

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

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## Abstract

**Background:** Fibromyalgia and functional gastrointestinal disorders (FGID) including irritable bowel syndrome (IBS) are common conditions presenting in clinical settings and are more prevalent in women. While the relationship between IBS and fibromyalgia has been demonstrated, a review of the prevalence of the broader group of FGID in adults with fibromyalgia has not been undertaken. The aim of this review was to systematically review the published literature, identifying the comorbidity of FGID in people with fibromyalgia, and to discuss the clinical implications, limitations of current research and areas of interest for future research. **Methods:** Medline, Embase, CINAHL and Web of Science were searched during June 2019. Results were screened for original research articles meeting established criteria for identification of FGID in adults diagnosed with fibromyalgia.

**Results:** A total of 14 studies involving 1340 adults with fibromyalgia, 363 healthy controls and 441 adults with other pathologies were included in this review. Only 1 of the 14 studies included surveyed the full range of FGID. Functional gut disorders were matched to Rome II criteria for reporting and comparison. In addition to increased abdominal pain and functional bloating or gas, IBS of mixed-pattern and constipation-types appear to be more prevalent than diarrhoea-predominant IBS in adults with fibromyalgia.

**Conclusion:** This review confirms previous reports that IBS is common in people living with fibromyalgia and suggests that IBS-mixed and constipation types predominate. An association with a range of FGID other than IBS is suggested, but data are limited. Research exploring the association between fibromyalgia and functional gastrointestinal dysfunction beyond IBS are warranted.

**Keywords:** comorbidity, diagnostic criteria, FGID, fibromyalgia, functional gastrointestinal disorders, IBS, irritable bowel syndrome, women's health

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## Background

Both functional gastrointestinal disorders (FGID) and fibromyalgia are poorly understood syndromes significantly impacting quality of life and contributing to high levels of work absenteeism.<sup>1</sup> The two conditions are associated with increased visits to physicians and impose a substantial financial burden,<sup>2–4</sup> with healthcare-associated costs reaching up to quadruple that of a reference population.<sup>5</sup>

The FGID were defined in 1989 as ‘a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. This may include syndromes attributed to the oesophagus, stomach, biliary tree, small or large intestines, or anus’.<sup>6</sup> Both fibromyalgia and FGID are more commonly identified in women, with fibromyalgia estimated to affect 3.98% (95% CI: 2.8–5.2) of women and 0.01 (95% CI: 0.04–0.06) of men.<sup>7</sup>

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With few exceptions, the broad range of FGID are more prevalent in women,<sup>2,8</sup> with medically diagnosed IBS affecting approximately four times as many women as men.<sup>9</sup>

It is thought that both fibromyalgia and FGID are attributable to sympathetic dysfunction with resultant central sensitisation.<sup>10,11</sup> Both conditions were recently categorised as ‘Central Sensitivity Syndromes’.<sup>12,13</sup> While a common etiology has been proposed,<sup>14</sup> there is currently no compelling evidence to support a targeted intervention.

Fibromyalgia accounts for about 15% of all referrals to rheumatology clinics and has a global prevalence of around 2% with wide variation (0.2–6.6%) depending on the country and assessment tool used.<sup>7,15–17</sup> Reports consistently concur a higher prevalence for females – up to 10-fold that of males.<sup>7,16,18,19</sup> The higher prevalence rates in women have been contested as being driven primarily by selection bias and that rates in men and women are possibly quite similar.<sup>15</sup>

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, as well as digestive disorders, including IBS.<sup>20</sup>

It is estimated that about 50% of all digestive disorders presented in primary and secondary care are functional in nature,<sup>21</sup> with IBS being the most common FGID diagnosed.<sup>22</sup> The high comorbidity of IBS with other somatic disorders including fibromyalgia has previously been established,<sup>23</sup> but results of co-prevalence studies vary greatly. Triadafilopoulos *et al.* reported that 73% of patients with fibromyalgia had altered bowel patterns.<sup>24</sup> Lubrano and colleagues, using Rome Foundation criteria for IBS and ACR 1990 for fibromyalgia, reported fibromyalgia in 20% of patients with IBS ( $n=130$ ).<sup>25</sup> 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, suggesting a bi-directional relationship.<sup>23</sup> A recent systematic review by Heidari *et al.* calculated the prevalence of fibromyalgia in those with IBS at 12.9% (95% CI 12.70–13.10).<sup>7</sup> These variations in prevalence reports are likely associated with the heterogeneous study designs, 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.

Other disorders not typically related to IBS, such as functional nausea, vomiting and belching, are also commonly reported in patients with fibromyalgia.<sup>26</sup> While the relationship between IBS and fibromyalgia has been demonstrated, a review of the prevalence of the broader group of the FGID in adults with fibromyalgia has not been undertaken.

