IBS. Yunus et al. (33) did not include a female control group as their purpose was comparing fibromyalgia in men and women; a small group of male controls were included, for whom data was not compared to females.

While all studies reported IBS, further detail allowing separation of IBS sub-types was reported by five (20, 31, 35, 39, 41). Three studies (20, 35, 41) compared prevalence of sub-types of IBS to normal controls; these are detailed in Table 4.

Almansa et al. (41) reported at least one FGID in 98% of patients and 39% of controls. High rates of oesophageal and gastroduodenal conditions were also reported, with all symptoms except vomiting present at significantly higher rates in patients than in controls ($p < 0.05$) (data not shown). IBS had the strongest association to fibromyalgia, followed by functional bloating and functional faecal incontinence, as outlined in Table 4.

The overall prevalence of IBS in the study by Triadafilopoulos et al. (20) presented in Tables 3 and 4 above is extracted from data presented in Table 2 of their report. Notably, this is at odds with their in-text report, which stated that 81% of patients had “normal alternating with irregular bowel pattern”, meeting their Category 1 “alternating bowel pattern”. The figure in column C* in Table 4 (above) is for those with IBS-alternating/mixed (IBS-M) by Rome II criteria.

Table 4

Prevalence of Sub-types of FGID in Fibromyalgia and Healthy Controls from Five Studies (%)

Author	IBS (C1)		Alternating constipation & diarrhoea (C*)		Bloating (or "gas") (C2)		Constipation (C3)		Diarrhoea (C4)		Abdominal pain (D1)		Unspecified functional abdominal pain (D2)		Faecal incontinence (F1)	
	FMS	NC	FMS	NC	FMS	NC	FMS	NC	FMS	NC	FMS	NC	FMS	NC	FMS	NC
Triadafilopoulos (20)	60.0	0	62.6	0	59.0	13.0	12.0	13.0	9.0	2.0#	54.0	4.0	-	-	-	-
Sivri (35)	41.8	16.0	41.8	20.0	45.5	-	30.7	8.0	7.0	1.0	38.2	8.0	-	-	-	-
Kurland (39)	81.0	-	61.0	-	-	-	15.2	-	4.8	-	-	-	-	-	-	-
Almansa (41)	39.0	3.0	-	-	34	12.0	15.0	5.0	2.0	0	75.0	0.0	19.0	1.0	56.0	25.0
Marum (31)	95.0	-	22.2	-	-	-	69.4	-	8.3	-	-	-	-	-	-	-
FGID average@	67.2		52.9		65.4		21.3		6.0		57.1		19.0		56.0	

Key: FMS = fibromyalgia patients; NC = normal controls; #=estimated from Triadafilopoulos Fig. 2 (data not provided); @= calculated from studies reporting that FGID

None of the included studies provided detail regarding coexistence of more than one FGID in subjects. For example, Almansa's group (41) reported functional constipation in 15% of subjects, 39% had IBS, and while at least one FGID was found in 98% of subjects, data on comorbidity of multiple FGIDs is not provided.

Discussion

The relationship between fibromyalgia and the group of gastrointestinal disorders that are collectively grouped as "functional" beyond IBS is underexplored. Of the studies included in our review, just one sought to answer this question. This systematic review found that half of people with fibromyalgia have at least one FGID, with a heavy weighting of IBS prevalence data. Without further investigation, the totality of FGID in subjects with fibromyalgia, and therefore the true comorbidity, remains undetermined.

Our review included research in which data on the presence of an FGID and fibromyalgia was reported. In some cases, this was not an objective of the included study, rather part of the description of the cohort. In the papers reviewed, one provided detailed data. In the remainder, information provided was seldom adequate to classify IBS into its sub-groups, limiting analysis of the prevalence of the various presentations of IBS.

Our initial results included papers reporting a relationship between dyspepsia, reflux and gastro-oesophageal reflux disease (GERD) and fibromyalgia. However, as GERD can be secondary to an organic disease aetiology, including infection and as a side effect of medication, researchers sometimes include dyspepsia under the GERD category (43) we excluded cases of GERD or dyspepsia where there was doubt as to the aetiology. The only study in our results reporting functional dyspepsia found it occurred in fibromyalgics at seven times the rate of controls (41).

Some of the earliest studies examining associations between fibromyalgia and IBS revealed a strong bidirectional relationship (32, 34). The overall prevalence of IBS in people with fibromyalgia identified in our review is 46.2%, closely aligning with the 49.2% found in Whitehead's 2002 systematic review (19), and is about four times the 11% estimated global prevalence of IBS (44). The variation in reported prevalence identified in our results (13% – 95%) was somewhat broader than Whitehead's (28% – 65%).

