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Increased Disease Burden in Irritable Bowel Syndrome With Comorbid Conditions and Psychiatric Diagnoses in a Multinational European Cohort: Results From the DISCOvERIE Project

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ABSTRACT

Background: Patients with Irritable bowel syndrome (IBS) frequently suffer from comorbid psychiatric or somatic conditions, but the association with overall GI symptom severity and disease burden in IBS has not yet been established.

Objective: This pan-European project, the DISCOvERIE project, aimed to characterize IBS patients with and without comorbid psychiatric (anxiety, depression) and/or somatic (fibromyalgia, chronic fatigue syndrome) conditions, and to compare them with disease (psychiatric and/or somatic condition without IBS) and healthy controls to further elucidate the effect of comorbid conditions on the disease burden in IBS.

Methods: Participants from nine different European centers were included: IBS patients (Rome IV criteria) with and without comorbid conditions, disease controls, and healthy controls. The presence of comorbidities was assessed through the Mini International Neuropsychiatric Interview (MINI) for anxiety or depression or through diagnostic criteria for fibromyalgia or

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chronic fatigue syndrome. Validated questionnaires on IBS (IBS-SSS), depressive (PHQ-9), anxiety (GAD-7) and somatic symptom severity (PHQ-12), fibromyalgia symptoms (FIQ) and fatigue (MFI) were completed.

Results: In total, 842 participants were recruited between March 2021 and January 2023, of which 607 had IBS, 161 were disease controls and 74 were healthy controls. IBS, anxiety, depression, somatic symptoms and fatigue were more severe in IBS patients with comorbidities compared with IBS patients without comorbidities. The severity of the abovementioned symptoms all increased gradually with increasing number of comorbidities (all $p < 0.001$).

Conclusion: This large pan-European study highlights the significant impact of psychiatric and somatic comorbidities in IBS, and their strong link with outcomes and disease burden.

1 | Introduction

Irritable bowel syndrome (IBS) is a common and debilitating disorder of gut-brain interaction (DGBI) with a 4% worldwide prevalence. [1] This female predominant disorder is characterized by recurrent abdominal pain related to defecation and/or a change in frequency or form of stool. [2] In addition to IBS, many of the affected patients report psychiatric or somatic comorbid conditions, such as anxiety and/or depression, [3–5] fibromyalgia, [6, 7] and/or chronic fatigue syndrome (CFS). [6] Although the knowledge of the etiology and pathophysiology of IBS has increased through previous research projects, [1, 8, 9] the understanding of the impact of comorbidities remains incompletely understood.

Comorbid psychiatric conditions, such as generalized anxiety disorder and major depressive disorder are some of the most studied and most common comorbidities in IBS. Although common, most studies utilize proxy measures instead of diagnosis to assess the prevalence of these comorbidities. A clinical diagnosis of depression disorder has been previously reported in 6%–23% of IBS patients [5, 10], whereas reports of diagnosed anxiety disorder vary even more, with a range between 4% and 88% of IBS patients. [5, 10, 11] In addition to psychiatric comorbidities, somatic comorbidities such as diagnosed fibromyalgia and CFS also seem to be prevalent among patients with IBS, with diagnosed fibromyalgia ranging from 26% to 65%, [12], whereas diagnosed CFS in IBS shows 14% prevalence. [12].

A few previous studies have evaluated the impact of comorbid diagnosed conditions on overall symptom severity and disease burden in IBS, showing a greater GI symptom burden in IBS with psychiatric disorders [13, 14] or fibromyalgia. [7] Studies on symptom severity in IBS with CFS or both psychiatric and somatic comorbidities are lacking to the best of our knowledge. The scarcity of studies of this large patient group is notable, despite the large societal and economic burden of both IBS and its common comorbidities, and reveals a need for a well-sized study assessing this common and complex patient group.

Therefore, the aim of this pan-European study was to characterize IBS patients with and without psychiatric and/or somatic comorbidities in comparison with disease (psychiatric, somatic) and healthy controls to further elucidate the effect of comorbidities and psychiatric diagnoses in IBS on overall severity of symptoms and disease burden.

2 | Material and Methods

2.1 | Study Population and Setting

We recruited study participants prospectively at nine European centers in eight different countries as part of the Horizon 2020 project DISCOvERIE (Table S1). The overall goal of this EU-funded project was to provide an enhanced understanding of IBS and its comorbidities' etiologies, mechanisms and risk factors. The study cohort consisted of IBS patients with a diagnosis of IBS based on the Rome IV criteria [15] and with and without diagnosed comorbid psychiatric (anxiety disorder (DSM-V), hereafter called anxiety, [16] and/or depression disorder (DSM-V), hereafter called depression [16]) and/or somatic (fibromyalgia (ACR 2010) [17] and/or CFS (IOM/SEID 2015) [18]) comorbidities. In addition, we included disease controls with diagnosed comorbid diseases (psychiatric, somatic) but without IBS, and healthy controls without the abovementioned disorders. The targeted group sizes, planned for prespecified analyses in the overall research project, were: IBS without comorbidity, $n = 200$; IBS with one comorbidity (psychiatric *or* somatic), $n = 200$; IBS with two comorbidities (psychiatric *and* somatic), $n = 200$; disease control with psychiatric condition, $n = 50$; disease control with somatic condition, $n = 50$; disease control with psychiatric *and* somatic condition, $n = 50$; and healthy controls, $n = 50$. Recruitment was made at regular clinic visits, through adverts or from lists of previous study participants. Only participants fulfilling the inclusion and exclusion criteria (Table 1) were included.