This paper presents a systematic review of the published literature reporting the relationship between the spectrum of FGID and fibromyalgia in adults. Clinical implications, limitations and areas for future research, are discussed.

## Methods

To identify literature relevant to the research question: ‘What is the prevalence of any of the FGID in adults with fibromyalgia?’, 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.

For inclusion, the following criteria were applied: published in English, available as full-text article, reported the prevalence of any FGID in subjects with fibromyalgia, included adults ( $\geq 18$  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. If no response was obtained, that specific paper was removed from the analysis. For inclusion, fibromyalgia diagnosis based on specifications as outlined by Yunus (1985)<sup>27</sup> Smythe (1985)<sup>28</sup> or American College of Rheumatology (ACR) criteria (1990<sup>29</sup>, 2010<sup>30</sup> or 2011<sup>31</sup>) were required. Studies detailing a diagnosis of FGID based on Manning,<sup>32</sup> Drossman,<sup>33</sup> Kruis<sup>34</sup> or any of the Rome criteria (Table 1) were retained.

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.

**Table 1.** Comparative classifications of irritable bowel syndrome.

<b>Manning<sup>32</sup></b>	<b>Drossman<sup>33</sup></b>	<b>Rome I<sup>35</sup></b>	<b>Rome II<sup>36</sup></b>	<b>Rome III<sup>37</sup></b>	<b>Rome IV<sup>38</sup></b>
Two or more of:	A. Irregular or varying bowel pattern > 25% of the time	A minimum 3 months of: Continuous or recurrent abdominal pain;	Minimum 12 weeks out of the previous 12 months	Minimum 3 of previous 6 months:	Minimum of last 3 months, onset at least 6 months before diagnosis:
- Abdominal distension	- Relieved by passing stool or	Abdominal discomfort or pain plus 2 of the following:	- Relieved by passing stool	- Improvement with defaecation	- Related to defaecation
- Pain improved with passing stool	- Associated with change in frequency or consistency of stool	AND at least 3 of: (for at least 25% of days)	- Onset associated with a change in frequency of stool	- Onset associated with change in stool frequency	- Associated with a change in stool frequency
- Frequent stool, with onset of pain	- Pain relieved by bowel movement	- Altered stool frequency	- Onset associated with a change in form (appearance) of stool.	- Onset associated with a change in form (appearance) of stool	- Associated with a change in stool form (appearance)
- Looser stool, with onset of pain	- Loose stools associated with the pain	- Altered stool form	Supportive symptoms include:	Supportive symptoms as for Rome II	
- Passing mucous	- More frequent stools associated with the pain	- Altered stool passage (straining, urgency, sense of incomplete evacuation)	- Abnormal stool frequency (>3/day and < 3/week);		
- Sensation of incomplete evacuation	- Abdominal distension	- Bloating or feeling of abdominal distension	- Abnormal stool form (lumpy/hard or loose/watery stool);		
	- Mucous in the stool	- Sense of incomplete evacuation	- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)		
	- Sense of incomplete evacuation	- Straining at the stools > 25% of the time OR	- Passage of mucous		
	- Two or fewer stools per week	- Diarrhoea:	- Bloating or feeling of abdominal distension		
	- Loose or watery stools > 25% of the time, or	- More than 21 stools per week			

**Table 2.** Summary of 14 Studies reporting FGID in fibromyalgia.

Author (Year)	Country	Fibromyalgia cases		Controls	Diagnostic criteria		Quality score
		n = (% female)	AGE mean SD (range)		FMS	FGID	
Triadafilopoulos (1991) <sup>24</sup>	US	123 (921.9)	47 (24–64)	46 NC, 54 DJD	ACR1990	Drossman*	83%
Veale (1991) <sup>44</sup>	Ireland	20 (75)	(33–36)	20 NC, 20 IBD, 20 IA	Smythe	Manning	83%
Sivri (1996) <sup>45</sup>	Turkey	75 (87)	36.3 ± 11	50 NC	ACR1990	Drossman*	83%
Sperber (1999) <sup>42</sup>	Israel	100 (100)	48.6 ± 10.8 – ± 14.9	0	ACR1990	Rome I	92%
Yunus (2000) <sup>43</sup>	US	♀469 (100)	46.3 ± 13.2	0	ACR1990	Manning	79%
		♂67 (0)	47.1 ± 13.3	36 NC			
Choudhury (2001) <sup>46</sup>	Bangladesh	30 (90)	28.6 ± 10	30 NC, 30 RA	ACR1990	Manning	75%
Pace (2001) <sup>47</sup>	Italy	27 (92.6)	51(25–73)	25 NC, 32 IBS	ACR1990	Rome I	83%
Pimentel (2004) <sup>48</sup>	US	42 (86)	46.6 ± 0.3	15 NC, 111 IBS	ACR1990	Rome I	92%
Kurland (2006) <sup>49</sup>	US	105 (93)	52.9 ± 11.3	62 OR	ACR1990	Rome II*	92%
Zoppi (2008) <sup>50</sup>	Italy	67 (97)	55.6 ± 11.01	0	ACR1990	Rome II	50%
Almansa (2009) <sup>51</sup>	Spain	100 (93)	50.5 ± 9.6	100 NC	ACR1990	Rome II*	92%
Akkaya (2011) <sup>40</sup>	Turkey	65 (100)	36.21 ± 7.42	41 NC	ACR1990	Rome Ia	92%
Okumus (2011) <sup>52</sup>	Turkey	12 (54.8)	40.1 ± 4.4	112 PD	ACR1990	Rome II	75%
Marum (2017) <sup>41</sup>	Portugal	38 (100)	51 (>18)	0	ACR2011	Rome III* <sup>a</sup>	88%
Total		1340 (90.7)		NC 363, Other 441			