Two of the fourteen studies in our analysis reported fibromyalgia-FGID comorbidity rates of less than 20%. Okumus (42) investigated IBS in patients with end-stage renal disease (ESRD) and found that 16.7% of patients with both ESRD and fibromyalgia had IBS, compared to 7.1% of those without fibromyalgia. Given the known alterations to the gut microbiome in patients with renal disease (45), the low comorbidity suggests the small patient group (n = 12 with ESRD plus fibromyalgia versus those with ESRD-only n = 112) may underlie the non-significant difference (p-value not given). Zoppi et al. (40) acknowledged that the 14.9% IBS rate in their cohort was the only feature occurring at lower rates than either the general population or other fibromyalgia studies at that time. A control group was not included and there is insufficient information provided in their report to inform further discussion.

Conversely, with a 95% comorbidity, Marum et al. (31) recruited subjects evaluated by a rheumatologist with a dietitian in attendance with the purpose of assessing the effect of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) on fibromyalgia symptoms. Hence a selection bias towards patients with gastrointestinal symptoms undoubtedly underlies the high rate of IBS in this study. The cohort was small (n = 38) and removal of this study from our analysis reduced the overall prevalence of IBS from 46.2–44.8% and IBS-constipation (IBS-C) from 21.3–17.1%. A significant reduction in a range of symptoms and disease scores related to both fibromyalgia and IBS was noted after four weeks of adherence to the low FODMAP diet (all $p < 0.05$). Consuming a diet that is low in fermentable compounds has been shown to be effective in the management of IBS (46, 47) including in subjects with fibromyalgia (48). Lowering the intake of fermentable foods is known to alter gut bacterial populations (49), and as yet the effect of such a diet on global symptoms of fibromyalgia is unexplored.

Of note, investigators tended to regard IBS as a single entity, rather than a condition with several subtypes, a shortcoming which has been reported previously (50). This limits interpretation of results in the current era where an altered microbiome has been identified in patients with IBS (51) and a deeper understanding of the role the human gut microbiota has on gastrointestinal functions such as gas production and dynamics, bloating and motility is evolving.

From the five studies providing detail beyond the generic classification of IBS (Table 4), IBS-M was the most common subtype reported, followed by IBS-C which affected subjects at more than three times the rate of diarrhoea predominant IBS (IBS-D). In other studies excluded from this review due to not meeting our criteria for identification of FGID, varying rates of constipation were noted; 12% by Garcia-Leiva et al. (alternating pattern in 63%) (52), 55.5% (double the rate of diarrhoea) by Rios' group (53) and 56.5% in Zanetti's cohort (54). Conversely,

Author	IBS (C1)	Alternating constipation & diarrhoea (C*)	Bloating (or gas*) (C2)	Constipation (C3)	Diarrhoea (C4)	Abdominal pain (D1)	Unspecified functional abdominal pain (D2)	Faecal incontinence (F1)

Buchwald et al. (55) reported diarrhoea in 62% of their fibromyalgia cohort and provided no information regarding constipation or alternating bowel habit. Constipation is estimated to occur in 12–19% of the general population and where not secondary to other conditions, may be associated with a number of dietary and lifestyle factors as well as medications (56). Technically, these factors should be ruled out before a diagnosis of IBS-C is made but this is not consistent amongst clinicians (44). Also associated with an increase in methanogenic bacteria, IBS-C is predictable by methane gas production as measured in human breath, with 91.7% sensitivity and 81.3% specificity (57). Pimentel et al. (38) conducted hydrogen-methane testing in subjects with fibromyalgia but did not report either methane levels or IBS sub-types.

Three studies included control subjects with other musculoskeletal pathologies (34, 36, 39). Both healthy controls and those with rheumatoid arthritis (RA) had low rates of IBS in Choudhury's small study (n = 30 in each group) (36). The Manning criteria was used, application of which results in a much higher rate of IBS diagnosis compared to the Rome II criteria (58, 59) (see Table 1). Kurland's control group comprised patients with a range of conditions, including RA, osteoarthritis and lupus, in whom the overall prevalence of IBS was 24% (39). This is higher than the estimated prevalence in the United States of 14.1% (58), suggesting a gut-musculoskeletal relationship may be at play. There were four comparison groups in Veale's study: IBD, inflammatory arthritis (IA), normal controls (NC) and a group with IBS for bidirectional comparison (34). We detected an error in data reporting IBS prevalence, whereby the text states "IBD = 1, IA = 2, NC = 2" (i.e. n = 5), yet "all control patients… 6 had IBS". The latter matches data in their Fig. 1b, where the bar for IA appears to represent n = 3 (not n = 2). While numbers are small, this difference means 15% of the group with IA had IBS, not 10%.