At the inclusion visit, the participants provided oral and written informed consent for study participation. They were thoroughly characterized by a physician, specially trained nurse or researcher through a clinical interview with a case report form assessing demographics and clinical characteristics. In addition, current diagnostic criteria were used during the structured diagnostic interview to confirm the diagnoses of IBS, [15] anxiety disorders, [16] depressive disorders, [16] fibromyalgia [17] and CFS. [18] A depression diagnosis used for inclusion or to define which group a patient with IBS belonged to included current and recurrent depressive episodes and the presence of the disorder during the last 12 months [16] An anxiety diagnosis used for inclusion or to define which group a patient with IBS belonged to included generalized anxiety disorder, panic disorder, agoraphobia or social anxiety disorder. After the clinical interview, participants completed validated questionnaires as specified below. The collected data was saved in a study-specific multilingual digital platform, CASTOR. Before the study start,

Key Summary

- Summarise the established knowledge on this subject?
  - IBS often presents with comorbid conditions, but the effect of these conditions on the overall disease burden is not well elucidated.
- What are the significant and/or new findings of this study?
  - In this study, we characterize and compare IBS with and without anxiety disorder, depression disorder, fibromyalgia and/or chronic fatigue syndrome to disease and healthy controls.
  - The symptom burden of gastrointestinal and non-gastrointestinal symptoms is more severe in IBS with comorbidities compared with IBS without comorbidities.
  - Furthermore, the symptom burden increases gradually with increasing number of comorbidities as well as with the number of psychiatric diagnoses in IBS.

local ethical authorities in all the participating countries approved the protocol. In addition to the phenotypic characterization at the baseline visit presented in this manuscript, biological samples were collected (blood, urine, feces, colonic biopsies), other investigations were performed, and one- and 2-year follow-ups were executed. This will be reported in subsequent publications from this pan-European project.

2.2 | Data Collection

The following questionnaires and interview-based assessments were used for the analyses in this study.

The bowel module of the Rome IV diagnostic questionnaire was used to determine the presence of symptoms corresponding to IBS according to the Rome IV criteria [15]. IBS subtypes were defined based on this questionnaire, dividing the IBS patients into IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS unclassified (IBS-U). [2].

The IBS Severity Scoring System (IBS-SSS) consists of five questions on IBS symptoms: abdominal pain frequency and severity, bloating severity, bowel habit dissatisfaction and overall life interference, with a total score range of 0–500. [19] *The Patient Health Questionnaire-12 (PHQ-12)* determines the severity of 12 somatic non-GI symptoms (0–2) during the last 4 weeks, with a score range of 0–24. [20] *The Generalized Anxiety Disorder 7-Item Scale (GAD-7)* measures the severity of anxiety symptoms over the last 2 weeks through seven questions with a score range of 0–21. [21] *The Patient Health Questionnaire-9 (PHQ-9)* measures the severity of depressive symptoms during the last 2 weeks with a score range of 0–27. [22] *The Multidimensional Fatigue Inventory (MFI)* evaluates the severity of fatigue through a 20-item scale divided into five domains: general fatigue, physical fatigue, reduced motivation, reduced activity and mental fatigue, with score ranges of 0–20 for each domain. [23] *The Fibromyalgia Impact Questionnaire (FIQ)* measures the severity of fibromyalgia symptoms through 10 items, where the first item consists of 10 questions, with each item having a maximum score of 10, and the total maximum score is 100. [24] For all these questionnaires, higher scores indicate more severe symptoms.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
18 years or older	Organic gastrointestinal disease
For IBS patients: IBS according to Rome IV criteria	Severe diseases that could interfere with study evaluations, such as neurological disease, severe heart disease, malignancy or kidney disease
For disease controls: Diagnosis of anxiety, depression, fibromyalgia and/or chronic fatigue syndrome	Severe psychiatric diseases (other than anxiety or depression) that require additional psychopharmacotherapy or psychiatric intervention involving day-care/inpatient treatment, such as bipolar disorder or schizophrenia.
For healthy controls: No disorder as specified in the other groups above	Drug or alcohol abuse the last 6 months prior to the screening visit
	Antibiotics used within 3 months prior to the screening visit
	Gastrointestinal infection during the last month prior to the screening visit
	Pregnancy or lactation
	Symptoms indicative of other severe diseases, such as GI bleeding, weight loss, or fever
	Clinically relevant abnormal test results on screening laboratory tests
	Symptoms compatible with a cold, influenza, or having a positive test of Covid-19 the last 14 days prior to screening visit

The Brief Trauma Questionnaire (BTQ) is a self-report questionnaire assessing a history of traumatic and life-threatening situations/injuries as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Criterion A.1. [25] For this study, the presence of either a traumatic or a life-threatening situation/injury defined a history of trauma.