<sup>a</sup>Information provided by email.

\*Separated IBS sub-types.

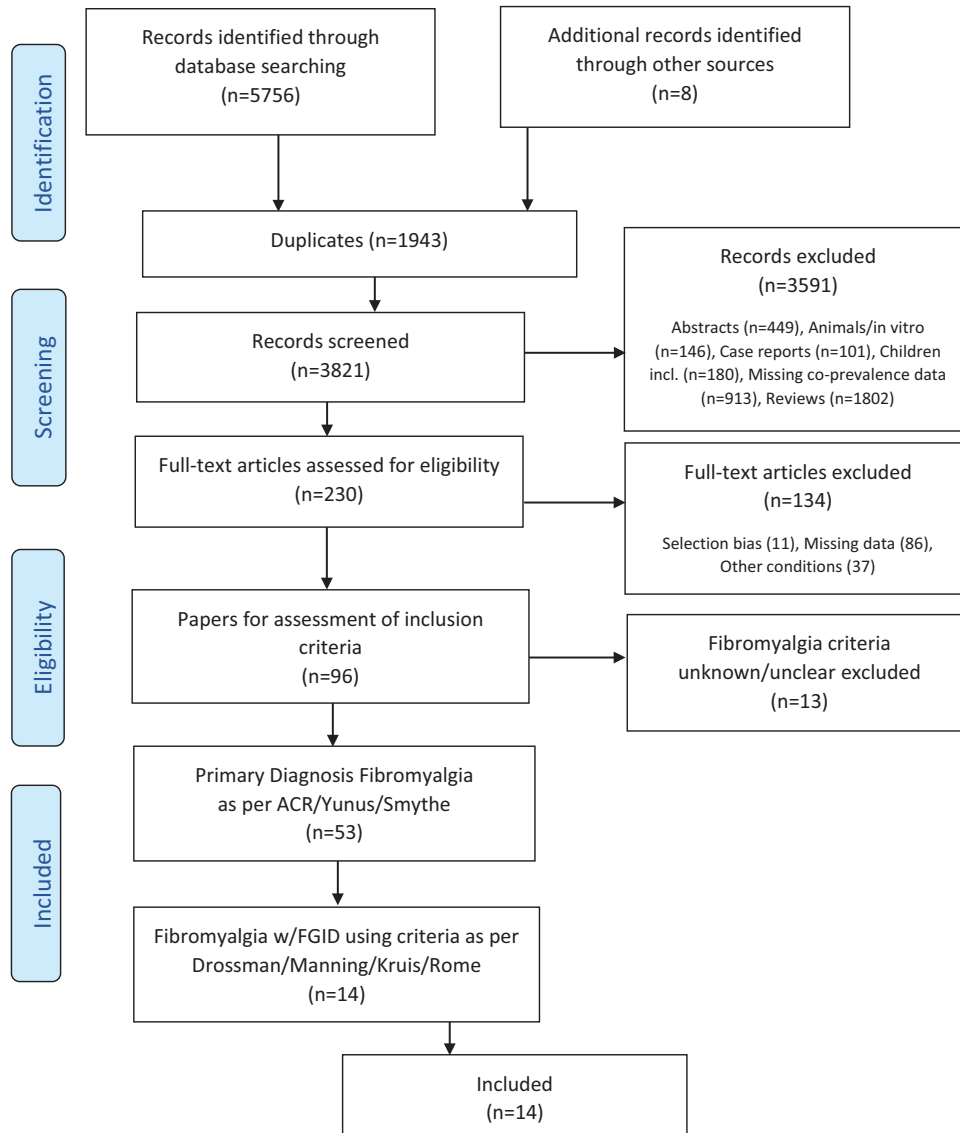
ACR, American College of Rheumatology; DJD, degenerative joint disease; FGID, functional gastrointestinal disorders; FMS, fibromyalgia; IA, inflammatory arthritis; IBD, inflammatory bowel disease; NC, normal controls; OR, other rheumatic diseases; PD, peritoneal dialysis; RA, rheumatoid arthritis; SD, standard deviation; US, United States.