A proposed explanation for the pain in fibromyalgia is sensitisation of the central nervous system, (14) but an underlying mechanism remains elusive. Increasingly, research reports indicate an important role of the gastrointestinal milieu in health and a wide range of conditions, from chronic kidney disease (45) to allergies (60) and diseases of connective tissue (61). Recent advances have also expanded understanding of the possible role of the gut ecological environment on pain signaling and peripheral sensitisation (62), and identifying commensal gut bacteria at sub-infective levels in synovial fluid (63) and joint cartilage (64) adds credence to what currently is a hypothetical gut microbiota - musculoskeletal interaction (65). While we did not seek to explore FGIDs in other rheumatic or musculoskeletal conditions, these groups are often used in comparison to fibromyalgia. Interestingly, we found higher rates of IBS in subjects with other rheumatological conditions compared to healthy controls further supporting an interaction between the gut microbiota and the musculoskeletal system (66, 67).

Sperber et al. (32) reported that fibromyalgics with IBS had worse symptoms of fatigue, morning tiredness and pain, compared to those without IBS. This is consistent with several other reports linking aggravation of digestive symptoms during periods of exacerbations of fibromyalgia (20). Iovino et al. (68) demonstrated that patients with mild IBS were invariably negative for fibromyalgia, whereas moderate to severe symptoms of IBS were significantly associated with fibromyalgia. Lubrano et al. (21) also found a significant association between fibromyalgia and the severity of IBS symptoms ($p = 0.002$).

Emerging evidence suggests that the gut bacterial community may be altered in IBS (69), constipation (70), and in fibromyalgia (71). This is supported by pain reduction subsequent to antibiotic treatment (72) and following Marum's dietary intervention in patients with fibromyalgia (31). While a low FODMAP diet may improve IBS symptoms (73), associated with changes to the gut microbiome (46) and intestinal gas production (74), the effect on fibromyalgia symptoms had not been previously investigated. However, some dietary interventions that have been studied in fibromyalgia are associated with clinical improvements (75).

Our review also concludes a high prevalence of functional bloating and/or gas (65.4%), similar to Zanetti et al's reported prevalence of 56.5% in women with fibromyalgia (54), although in their report a "functional" classification was not specified. Bloating is associated with bacterial fermentation of fermentable compounds (74, 76) and increased hydrogen and methane gas production (76, 77). The small number of studies (n = 3) in our results reporting gas/bloating precludes generalisability but significantly higher rates of fibromyalgia have been reported in people with IBS-bloating compared to those with IBS without bloating (78). This suggests that diet and/or an altered microbiome may play an important role in fibromyalgia.

A meta-analysis published in 2017 estimated the prevalence of fibromyalgia in patients with IBS in three included studies to be 12.9% (95% CI 12.7–13.1). Inclusion criteria for fibromyalgia in that report were less stringent than ours and prevalence ranged from 0.71–4.82%, depending on the diagnostic tool used (10). The odds ratio of fibromyalgia in subjects with IBS is 1.8 (79), and a bidirectional relationship between the two conditions was reported in a systematic review, with 32.5% (range 28–65%) of IBS patients having fibromyalgia, and 48% of patients with fibromyalgia having IBS (range 32–77%) (19).

The large variance in the prevalence of FGID in our studies may be explained– at least in part – by changes in understanding of functional gut disorders over time and the various diagnostic criteria employed.

Strengths

Our search terms captured the spectrum of FGIDs. Including studies employing established diagnostic criteria for both fibromyalgia and FGID is a further strength, and the rigour of our process ensures minimal likelihood of non-fibromyalgia groups being captured. For purposes of analysis we chose to utilise Rome II criteria as 9 of the 14 studies employed pre-Rome II tools, 4 used Rome II, one used Rome III and none used the most recent Rome IV. While attempts to match symptoms as reported in earlier studies to Rome II were made, the potential for misclassification exists. It was observed that terms such as constipation, diarrhoea, abdominal pain, etc., are seldom described as "functional". We hypothesised that organic causes of these conditions would have meant any affected subjects were removed from the initial cohort, as was stated by some authors and was previously a requirement for IBS diagnosis, as in Rome I (26).

Weaknesses

Limitations in our study relate directly to the inherent quality of the studies included. Stringent inclusion criteria resulted in a smaller cohort for evaluation. In calculating the prevalence of FGID, we relied on author's reports; yet overlaps in the data are possible. For example, Sivri et al. (35) using Drossman's 1982 criteria (Table 1), pooled the data for altered bowel patterns to arrive at an overall prevalence of IBS of 41.8%, which is the same as their figure for alternating pattern, but less than the reported rate of bloating of 45.5%.

The time-span of the included studies is some 26 years, over which time diagnostic criteria for IBS, FGID and fibromyalgia underwent several changes, each of which has the potential to alter results. This has been demonstrated with application of more recent Rome II criteria in a population survey resulted in lower rates of IBS than Rome I (58), although Kurland et al. (39) found the opposite to be true in fibromyalgia.