The *Mini International Neuropsychiatric Interview* (MINI) is a structured diagnostic interview for the most common disorders in

mental health according to DSM-5 and ICD-10. [16] For this study, MINI was used with permission as a diagnostic tool for the presence of anxiety and depressive disorders as well as other psychiatric diagnoses. However, it should be noted that one of the exclusion criteria for this project was having severe psychiatric diseases other than anxiety or depressive disorders (Table 1).

2.3 | Statistical Analysis

All statistical analyses were performed in *R* version 4.3.3 or SPSS version 24. Demographic and clinical characteristic data were presented as median with interquartile range or number and proportion (%), as appropriate. Mann-Whitney U tests or Kruskal-Wallis tests with Dunn's test and Benjamini-Hochberg false discovery rate (FDR) correction for multiple comparisons were used for between-group comparisons of continuous data. Comparisons between categorical data were performed using Chi-square tests or Fisher's tests with FDR correction for multiple comparisons. One-way ANOVA with linear trend analyses was executed to discover potential linear trends between the number of comorbidities or psychiatric diagnoses and symptom severity measures in IBS. A p-value of < 0.05, after adjustment for multiple comparisons when appropriate, was considered statistically significant for all comparisons. Missing individual items in the questionnaires were replaced with the mean item scores of the questionnaire when less than half of the items were missing.

3 | Results

3.1 | Participants

This multi-national study included 842 participants between March 2021 and January 2023. The cohort consisted of 607 IBS patients (IBS without comorbidities ($n = 267$); IBS with one comorbidity ($n = 218$); IBS with two comorbidities ($n = 122$)); 161 disease controls (with one disorder ($n = 108$); with two disorders ($n = 53$)) and 74 healthy controls. Overall characteristics and symptom severity in the three main groups are displayed in Table 2 and Table S2. The IBS, disease controls and healthy control groups were all female predominant and the disease control group had the highest mean age. The reported severity of IBS, anxiety, depression and somatic symptoms were different between the groups, with the highest severity of IBS symptoms, as expected, among IBS patients, but with more severe anxiety, depression, and somatic symptoms among disease controls. No differences in the rates of appendectomy or cholecystectomy were seen between IBS, disease controls or healthy controls. Adherence to lactose free and FODMAP (fermentable oligo-, di-, and monosaccharides and polyols) diets, avoidance of certain foods, and use of probiotics were most commonly reported among IBS patients, whereas a diet high in fiber was most common in disease controls. Food allergy was more frequently reported by the patient groups, whereas a previous COVID-19 infection was more common among healthy controls. Inability to work was almost exclusively seen among IBS patients and disease controls. Alcohol consumption was most common, and the use of medication was least common, among healthy controls compared with IBS and disease controls.

3.2 | Characteristics of Groups With and Without Comorbidities

Overall characteristics and symptom severities in the groups divided by presence of comorbid conditions are displayed in Table 3. Statistical comparisons were made between IBS with and without psychiatric and/or somatic comorbidity, disease controls with psychiatric and/or somatic disorders and healthy controls, as well as among the IBS groups. In general, the female predominance was most pronounced in the IBS groups, and in particular in the groups with comorbidities, and the mean age was lower among healthy controls compared with IBS and disease control groups. IBS symptom severity was higher in IBS patients with comorbidities compared to IBS without comorbidities. In general, congruent findings in the different groups regarding severity of fatigue, fibromyalgia symptoms, overall somatic symptoms, anxiety and depression were demonstrated, with the highest severity in the groups with the respective comorbidity/morbidity (fatigue, fibromyalgia, anxiety and depression), and in the groups with more than one comorbidity. An overlap between anxiety, depression, fibromyalgia and CFS was common among IBS patients (Figure 1). The proportion of diagnosed anxiety, depression, fibromyalgia and CFS did not differ among IBS subtypes (all $p > 0.05$), but IBS-C and IBS-M reported the most severe IBS symptoms, followed by IBS-D, whereas IBS-U had the mildest IBS symptoms (IBS-SSS 270 [200–350], 270 [202–340], 241 [179–299], and 183 [133–270], respectively; $p < 0.001$).

3.3 | Psychiatric Diagnoses in IBS

The most common psychiatric diagnoses in IBS and disease controls were depression (consisting of current and recurrent depressive episode and disorder) (30% and 46%, respectively), generalized anxiety disorder (28% and 41%, respectively), and panic disorder (12% and 21%, respectively) (Table S3). A small number (5%) of healthy controls fulfilled the criteria for one psychiatric disorder (MINI), although none had received a diagnosis from a physician or were treated for this condition. In IBS, 303 patients (52%) had no psychiatric diagnoses, 149 (25%) had 1 diagnosis, 90 (15%) had 2 diagnoses and 45 (8%) had three or more psychiatric diagnoses. The most common combination of psychiatric diagnoses in IBS was generalized anxiety disorder and depression (25%) (Figure 2).