As we set out to evaluate correlations reported in epidemiological data rather than results of clinical trials and their validity, the *Joanna Briggs Critical Appraisal Checklist for Studies Reporting Prevalence Data* was used to assess all included papers.<sup>39</sup> This was carried out independently by two authors (SE and JEH), and any disagreements were resolved by consensus. Average scores were calculated as percentages and are shown in Table 2. This systematic review was registered with PROSPERO (Reg no: CRD42019139878).

## Results

The search retrieved 5765 records. A diagrammatic representation of the selection process is shown in Figure 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 14 studies reported data on 1340 subjects with fibromyalgia. Of these 14 studies, 12 employed the ACR 1990 criteria (Table 2), representing 96% of the



**Figure 1.** PRISMA flow diagram showing study selection process.

ACR, American College of Rheumatology; FGID, functional gastrointestinal disorders; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

total fibromyalgia cohort in this systematic review. Nine used a healthy control population ( $n = 363$ ). Other comparison populations variously comprised other rheumatological conditions ( $n = 166$ ), IBS or inflammatory bowel disease (IBD) ( $n = 162$ ) and other control subjects with a range of pathologies ( $n = 112$ ). The mean age ranged from 28.6–55.6 years, [standard deviation (SD)  $\pm 0.3$  to  $\pm 14.9$ ].

Three studies exclusively included women,<sup>40–42</sup> one provided age data for males and females separately and is reflected accordingly in Table 2.<sup>43</sup> The

pooled population across all studies was 90.7% female, which decreases marginally to 89.1% when female-only studies are removed. Table 2 outlines key information from the included studies.

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% to 95%, and all except one<sup>41</sup> 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

**Table 3.** Summary of FGID types and prevalence reported in 14 included studies.

Author	FGID Type (Rome II)	Fibromyalgia		Normal controls		Other controls	
		FGID %	IBS%	IBS %	p value	IBS %	p value
Triadafilopoulos <sup>24</sup>	C1, C2, C3, C4, D1	74.0	60.0	0	nr	DJD 13	nr
Veale <sup>44</sup>	C1	70.0	70.0	10	nr	IBD 5	nr
						IA 15	nr
Sivri <sup>45</sup>	C1, C*, C2, C3, C4, D1	41.8	41.8	16	<0.05	-	-
Sperber <sup>42</sup>	C1	32.0	32.0	-	-	-	-
Yunus <sup>43</sup>	C1	♀38.9	38.9	0	<0.03	-	-
		♂13.8	13.8	-	-	-	-
Choudhury <sup>46</sup>	C1	30.0	30.0	7	0.02	RA 3	< 0.02
Pace <sup>47</sup>	C1	66.7	66.7	0	nr	-	-
Pimentel <sup>48</sup>	C1	52.4	52.4	nr	-	-	-
Kurland <sup>49</sup>	C1, C*, C3, C4	81.0	81.0	-	-	OR 24	<0.001
Zoppi <sup>50</sup>	C1	14.9	14.9	-	-	-	-
Almansa <sup>51</sup>	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 <sup>40</sup>	C1	61.5	61.5	nr	-	-	-
Okumus <sup>52</sup>	C1	16.7	16.7	-	-	PD 7	0.25
Marum <sup>41</sup>	C1, C*, C3, C4	95.0	95.0	-	-	-	-
Pooled data		50.8	46.2	4.9		11.7	

A1, Globus; A2, Rumination syndrome; A3, Fx chest pain; A4, Fx heartburn; A5, Fx dysphagia; B1, Fx dyspepsia; B2, Aerophagia; B3, Fx vomiting; C\*, Alternating constipation and diarrhoea; C1, IBS; C2, Fx bloating; C3, Fx constipation; C4, Fx diarrhoea; D1, abdominal pain; D2, unspecified functional pain; DJD, degenerative joint disease; E1, gallbladder dysfunction; E2, sphincter of Oddi dysfunction; F1, Fx incontinence; F2a, levator ani syndrome; F2b, proctalgia fugax; F3, pelvic floor dysfunction; FGID, functional gastrointestinal disorder; Fx, functional; IA, inflammatory arthritis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NC, normal controls; nr, not reported; OR, other rheumatic diseases; PD, peritoneal dialysis; RA, rheumatoid arthritis.

of FGID in subjects of 50.8%, and 46.2% for IBS. It should be noted that 11 of the 14 studies reported only IBS, hence FGID and IBS prevalence in these does not differ. Sivri *et al.* reported abdominal pain in 38.2% of those with fibromyalgia.<sup>45</sup> No data are provided that confirm whether these are independent of, or included in, any other group.