While we aimed to exclude known cause-and-effect reported FGID (such as narcotic bowel syndrome), few studies provided sufficient detail for certainty in this regard. For example, it is possible that constipation rates reported may be associated with factors such as diet, fluid intake, exercise or drug use (such as analgaesics), which we were unable to determine.

Clinical Implications

Our data is strongly representative of females with fibromyalgia even when all-female cohorts were excluded from the analysis. Epidemiological data from community-dwelling subjects in Europe indicates the prevalence in women is just double that of men (12), suggesting men are less likely to seek healthcare for their condition.

Approximately 70% of people with IBS do not seek medical input for their gastrointestinal complaint (44) and up to 13% of a population may have undiagnosed fibromyalgia (12). Exposing an opportunity to evaluate the coexistence of these disorders in patients presenting to primary or secondary practice. While the causes of any FGID and how these may influence the clinical features of fibromyalgia is undetermined, strategies to address contributing factors and thus improve gastrointestinal function have potential to contribute to disease modification of both conditions.

Author	IBS (C1)	Alternating constipation & diarrhoea (C*)	Bloating (or gas) (C2)	Constipation (C3)	Diarrhoea (C4)	Abdominal pain (D1)	Unspecified functional abdominal pain (D2)	Faecal incontinence (F1)

Conclusion

The results of this review confirm previous reports that IBS is common in people living with fibromyalgia and reveals that this is predominantly mixed and constipation types. A significant gap exists in the research regarding the relationship with other FGIDs. Indications that reductions in gastrointestinal symptoms correlates with improvements in fibromyalgia suggests patients may benefit from identification of the wider range of gastrointestinal disorders and implementation of clinical strategies to address contributing factors. Future studies should include an evaluation of the full range of FGIDs in subjects with fibromyalgia using established criteria for both conditions. Reporting should include adequate detail related to confounders such as medication use, diet and lifestyle. Thorough examination of the FGID - gut ecology relationship would provide further insights in this patient population.

List Of Abbreviations

ACR American College of Rheumatology

CWP chronic widespread pain

ESRD end-stage renal disease

FGID functional gastrointestinal disorder

FODMAPS fermentable oligosaccharides, disaccharides, monosaccharides and polyols

GERD gastro-oesophageal reflux disease

IA inflammatory arthritis

IBD inflammatory bowel disease

IBS irritable bowel syndrome

IBS-C irritable bowel syndrome, constipation-predominant

IBS-D irritable bowel syndrome, diarrhoea-predominant

IBS-M irritable bowel syndrome, alternating or mixed constipation and diarrhoea

NC normal controls

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RA rheumatoid arthritis

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Data sharing not applicable to this article as no datasets were generated. All datasets reviewed in this article are cited in the Results section.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' contributions: SE co-designed the study, conducted the searches, sorted the results and created the initial draft of the manuscript.

JAH co-designed the study, assisted in interpretation of the data, and edited the manuscript. SPM assisted in interpreting the data and editing the manuscript.

JEH co-designed the study, contributed to interpretation of data, and was a major contributor in writing the manuscript.

All authors read and approved the final manuscript.

Acknowledgements: Thanks to Dr Yulia Ulyannikova for guidance in structuring and conducting the systematic review.

References

1. Corsetti M, Tack J, Attara G, Sewell M. IBS Global Impact Report 2018. Uncovering the true burden of irritable bowel syndrome (IBS) on people's lives. Allergan & Gastrointestinal Society; 2018.
2. Buono JL, Mathur K, Averitt AJ, Andrae DA. Economic burden of irritable bowel syndrome with diarrhea: Retrospective analysis of a U.S. commercially insured population. J Manag Care Spec Pharm. 2017;23(4):453-60.