3.4 | Association Between Comorbidities and Symptom Severity in IBS

The severity of IBS symptoms, depressive, anxiety, and somatic symptoms, fibromyalgia symptoms, and symptoms of fatigue all increased gradually in a linear fashion with increasing number of comorbidities in IBS (Figure 3). These symptom severities also increased in a similar and linear fashion with increasing number of psychiatric diagnoses according to the MINI interview (Figure 4). The strongest linear trends were found between increasing number of comorbidities and severity of fibromyalgia, depressive, and anxiety symptoms (partial η^2 0.364, 0.286 and 0.284, respectively, all $p < 0.001$), and between increasing

TABLE 2 | Demographic, symptom severity, and disease-related information.

	IBS ($N = 607$)	Disease controls ($N = 161$)	Healthy controls ($N = 74$)	p value
Age	44 [31–56]	50 [34–59]	33 [24–47]	$< 0.001^{abc}$
Female sex	485 (80%)	114 (71%)	44 (59%)	$< 0.001^{ab}$
BMI (kg/m^2)	24.2 [21.1–27.4]	26.4 [23.4–31.3]	22.6 [20.7–24.9]	$< 0.001^{abc}$
IBS subtype (IBS-C/IBS-D/IBS-M/IBS-U)	170/200/162/29 (30%/36%/29%/5%)	NA	NA	
IBS-SSS	252 [190–327]	110 [77–183]	5 [0–33]	$< 0.001^{abc}$
GAD-7	5 [2–9]	8 [5–12]	1 [0–3]	$< 0.001^{abc}$
PHQ-9	7 [3–11]	10 [7–16]	1 [0–3]	$< 0.001^{abc}$
PHQ-12	7 [4–11]	10 [7–13]	2 [1–3]	$< 0.001^{abc}$
FIQ	23 [10–43]	44 [30–59]	3 [0–10]	$< 0.001^{abc}$
BTQ*	237 (42%)	95 (62%)	20 (29%)	$< 0.001^{abc}$
MFI general fatigue	14 [10–18]	16 [14–19]	8 [5–10]	$< 0.001^{abc}$
MFI physical fatigue	13 [10–14]	13 [12–15]	10 [8–12]	$< 0.001^{abc}$
MFI reduced activity	12 [10–14]	13 [11–14]	9 [8–11]	$< 0.001^{abc}$
MFI reduced motivation	10 [7–13]	11 [9–14]	6 [4–8]	$< 0.001^{abc}$
MFI mental fatigue	12 [8–16]	14 [10–16]	7 [5–11]	$< 0.001^{abc}$
Alcohol	255 (45%)	71 (44%)	51 (75%)	$< 0.001^{bc}$
Smoking	98 (17%)	42 (26%)	15 (22%)	0.03^{a}
Diet: Gluten free	68 (11%)	11 (7%)	5 (7%)	0.19
Diet: Vegetarian	29 (5%)	7 (4%)	5 (7%)	0.61
Diet: Vegan	10 (2%)	3 (2%)	2 (3%)	0.56
Diet: Lactose free	140 (23%)	19 (12%)	3 (4%)	$< 0.001^{ab}$
Diet: LCHF	7 (1%)	6 (4%)	0 (0%)	0.06
Diet: High fiber	7 (1%)	15 (9%)	1 (1%)	$< 0.001^{ac}$
Diet: FODMAP	61 (10%)	4 (2%)	0 (0%)	$< 0.001^{ab}$
Diet: Other	40 (7%)	21 (13%)	4 (6%)	0.03^{a}
Diet: no special diet	344 (57%)	104 (65%)	52 (76%)	0.003^{b}
Dietary restrictions due to IBS symptoms	289 (52%)	NA	NA	
Avoidance of certain food products	406 (71%)	68 (42%)	23 (34%)	$< 0.001^{ab}$
Avoidance helps IBS symptoms	351 (88%)	NA	NA	
Probiotics usage y/n	127 (22%)	18 (11%)	4 (6%)	$< 0.001^{ab}$

Note: The table presents medians with interquartile range or number with percentage in IBS patients, disease controls and healthy controls. Chi squared tests or Kruskal-Wallis test analyzed differences between groups, and Dunn's tests were used post-hoc with FDR correction for correction of multiple comparisons in continuous data, and FDR correction after Chi squared tests for count data.

* Proportion with either a traumatic or a life-threatening situation/injury as described in BTQ. a: $p < 0.05$ between IBS and disease controls. b: $p < 0.05$ between IBS and healthy controls. c: $p < 0.05$ between disease controls and healthy controls.

Abbreviations: BMI: Body mass index; BTQ: Brief Trauma Questionnaire; FIQ: Fibromyalgia Impact Questionnaire, FODMAP: Fermentable oligo-, di-, monosaccharides and polyols, GAD-7: Generalized Anxiety Disorder 7 item; IBS-SSS: IBS Severity Scoring System, LCHF: Low Carb High Fat, MFI: Multidimensional Fatigue Inventory, NA: Not applicable, PHQ-9: Patient Health Questionnaire 9 items; PHQ-12: Patient Health Questionnaire 12 items.

number of psychiatric diagnoses and severity of anxiety and depressive symptoms (partial η^2 0.213 and 0.191, respectively, $p < 0.001$ for both). Furthermore, a history of trauma in IBS was associated with more severe overall symptoms, except for IBS symptoms, with the strongest effect for anxiety ($r = -0.252$) (Table S4).