One study set out to examine the prevalence of the range of FGIDs in fibromyalgia,<sup>51</sup> five focused on IBS.<sup>24,42,44,45,49</sup> In four studies,<sup>41,43,46,50</sup> IBS was recorded as part of a bigger research question, and in the remaining four

studies IBS data was reported as a secondary not primary outcome measure.<sup>40,47,48,52</sup> Four studies included additional cohorts of patients with IBS<sup>42,44,47,48</sup>; 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 and chronic kidney failure.<sup>44,52</sup> 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.* was selected based on absence of both fibromyalgia and IBS.<sup>48</sup> Yunus *et al.* did not include a female control group as their purpose was comparing fibromyalgia in men and women<sup>42</sup>; a small group of male controls were included, for whom data was not compared with females.

While all studies reported IBS, further detail allowing separation of IBS sub-types was reported by five.<sup>24,41,45,49,51</sup> Three studies compared prevalence of sub-types of IBS with that of normal controls<sup>24,45,51</sup>; these are detailed in Table 4.

Almansa *et al.* reported at least one FGID in 98% of patients and 39% of controls.<sup>51</sup> 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 with 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.* presented in Tables 3 and 4 above is extracted from data presented in Table 2 of their report.<sup>24</sup> 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 is for those with IBS-alternating/mixed (IBS-M) by Rome II criteria.

None of the included studies provided detail regarding coexistence of more than one FGID in subjects. For example, Almansa's group reported functional constipation in 15% of subjects,<sup>51</sup> 39% had IBS, and while at least one FGID was found in 98% of subjects, data on comorbidity of multiple FGIDs are 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

**Table 4.** Prevalence of sub-types of FGID in fibromyalgia and healthy controls from five studies (%).

Author	IBS (C1)		Alternating constipation and 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 <sup>24</sup>	60.0	0	62.6	0	59.0	13.0	12.0	13.0	9.0	2.0 <sup>a</sup>	54.0	4.0	-	-	-	-
Sivri <sup>45</sup>	41.8	16.0	41.8	20.0	45.5	-	30.7	8.0	7.0	1.0	38.2	8.0	-	-	-	-
Kurland <sup>49</sup>	81.0	-	61.0	-	-	-	15.2	-	4.8	-	-	-	-	-	-	-
Almansa <sup>51</sup>	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 <sup>41</sup>	95.0	-	22.2	-	-	-	69.4	-	8.3	-	-	-	-	-	-	-
FGID average <sup>b</sup>	67.2	-	52.9	-	65.4	21.3	21.3	6.0	6.0	57.1	19.0	56.0	19.0	56.0	56.0	25.0

<sup>a</sup>Estimated from Triadafilopoulos Figure 2 (data not provided).

<sup>b</sup>Calculated from studies reporting that FGID.

FGID, functional gastrointestinal disorder; FMS, fibromyalgia patients; NC, normal controls.

subjects with fibromyalgia and, therefore, the true comorbidity, remains undetermined.

The odds ratio (OR) of fibromyalgia in subjects with IBS is 1.8 and some of the earliest studies examining associations between fibromyalgia and IBS revealed a strong bidirectional relationship.<sup>42,44</sup> This was confirmed in Whitehead's 2002 systematic review, with 32.5% (range 28–65%) of IBS patients having fibromyalgia, and 48% of patients with fibromyalgia having IBS (range 32–77%).<sup>23</sup> The overall prevalence of IBS in people with fibromyalgia identified in our review is 46.2%, closely aligning with Whitehead findings, and is about four times the 12.9% [95% confidence interval (CI) 12.7–13.1] co-prevalence reported in the 2017 meta-analysis by Heidari *et al.*, and the 11% estimated global prevalence of IBS.<sup>7,54</sup> The variation in reported prevalence identified in our results ranged from 13% to 95%, which is somewhat broader than Whitehead's 28–65%.<sup>23</sup> Inclusion criteria for fibromyalgia in Heidari's report were less stringent than ours and the prevalence they determined ranged from 0.71% to 4.82%, depending on the diagnostic tool used.<sup>7</sup>

Some of the earliest studies examining associations between fibromyalgia and IBS revealed a strong bidirectional relationship.<sup>42,44</sup> 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 systematic review,<sup>23</sup> and is about four times the 12.9% co-prevalence reported by Heidari *et al.* and the 11% estimated global prevalence of IBS.<sup>7,54</sup> The variation in reported prevalence identified in our results ranged from 13% to 95%, which is somewhat broader than Whitehead's 28% to 65%.<sup>23</sup>