3. Tack J, Stanghellini V, Mearin F, Yiannakou Y, Layer P, Coffin B, et al. Economic burden of moderate to severe irritable bowel syndrome with constipation in six European countries. BMC Gastroenterol. 2019;19(1):69.
4. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. Int J Clin Pract. 2007;61(9):1498-508.
5. Martínez-Martínez L-A, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: A review of case-control studies. J Clin Rheumatol. 2014;20(3):146-50.
6. Sarzi-Puttini P, Atzeni F, Di Franco M, Buskila D, Alciati A, Giacomelli C, et al. Dysfunctional syndromes and fibromyalgia: A 2012 critical digest. Clinical and Experimental Rheumatology. 2012;30(SUPPL.74):S143-S51.
7. Yunus MB. Central sensitivity syndromes: A new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008;37(6):339-52.
8. Slim M, Calandre EP, Rico-Villademoros F. An insight into the gastrointestinal component of fibromyalgia: Clinical manifestations and potential underlying mechanisms [Review]. Rheumatol Int. 2015;35(3):433-44.
9. Chang L. The association of functional gastrointestinal disorders and fibromyalgia [Review]. The European journal of surgery Acta chirurgica Supplement. 1998:32-6.
10. Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. Rheumatol Int. 2017;37(9):1527-39.
11. Wolfe F, Walitt B, Perrot S, Rasker JJ, Hauser W. Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. PLoS One. 2018;13(9):e0203755-e.
12. Branco JC, Bannwarth B, Failde I, Carbonell JA, Blotman F, Spaeth M, et al. Prevalence of fibromyalgia: A survey in five European countries. Semin Arthritis Rheum. 2010;39:448-53.
13. Marques AP, Santo AdSdE, Berssaneti AA, Matsutani LA, Yuan SLK. Prevalence of fibromyalgia: Literature review update. Rev Bras Reumatol Engl Ed. 2017;57(4):356-63.
14. Queiroz LP. Worldwide epidemiology of fibromyalgia. Current Pain and Headache Reports. 2013;17(8):356-.
15. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, et al. The incidence of fibromyalgia and its associated comorbidities: A population-based retrospective cohort study based on international classification of diseases, 9th revision codes. J Clin Rheumatol. 2006;12(3):124-8.
16. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46(3):319-29.
17. Thompson WG. The road to Rome. Gastroenterol. 2006;130(5):1552-6.
18. Shivaji UN, Ford AC. Prevalence of functional gastrointestinal disorders among consecutive new patient referrals to a gastroenterology clinic. Frontline Gastroenterol. 2014;5(4):266-71.
19. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? Gastroenterol. 2002;122(4):1140-56.
20. Triadafilopoulos G, Simms RW, Goldenberg DL. Bowel dysfunction in fibromyalgia syndrome. Dig Dis Sci. 1991;36(1):59-64.
21. Lubrano E, Iovino P, Tremolaterra F, Parsons WJ, Ciacci C, Mazzacca G. Fibromyalgia in patients with irritable bowel syndrome: An association with the severity of the intestinal disorder. Int J Colorectal Dis. 2001;16(4):211-5.
22. Pamuk ON, Ümit H, Harmandar O. Increased frequency of gastrointestinal symptoms in patients with fibromyalgia and associated factors: a comparative study. J Rheumatol. 2009;36(8):1720-4.
23. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. Br Med J. 1978;2(6138):653-4.
24. Drossman DA, Sandler RS, McKee DC, Lovitz AJ. Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. Gastroenterol. 1982;83(3):529-34.
25. Kruis W, Thieme C, Weinzierl M, Schüssler P, Holl J, Paulus W. A diagnostic score for the irritable bowel syndrome: Its value in the exclusion of organic disease. Gastroenterol. 1984;87(1):1-7.
26. Drossman DA, Thompson WG, Talley NJ, Funch-Jensen P, Janssens J, Whitehead WE. Identification of sub-groups of functional gastrointestinal disorders. Gastroenterology International. 1990;3(4):159-72.
27. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut. 1999;45 Suppl 2(Suppl 2):II43-II7.
28. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders [Review]. Gastroenterol. 2006;130(5):1480-91.
29. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders [Review]. Gastroenterol. 2016;150(6):1393-407.e5.
30. Akkaya N, Akkaya S, Polat Y, Turk M, Turk T, Turhal E, et al. Helicobacter pylori seropositivity in fibromyalgia syndrome. Clin Rheumatol. 2011;30(1):43-9.
31. Marum AP, Moreira C, Tomas-Carus P, Saraiva F, Guerreiro CS. A low fermentable oligo-di-mono-saccharides and polyols (FODMAP) diet is a balanced therapy for fibromyalgia with nutritional and symptomatic benefits. Nutr Hosp. 2017;34(3):667-74.
32. Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, et al. Fibromyalgia in the irritable bowel syndrome: Studies of prevalence and clinical implications. Am J Gastroenterol. 1999;94(12):3541-6.
33. Yunus MB, Inanici F, Aldag JC, Mangold RF. Fibromyalgia in men: Comparison of clinical features with women. J Rheumatol. 2000;27(2):485-90.
34. Veale D, Kavanagh G, Fielding JF, Fitzgerald O. Primary fibromyalgia and the irritable bowel syndrome: Different expressions of a common pathogenetic process. Br J Rheumatol. 1991;30(3):220-2.
35. Sivri A, Cindas A, Dincer F, Sivri B. Bowel dysfunction and irritable bowel syndrome in fibromyalgia patients. Clin Rheumatol. 1996;15(3):283-6.
36. Choudhury AK, Yunus MB, Haq SA, Alam MN, Sebrina F, Aldag JC. Clinical features of fibromyalgia syndrome in a Bangladeshi population. J Musculoskelet Pain. 2001;9(1):25-33.
37. Pace F, Sarzi-Puttini P, Manzionna G, Molteni P, Turiel M, Panni B, et al. Visceral hypersensitivity is not a feature of fibromyalgia syndrome. J Musculoskelet Pain. 2001;9(1):47-55.
38. Pimentel M, Wallace D, Hallegua D, Chow E, Kong Y, Park S, et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. Ann Rheum Dis. 2004;63(4):450-2.
39. Kurland JE, Coyle WJ, Winkler A, Zable E. Prevalence of irritable bowel syndrome and depression in fibromyalgia Dig Dis Sci. 2006;51(3):454-60.
40. Zoppi M, Maresca M. Symptoms accompanying fibromyalgia. Reumatismo. 2008;60(3):217-20.
41. Almansa C, Rey E, Sanchez RG, Sanchez AA, Diaz-Rubio M. Prevalence of functional gastrointestinal disorders in patients with fibromyalgia and the role of psychologic distress. Clin Gastroenterol Hepatol. 2009;7(4):438-45.