4 | Discussion

In this pan-European study, we have demonstrated that the disease burden of GI and non-GI symptoms is more severe in IBS patients with psychiatric and/or somatic comorbid conditions compared with IBS patients without these comorbidities.

TABLE 3 | Characteristics of all study groups.

	IBS alone ($N = 267$)	IBS + psychiatric comorbidity ($N = 169$)	IBS + somatic comorbidity ($N = 49$)	IBS + psychiatric & somatic comorbidity ($N = 122$)	*p* value IBS groups	Disease control psychiatric ($N = 57$)	Disease control somatic ($N = 51$)	Disease control psychiatric & somatic ($N = 53$)	Healthy controls ($N = 74$)	*p* value all groups
Female sex	199 (75%)	139 (83%)	42 (86%)	105 (86%)	0.04	38 (67%)	40 (78%)	36 (68%)	44 (59%)	< 0.001
Age	44 [31–59]	38 [28–53]	51 [43–57]	47 [37–54]	0.007	38 [32–57]	53 [41–61]	53 [40–61]	33 [24–47]	< 0.001
BMI (kg/m^2)	23.6 [21.2–26.9]	24.1 [20.8–27.1]	24.0 [21.8–28.6]	25.1 [22.0–29.7]	0.07	25.4 [22.8–30.7]	27.0 [24.6–32.3]	26.3 [23.7–30.2]	22.6 [20.7–24.9]	< 0.001
IBS subtype (IBS-C/IBS-D/ IBS-M/IBS-U)	77/92/56/18 (32%/38%/ 23%/7%)	46/56/49/7 (29%/ 35%/31%/4%)	11/14/18/2 (24%/31%/ 40%/4%)	36/38/39/2 (31%/ 33%/34%/2%)	0.17					
IBS-SSS	226 [170–298]	257 [185–318]	292 [196–358]	289 [232–382]	< 0.001	100 [72–146]	119 [80–190]	118 [85–201	5 [0–33]	< 0.001
GAD-7	3 [0–6]	7 [4–11]	4 [2–7]	10 [7–13]	< 0.001	8 [6–11]	6 [3–9]	11 [7–13]	1 [0–3]	< 0.001
PHQ-9	4 [1–6]	9 [5–13]	8 [6–10]	13 [9–18]	< 0.001	11 [7–16]	9 [5–11]	12 [8–17]	1 [0–3]	< 0.001
PHQ-12	5 [3–8]	7 [4–10]	10 [8–13]	11 [9–15]	< 0.001	7 [5–10]	11 [9–13]	12 [9–15]	2 [1–3]	< 0.001
FIQ	12 [3–23]	24 [13–39]	45 [30–62]	50 [39–70]	< 0.001	31 [18–41]	52 [40–62]	52 [36–70]	3 [0–10]	< 0.001
BTQ*	81 (33%)	62 (39%)	23 (50%)	71 (62%)	0.002	29 (55%)	28 (57%)	38 (73%)	20 (29%)	< 0.001
MFI general fatigue	11 [7–15]	14 [10–17]	17 [15–19]	18 [16–20]	< 0.001	15 [12–18]	17 [16–19]	18 [15–20]	8 [5–10]	< 0.001
MFI physical fatigue	11 [9–13]	13 [11–14]	15 [13–16]	14 [13–16]	< 0.001	12 [10–13]	14 [13–15]	14 [12–16]	10 [8–12]	< 0.001
MFI reduced activity	10 [9–12]	12 [11–14]	13 [12–14]	14 [13–16]	< 0.001	12 [10–14]	13 [11–14]	14 [12–15]	9 [8–11]	< 0.001
MFI reduced motivation	8 [5–10]	11 [8–14]	11 [9–13]	13 [11–16]	< 0.001	11 [8–14]	10 [8–13]	12 [10–15]	6 [4–8]	< 0.001
MFI mental fatigue	8 [5–12]	13 [9–16]	13 [9–16]	16 [13–18]	< 0.001	13 [10–16]	13 [10–16]	15 [13–17]	7 [5–11]	< 0.001

Note: The table presents medians with interquartile range or number with percentage in the study groups. Chi squared tests/Fisher's test or Kruskal-Wallis test analyzed differences between groups.
* Proportion with either a traumatic or a life-threatening situation/injury as described in BTQ.
Abbreviations: BMI: Body mass index, BTQ: Brief Trauma Questionnaire, FIQ: Fibromyalgia Impact Questionnaire, GAD-7: Generalized Anxiety Disorder 7 item, IBS-SSS: IBS Severity Scoring System, MFI: Multidimensional Fatigue Inventory, PHQ-9: Patient Health Questionnaire 9 items; PHQ-12: Patient Health Questionnaire 12 items.