Of the 14 studies in our analysis, 2 reported fibromyalgia-FGID comorbidity rates of less than 20%. Okumus *et al.* investigated IBS in patients with end-stage renal disease (ESRD),<sup>52</sup> and found that 16.7% of patients with both ESRD and fibromyalgia had IBS, compared with 7.1% of those with ESRD but without fibromyalgia. Given the known alterations to the gut microbiome in patients with renal disease,<sup>55</sup> 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 reported. Zoppi *et al.* acknowledged that the 14.9% IBS rate in their cohort was the

only condition occurring at lower rates than either the general population or other fibromyalgia studies at that time.<sup>50</sup> A control group was not included and there is insufficient information provided in their report to inform further discussion.

Our review included research in which data on the presence of any 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, only one provided detailed FGID data. Generally, investigators tended to regard IBS as a single entity, rather than a condition with several subtypes, a shortcoming which has been reported previously.<sup>56</sup> This lack of differentiation limits a more comprehensive interpretation of results in the current era where an altered microbiome has been identified in patients with IBS,<sup>57</sup> is considered to play a role in FGIDs,<sup>58</sup> and where the role the human gut microbiota on gastrointestinal functions (such as gas production and dynamics, bloating and motility) is evolving.

The five studies that provided details beyond the generic classification of IBS (Table 4), reported that IBS-M was the most common subtype, 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%),<sup>59</sup> 55.5% (double the rate of diarrhoea) by Rios' group and 56.5% in Zanetti's cohort.<sup>60,61</sup> Conversely, Buchwald *et al.* reported diarrhoea in 62% of their fibromyalgia cohort and provided no information regarding constipation or alternating bowel habit.<sup>62</sup> Constipation is estimated to occur in 12–19% of the general population and, where not secondary to other conditions, may be associated with dehydration and other dietary and lifestyle factors as well as medications.<sup>63</sup> Technically, these and primary causes should be ruled out before a diagnosis of IBS-C is made, but this is not consistent amongst clinicians.<sup>59</sup> Also associated with an increase in methanogenic bacteria, IBS-C may be predictable by methane gas production as measured in human breath, with 91.7% sensitivity and 81.3% specificity.<sup>64</sup> Pimentel *et al.* conducted hydrogen-methane testing in subjects with fibromyalgia but did not report either methane levels or IBS sub-types.<sup>48</sup>



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,<sup>61</sup> although in their report a 'functional' classification was not specified. Bloating is associated with bacterial degradation of fermentable compounds and increased hydrogen and methane gas production.<sup>65–67</sup> 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 with bloating compared with those with IBS without bloating.<sup>68</sup> The significant correlation between peak breath hydrogen production and fibromyalgia pain ( $p<0.01$ ) as described in Pimentel's study,<sup>48</sup> irrespective of IBS status, also suggests that an altered microbiome may play an important role in fibromyalgia.

Marum *et al.* 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.<sup>41</sup> Hence, a selection bias towards patients with gastrointestinal symptoms undoubtedly underlies the high rate of IBS (95%) reported. The cohort was small ( $n=38$ ) and removal of this study from our analysis reduced the overall prevalence of IBS from 46.2% to 44.8% and IBS-constipation (IBS-C) from 21.3% to 17.1%. A significant reduction in a range of symptoms and disease scores related to both fibromyalgia and IBS was noted after 4 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,<sup>69,70</sup> including in subjects with fibromyalgia.<sup>71</sup> While lowering the intake of fermentable foods is known to alter gut bacterial populations,<sup>72</sup> the effect of such a diet on global symptoms of fibromyalgia is unexplored as yet.

IBS and functional dyspepsia are the most common FGIDs, with prevalence ranging from 5.3 to 20.4%.<sup>8</sup> Researchers sometimes include dyspepsia under the category of gastro-oesophageal reflux disease (GERD).<sup>73</sup> As GERD can be secondary to organic disease, including infection and as a side effect of medication, we excluded cases of GERD or dyspepsia where the aetiology was unclear. While we screened papers that reported dyspepsia, reflux and

GERD, only one study reported appropriately defined functional dyspepsia, and found it occurred in people with fibromyalgia at seven times the rate of controls.<sup>51</sup>