Author	IBS (C1)	Alternating constipation & diarrhoea (C2)	Bloating (or "gas") (C3)	Constipation (C4)	Diarrhoea (C5)	Abdominal pain (D1)	Unspecified functional abdominal pain (D2)	Faecal incontinence (F1)

Author	IBS (C1)	Alternating constipation & diarrhoea (C*)	Bloating (or "gas") (C2)	Constipation (C3)	Diarrhoea (C4)	Abdominal pain (D1)	Unspecified functional abdominal pain (D2)	Faecal incontinence (F1)

42. Okumus M, Parpucu H, Kocaoglu S, Ceceli E, Borman P, Duranay M. The frequency of fibromyalgia syndrome and the quality of life in patients with peritoneal dialysis. Open J Rheumatol Autoimmune Dis. 2011;63(10 Suppl. 1).
43. Silverman SL, Backonja M, Pau[illegible] J, B[illegible] P, Scavone JM, et al. Effect of baseline characteristics on the pain response to pregabalin in fibromyalgia patients with comorbid depression. Pain Medicine. 2018;19(3):419-28.
44. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol. 2014;6:71-80.
45. Hobby GP, Karaduta O, Dusio GF, Singh M, Zybailov BL, Arthur JM. Chronic kidney disease and the gut microbiome. Am J Physiol Renal Physiol 2019;316(6):F1211-F7.
46. Hustoft TN, Hausken T, Ystad SO, Valeur J, Brokstad K, Hatlebakk JG, et al. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterol Motil. 2017;29(4):1-9.
47. Varju P, Farkas N, Hegyi P, Garami A, Szabo I, Illes A, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet improves symptoms in adults suffering from irritable bowel syndrome (IBS) compared to standard IBS diet: A meta-analysis of clinical studies. PLoS One. 2017;12(8):e0182942.
48. Rossi A, Bellini M, Ricciardi A, Marchi S, Talarico S, Mosca M, et al. A low fermentable oligo-di-monosaccharides and polyols diet improves symptoms without affecting body composition and extracellular body water in fibromyalgic patients with irritable bowel syndrome. XVII Med Congr Rheumatol. Abstract-2: Clinical and Experimental Rheumatology; 2018. p. S59.
49. Sloan TJ, Jalanka J, Major GAD, Krishnasamy S, Pritchard S, Abdelrazig S, et al. A low FODMAP diet is associated with changes in the microbiota and reduction in breath hydrogen but not colonic volume in healthy subjects. PLoS One. 2018;13(7):18.
50. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. J Manag Care Pharm. 2013;19(9):755-64.
51. Wang L, Alammar N, Singh R, Nanavati J, Song Y, Chaudhary R, et al. Gut microbial dysbiosis in the irritable bowel syndrome: A systematic review and meta-analysis of case-control studies. J Acad Nutr Diet. 2019;28:28.
52. Garcia-Leiva JM, Carrasco JLO, Slim M, Calandre EP. Celiac symptoms in patients with fibromyalgia: A cross-sectional study. Rheumatol Int. 2015;35(3):561-7.
53. Rios G, Estrada M, Mayor AM, Vila LM. Factors associated with tender point count in Puerto Ricans with fibromyalgia syndrome. P R Health Sci J. 2014;33(3):112-6.
54. Zanetti CB, Domiciano DS. Celiac symptoms in Brazilian patients with fibromyalgia from a tertiary hospital [Conf Abstr]. 35th Brazilian Congr Rheumatol (SBR 2018); Rio de Janeiro. Abstracts: Advances in Rheumatology; 2018.
55. Buchwald D, Goldenberg DL, Sullivan JL, Komaroff AL. The "chronic, active Epstein-Barr virus infection" syndrome and primary fibromyalgia. Arthritis Rheum. 1987;30(10):1132-6.
56. Andrews CN, Storr M. The pathophysiology of chronic constipation. Can J Gastroenterol. 2011;25(Suppl. B):16B-21B.
57. Hwang L, Low K, Khoshini R, Melmed G, Sahakian A, Makhani M, et al. Evaluating breath methane as a diagnostic test for constipation-predominant IBS. Dig Dis Sci. 2010;55(2):398-403.
58. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: Prevalence, symptom patterns and impact. Aliment Pharmacol Ther. 2005;21(11):1365-75.