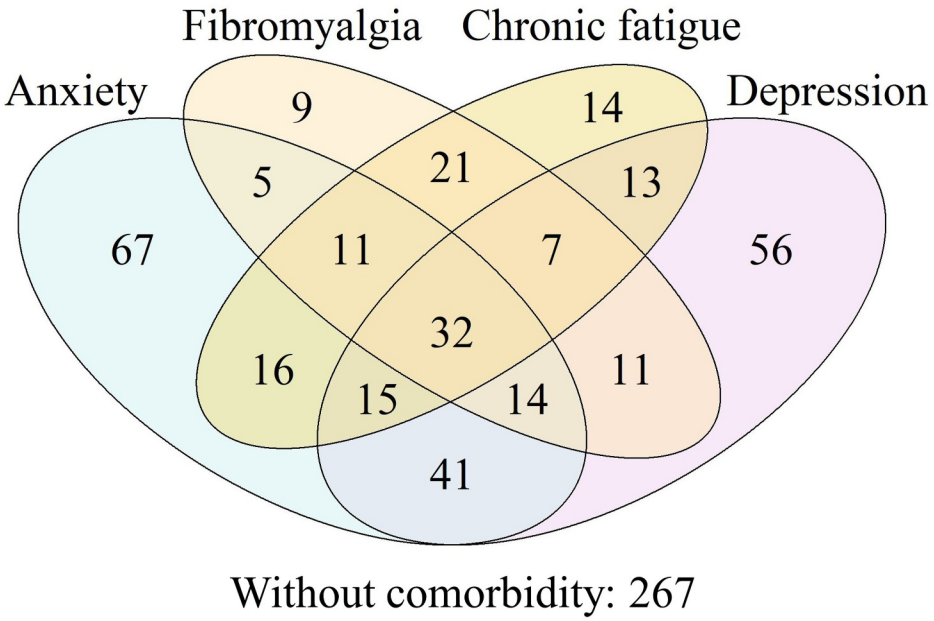

FIGURE 1 | Combinations of comorbidities in IBS patients. The number of IBS patients with specific combinations of comorbidities is presented in the figure. In addition to the IBS patients presented in the figure, eight had incomplete data and were excluded from the analysis.

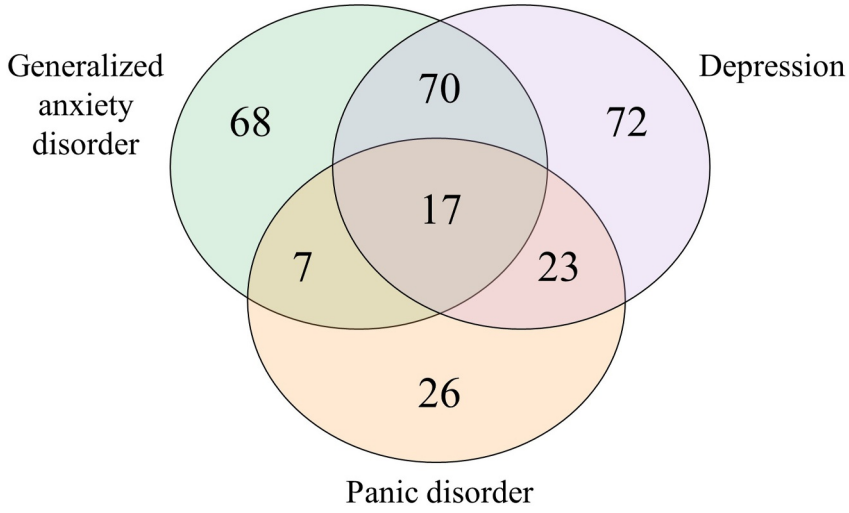

FIGURE 2 | Combinations of the most common psychiatric (MINI) diagnoses in IBS patients. The number of IBS patients with specific combinations of psychiatric diagnoses according to the MINI interview is presented in the figure. Depression is here specified as fulfilling criteria for either current or recurrent major depressive episodes. MINI: Mini International Neuropsychiatric Interview.

The severity of symptoms cumulatively increased with increasing number of comorbidities or psychiatric diagnoses among IBS patients. This clearly highlights the importance of these comorbid conditions for the overall disease burden in IBS.

In this pan-European study, the focus was on assessing GI and non-GI symptoms as well as other disease related factors in IBS patients with or without psychiatric and/or somatic comorbidities. As expected, IBS patients with comorbidities were found to have a higher GI and non-GI symptom burden. This is in line with previous literature, where more severe symptoms were seen in IBS patients with psychiatric comorbidities [13, 14] as well as in IBS patients with concurrent fibromyalgia. [7] Our large, multinational cohort study adds valuable information to the growing body of literature on symptom severity in IBS with diagnosed psychiatric and somatic comorbidities and strengthens the relevance of these in IBS.