A survey evaluating the relationship between body mass index (BMI) and functional dyspepsia, IBS, functional constipation and functional diarrhoea in over 35,000 subjects found that 10.4% had more than one FGID: for example, those presenting with functional dyspepsia also presented with IBS (23.5%) and functional constipation (15.1%).<sup>74</sup> While a significant limitation of that study is the exclusion of the broader range of FGIDs, it nevertheless serves to highlight the possibility of missing coexisting FGIDs. The authors did not report mixed-pattern IBS, yet the higher rates of IBS and functional constipation in women mirrors our finding in those with fibromyalgia – also primarily women. Functional dyspepsia was also more prevalent in women 4.5% compared with 2.0% in men ( $p<0.001$ ).<sup>74</sup>

Three controlled studies reporting the prevalence of IBS in fibromyalgics included control subjects with other musculoskeletal pathologies.<sup>44,46,49</sup> Both healthy controls and those with rheumatoid arthritis (RA) had low rates of IBS in Choudhury's small study ( $n=30$  in each group),<sup>46</sup> using the Manning criteria. These criteria report a much higher rate of IBS diagnosis compared with the Rome II criteria<sup>9,75</sup> (see Table 1). Kurland's control group comprised patients with a range of conditions, including RA, osteoarthritis and systemic lupus erythematosus (SLE), in whom the overall prevalence of IBS was 24%.<sup>49</sup> This is higher than the estimated prevalence in the United States (US) of 14.1%,<sup>9</sup> suggesting a possible gut-musculoskeletal relationship. SLE is an autoimmune condition more common in women and also associated with a higher incidence of IBS; where this was the case, subjects were more likely to have fibromyalgia (OR 2.87, 95% CI 1.11–7.43,  $p=0.02$ ).<sup>76</sup> There were four comparison groups in Veale's study: IBD, inflammatory arthritis (IA), normal controls (NC) and a group with IBS for bidirectional comparison.<sup>44</sup> 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. . . six had IBS'. The latter matches data in their Figure 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%.

Evidence suggests that the gut bacterial community may be altered in IBS,<sup>77</sup> constipation and fibromyalgia.<sup>58,78–80</sup> Increasingly, research reports indicate an important role of the gastrointestinal milieu in health and a wide range of conditions, from chronic kidney disease to allergies and diseases of connective tissue and in fibromyalgia.<sup>55,79–82</sup>

The identification of commensal gut bacteria at sub-infective levels in synovial fluid and joint cartilage in people with arthritis adds credence to what currently is a hypothetical gut microbiota-musculoskeletal interaction.<sup>83–85</sup> While we did not seek to explore FGIDs in other musculoskeletal conditions, these groups are often used in comparison with fibromyalgia. Our review found higher rates of IBS in subjects with other musculoskeletal conditions compared with healthy controls, further supporting an interaction between the gut microbiota and the musculoskeletal system.<sup>86,87</sup>

Sperber *et al.* reported that fibromyalgics with IBS had worse symptoms of pain, fatigue and morning tiredness compared with those without IBS.<sup>42</sup> This is consistent with other reports linking aggravation of digestive symptoms during periods of exacerbations of fibromyalgia.<sup>24</sup> Iovino *et al.* demonstrated that patients with mild IBS were invariably negative for fibromyalgia,<sup>88</sup> whereas moderate-to-severe symptoms of IBS were associated significantly with fibromyalgia. Lubrano *et al.* also found a significant association between fibromyalgia and the severity of IBS symptoms ( $p=0.002$ ),<sup>25</sup> supporting the notion that by-products associated with a dysbiotic gut environment may be drivers of exacerbations in actual pain, or pain perception. However, measurements of markers of gut-derived inflammation, such as calprotectin, lipopolysaccharide (LPS), intestinal fatty acid binding protein (iFABP), monocyte chemo-attractant protein-1 (MCP-1) and co-receptor soluble cluster of differentiation (sCD) have failed to demonstrate a relationship between these markers and the severity of symptoms associated with IBS or musculoskeletal pain.<sup>89</sup>

Recent advances have also expanded understanding of the possible role of the gut ecological environment on pain signalling and peripheral sensitisation,<sup>90</sup> with data suggesting a relationship between chronic pain and the intestinal microbiome exists in CRPS,<sup>80,91</sup> endometriosis,<sup>92</sup> interstitial cystitis,<sup>93</sup> restless leg syndrome (RLS) and migraine.<sup>94,95</sup>

An altered microbiota in patients with fibromyalgia is further supported by pain reduction subsequent to antibiotic treatment and following Marum's dietary intervention.<sup>41,96</sup> While a low FODMAP diet may improve IBS symptoms associated with changes to the gut microbiome and intestinal gas production,<sup>65,69,97</sup> the effect on fibromyalgia symptoms had not been investigated previously. Other dietary interventions that have been studied in fibromyalgia are also associated with clinical improvements,<sup>98</sup> which may be due to diet-driven alterations in gut microbial populations.