59. Ghoshal UC, Abraham P, Bhatia SJ, Misra SP, Choudhuri G, Biswas KD, et al. Comparison of Manning, Rome I, II, and III, and Asian diagnostic criteria: Report of the Multicentric Indian Irritable Bowel Syndrome (MIIBS) study. Indian J Gastroenterol. 2013;32(6):369-75.
60. Melli LC, do Carmo-Rodrigues MS, Araujo-Filho HB, Sole D, de Morais MB. Intestinal microbiota and allergic diseases: A systematic review. Allergol Immunopathol (Madr). 2016;44(2):177-88.
61. Talotta R, Atzeni F, Ditto MC, Gerardi MC, Sarzi-Puttini P. The microbiome in connective tissue diseases and vasculitides: An updated narrative review. J Immunol Res. 2017;2017(6836498):1-11.
62. Guo R, Chen L-H, Xing C, Liu T. Pain regulation by gut microbiota: Molecular mechanisms and therapeutic potential. Br J Anaesth. 2019;123(5):637-54.
63. Zhao Y, Chen B, Li S, Yang L, Zhu D, Wang Y, et al. Detection and characterization of bacterial nucleic acids in culture-negative synovial tissue and fluid samples from rheumatoid arthritis or osteoarthritis patients. Sci Rep. 2018;8(1):14305.
64. Dunn C, Velasco C, Rivas A, Andrews M, Jacob P, Jeffries M. Identification of a human cartilage microbial DNA signature and characterization of distinct microbiome profiles associated with osteoarthritis [abstract]. Arthritis Rheumatol. 2018;70(s10).
65. Li Y, Luo W, Deng Z, Lei G. Diet-intestinal microbiota axis in osteoarthritis: A possible role [Review]. Mediat Inflamm. 2016;2016:3495173.
66. Berthelot J-M, Sellam J, Maugars Y, Berenbaum F. Cartilage-gut-microbiome axis: a new paradigm for novel therapeutic opportunities in osteoarthritis [Review]. RMD Open. 2019;5(e001037).
67. Caminer AC, Haberman R, Scher JU. Human microbiome, infections, and rheumatic disease [Review]. Clin Rheumatol. 2017;36(12):2645-53.
68. Tomasello G, Mazzola M, Bosco V, Tomasello G, Damiani P, Sinagra E, et al. Intestinal dysbiosis and hormonal neuroendocrine secretion in the fibromyalgic patient. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2018;162(4):258-62.
69. Duan R, Zhu S, Wang B, Duan L. Alterations of gut microbiota in patients with irritable bowel syndrome based on 16S rRNA-targeted sequencing: A systematic review. Clin Transl Gastroenterol. 2019;10(2):12.
70. Ohkusa T, Koido S, Nishikawa Y, Sato N. Gut microbiota and chronic constipation: A review and update. Frontiers in Medicine (Lausanne). 2019;6(19):1-9.
71. Minerbi A, Gonzalez E, Brereton NJB, Anjarkouchian A, Dewar K, Fitzcharles MA, et al. Altered microbiome composition in individuals with fibromyalgia. Pain. 2019;18.
72. Pimentel M, Chow EJ, Hallegua D, Wallace D, Lin HC. Small intestinal bacterial overgrowth: A possible association with fibromyalgia. J Musculoskelet Pain. 2001;9(3):107-13.
73. Schumann D, Klose P, Lauche R, Dobos G, Langhorst J, Cramer H. Low fermentable, oligo-, di-, mono-saccharides and polyol diet in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. Nutrition. 2018;45.
74. Murray K, Wilkinson-Smith V, Hoad C, Costigan C, Cox E, Lam C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. Am J Gastroenterol. 2014;109:110-9.
75. Silva AR, Bernardo A, Costa J, Cardoso A, Santos P, de Mesquita MF, et al. Dietary interventions in fibromyalgia: A systematic review. Ann Med. 2019;51:S2-S14.
76. Wilder-Smith CH, Olesen SS, Materna A, Drewes AM. Fermentable sugar ingestion, gas production, and gastrointestinal and central nervous system symptoms in patients with functional disorders. Gastroenterol. 2018;155(4):1034-44.e6.
77. Huang Y, Jia L, Liu Y. The relationships between hydrogen gas and methane gas and the symptoms of irritable bowel syndrome as determined by a breath test. Int J Clin Exp Med. 2019;12(6):7356-64.
78. Hod K, Ringel Y, van Tilburg MAL, Ringel-Kulka T. Bloating in irritable bowel syndrome is associated with symptoms severity, psychological factors, and comorbidities. Dig Dis Sci. 2019;64(5):1288-95.