As expected, our IBS cohort had a larger number of females than males, consistent with IBS being a female predominant disorder. [2] This is also the case for the comorbid conditions evaluated in this study, that is anxiety, [26] depression, [27] fibromyalgia [28] and CFS. [29] In this study, the even more pronounced female predominance in the IBS groups with psychiatric and/or somatic comorbidities was noteworthy. This pattern has also been reported in previous studies of IBS with psychiatric comorbidities [3–5] and fibromyalgia. [7] The explanation for this is not completely understood, but factors

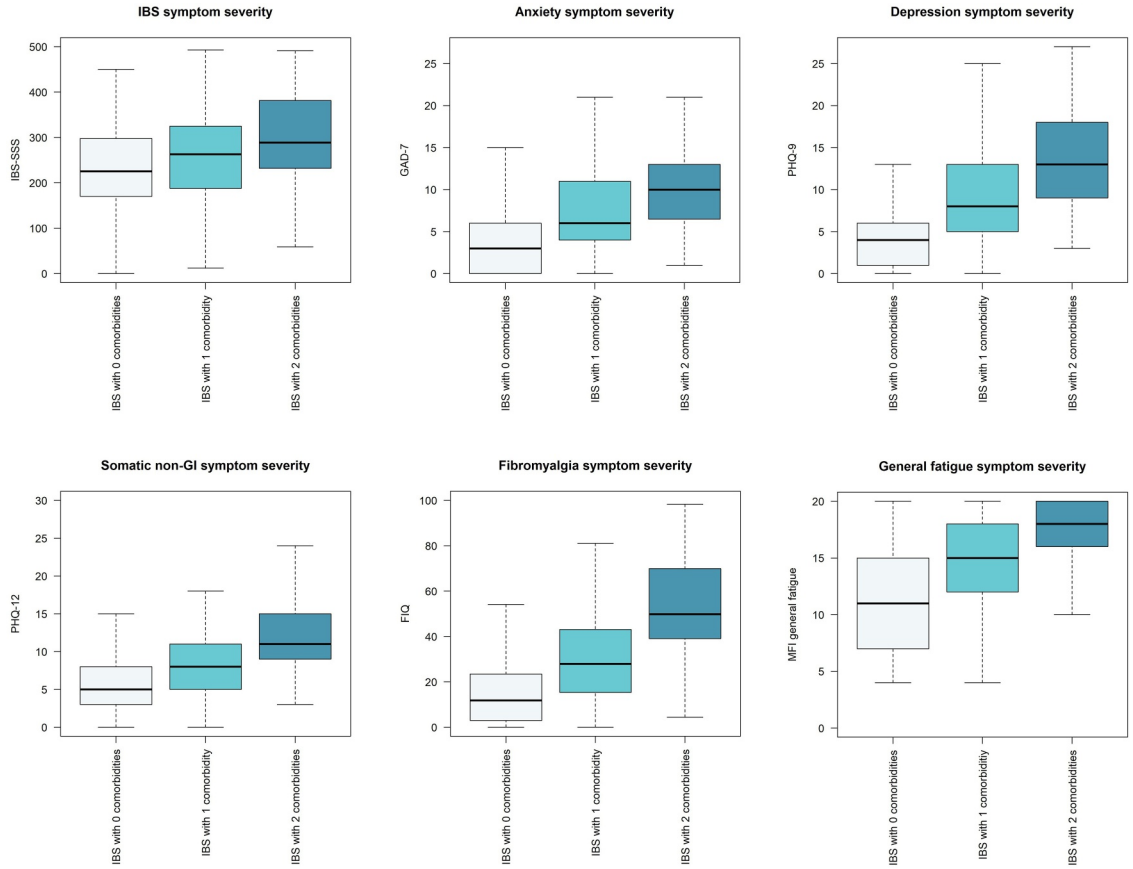

FIGURE 3 | Linear trends in symptom severity with increasing number of comorbidities in IBS patients. One-way ANOVA with linear trend analyses between the number of comorbidities in IBS patients and symptom severity. FIQ: Partial $\eta^2 = 0.286$, $p < 0.001$. GAD-7: Partial $\eta^2 = 0.284$, $p < 0.001$. IBS-SSS: Partial $\eta^2 = 0.034$, $p < 0.001$. MFI general fatigue: Partial $\eta^2 = 0.206$, $p < 0.001$. PHQ-9: Partial $\eta^2 = 0.364$, $p < 0.001$. PHQ-12: Partial $\eta^2 = 0.281$, $p < 0.001$. IBS with 1 comorbidity: IBS with psychiatric (i.e., anxiety and/or depression) or somatic (i.e., fibromyalgia and/or chronic fatigue) comorbidity. IBS with 2 comorbidities: IBS with both psychiatric and somatic comorbidities. FIQ: Fatigue Impact Questionnaire, GAD-7: Generalized Anxiety Disorder 7-item scale, IBS: Irritable Bowel Syndrome, IBS-SSS: IBS Severity Scoring System, MFI: Multidimensional Fatigue Inventory, MINI: Mini International Neuropsychiatric Interview, PHQ-9: Patient Health Questionnaire 9 item scale, PHQ-12: Patient Health Questionnaire 12 item scale.

related to the biological sex of the individual, as well as gender-related factors, etiology of depression and factors linked to our societal structures may all play a role. [30].