The ever-expanding research exploring the gut-brain axis has emerged as a possible candidate for unexplained pain syndromes.<sup>99</sup> Recent advances in understanding this axis and the intricate interplay of various hormones, chemokines, neurotransmitters and gut-derived metabolites are gaining traction,<sup>100</sup> including in fibromyalgia research.<sup>101,102</sup> As the technology enabling isolation and identification of not only organisms that previously eluded detection, but their metabolic processes and by-products evolves, so too does the understanding of the possible role these might play in extra-gastrointestinal pathologies with elusive aetiologies.

A proposed explanation for the pain in fibromyalgia is sensitisation of the central nervous system,<sup>18</sup> but an underlying mechanism remains elusive. Neuropathic pain syndrome is associated with pain, insomnia and fatigue as well as hyperalgesia. Women with fibromyalgia tend to present with higher rates of these symptoms compared with healthy controls ( $p<0.001$ ).<sup>103</sup> Other conditions associated with central sensitisation and sympathetic nervous system predominance include temporomandibular disorder, IBS, dyspepsia, RLS, chronic pelvic pain, interstitial cystitis, headache, migraine, chronic fatigue syndrome and vulvodynia all of which present at higher rates in women, and commonly coexist with other conditions from within the same classification.<sup>11,53,104–109</sup> The interplay of genetics and epigenetics relevant to each syndrome adds an additional layer of complexity to the determination of factors that may form a basis for comorbidity.<sup>8,110</sup>

Our search terms were crafted to capture the spectrum of FGIDs, yet results did not identify any co-prevalence data capturing the range until 2009,<sup>51</sup> with the exception of functional abdominal pain in two papers (1991 and 1996).<sup>24,45</sup> This

may reflect the emergence of the first detailed guideline for identification and classification of the FGIDs in 1990 and highlights a significant gap in the research.<sup>35</sup>

The large variance in the prevalence of FGID in our studies may be explained – at least in part – by changes in the understanding of functional gut disorders over time and the various diagnostic criteria employed. The timespan 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 Rome II criteria in a population survey resulting in lower rates of IBS than Rome I,<sup>9</sup> although Kurland *et al.* found the opposite to be true in fibromyalgia.<sup>49</sup>

The earliest diagnostic criteria for fibromyalgia employed by the included studies was that proposed by Smythe ( $n=1$ ), and 12 of the 14 studies utilised the ACR 1990 criteria, based on widespread pain and the determination of at least 11 of 18 specific tender points.<sup>111</sup> Just one paper used ACR 2011, which was a modification of the 2010 criteria, and more suited for use in survey-based screening. These criteria and the modification are detailed in Wolfe.<sup>112</sup>

Including studies employing established diagnostic criteria for both fibromyalgia and FGID is a strength of this review, and the rigour of our process ensures minimal likelihood of non-fibromyalgia groups being captured. For purposes of analysis, we utilised Rome II criteria as 9 of the 14 studies employed pre-Rome II tools, 4 used Rome II, 1 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.<sup>35</sup>

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 analgesics), which we were unable to determine.

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.* using Drossman’s criteria (Table 1),<sup>33</sup> pooled the data for altered bowel patterns to arrive at an overall prevalence of IBS of 41.8%,<sup>45</sup> which is the same as their figure for alternating pattern, but less than the reported rate of bloating of 45.5%.

Our data is strongly representative of females with fibromyalgia even when all-female cohorts were excluded from the analysis. This may not necessarily reflect a true epidemiological disparity; the possibility of gender-bias in fibromyalgia and FGID sample populations is a consideration that has been discussed in a review by Houghton *et al.*<sup>113</sup> Additionally, epidemiological data from community-dwelling subjects in Europe indicates the prevalence in women is just double that of men,<sup>16</sup> suggesting women are more likely to seek healthcare for their condition.

Approximately 70% of people with IBS do not seek medical input for their gastrointestinal complaint and up to 13% of a population may have undiagnosed fibromyalgia, exposing an opportunity to evaluate the coexistence of these disorders in patients presenting to primary or secondary practice, possibly with coexisting disorders associated with heightened pain sensitivity.<sup>16,54</sup> 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 the potential to contribute to disease modification of both conditions.

## Conclusion

This review confirms previous reports that IBS is common in people living with fibromyalgia and demonstrates that this appears to be predominantly mixed and constipation types. However, a significant gap exists in the research regarding the relationship with other FGIDs. Indications that reductions in gastrointestinal symptoms correlate 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 evaluating the full range of FGIDs in subjects with fibromyalgia using established criteria for both conditions should include adequate detail related to confounders such as medication use, diet and lifestyle. A comprehensive examination of the FGID-gut ecology relationship would provide further insights in this patient population and help elucidate its role in people with both FGID and fibromyalgia.

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### Author 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.

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### Supplemental material

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