79. Cole JA, Rothman KJ, Cabral HJ, Zhang Y, Farraye FA. Migraine, fibromyalgia, and depression among people with IBS: A prevalence study. BMC Gastroenterol. 2006;6(26).

Author	IBS (C1)	Alternating constipation & diarrhoea (C*)	Bloating (or "gas") (C2)	Constipation (C3)	Diarrhoea (C4)	Abdominal pain (D1)	Unspecified functional abdominal pain (D2)	Faecal incontinence (F1)

Figures

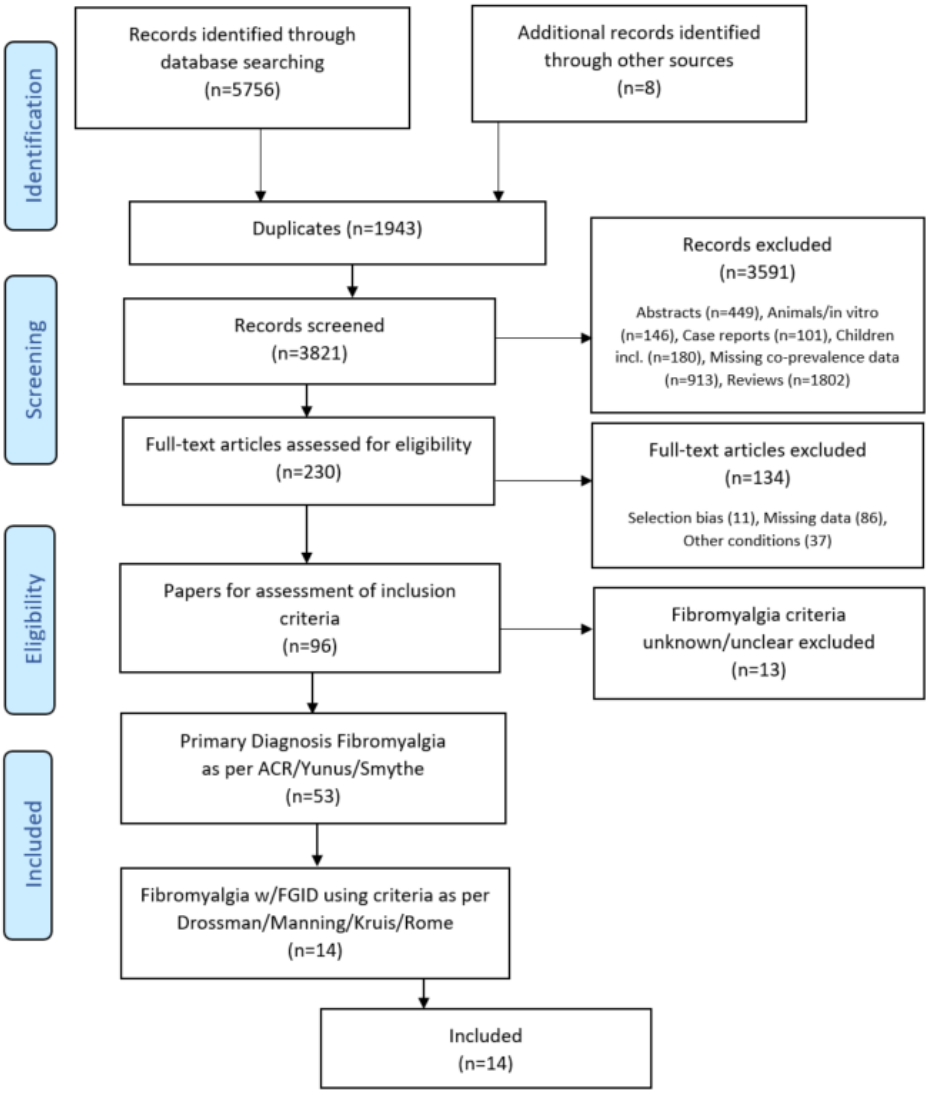

Figure 1

PRISMA Flow Diagram Showing Study Selection Process

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Erdrichetal2020FMSFGIDAppendixB.docx
- Erdrichetal2020FMSFGIDAppendixA.docx
- Erdrichetal2020PRISMAchecklist.docx