In addition, other expected differences across the groups of clinical and societal importance were seen in the present study, which were also in line with the previous literature. Avoidance of individual food items in IBS, as well as adherence to certain restrictive diets, have been previously described [31] and adds to the overall burden of IBS. This is also true for the substantial impact on work life, which was seen both in IBS patients and disease controls. Reduced work productivity and activity in IBS and other DGBI are common and clearly associated with overall symptom severity and disease burden. [32].

The commonness of comorbidities among IBS patients enabled us to study how these are associated with symptoms and disease burden. Anxiety together with depression, fibromyalgia together with CFS, and a combination of all four of the studied comorbidities were the three most common combinations of comorbidities in our IBS cohort. Previous studies have focused on the overlap of IBS and one or two of these comorbidities. [5–7, 10, 13] To the best of our knowledge, our study is the first to assess the overlap and impact of all four common comorbidities in IBS. In addition, by using the MINI to diagnose psychiatric disorders, we were also able to explore the effect of the overlap of these diagnoses in IBS. However, a limitation of this assessment is that severe psychiatric disorders other than anxiety and depression were an exclusion criterion, likely affecting the prevalence of the psychiatric diagnoses identified. However, even with this restriction, there was a substantial presence of and overlap between different psychiatric diagnoses enabling us to study their association with overall symptom burden in IBS.

Importantly, we demonstrated that the symptom severity of anxiety, depressive, somatic and fibromyalgia symptoms increased gradually among IBS patients with both an increasing number of comorbid conditions according to established diagnostic criteria, and with a number of psychiatric diagnoses

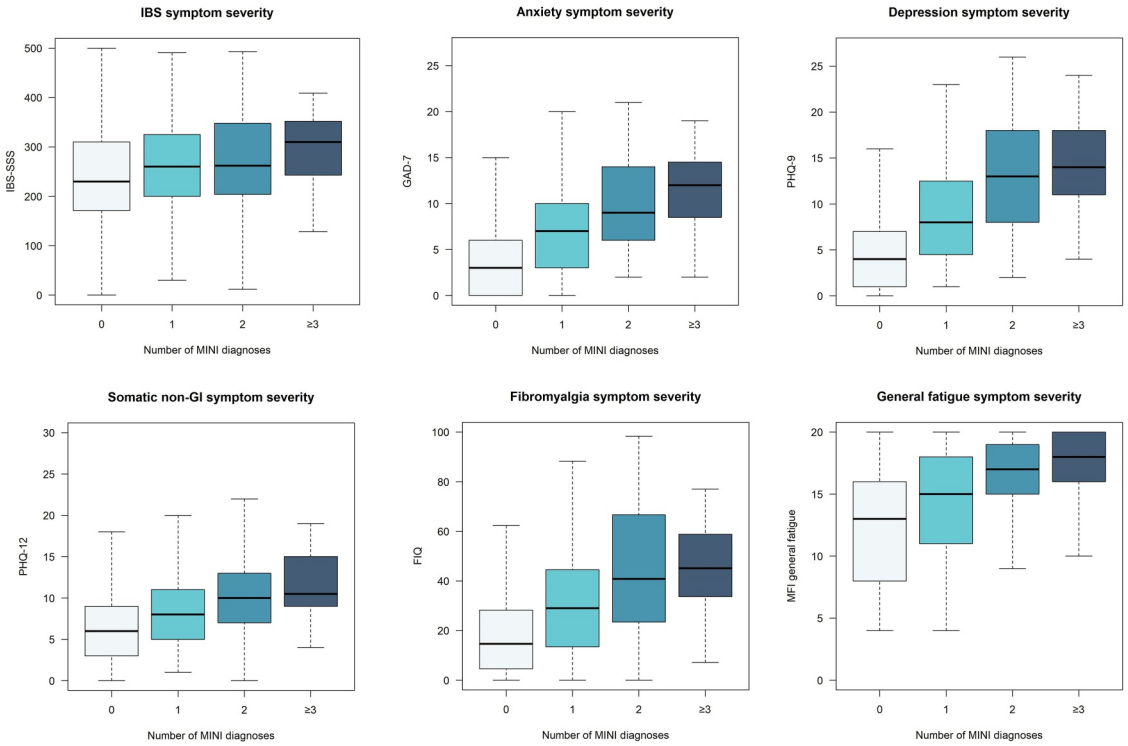

FIGURE 4 | Linear trends in symptom severity with increasing number of psychiatric (MINI) diagnoses in IBS patients. One-way ANOVA with linear trend analyses between the number of psychiatric diagnoses in IBS patients and symptom severity. FIQ: Partial $\eta^2 = 0.114$, $p < 0.001$. GAD-7: Partial $\eta^2 = 0.191$, $p < 0.001$. IBS-SSS: Partial $\eta^2 = 0.019$, $p < 0.001$. MFI general fatigue: Partial $\eta^2 = 0.094$, $p < 0.001$. PHQ-9: Partial $\eta^2 = 0.213$, $p < 0.001$. PHQ-12: Partial $\eta^2 = 0.097$, $p < 0.001$. FIQ: Fatigue Impact Questionnaire, GAD-7: Generalized Anxiety Disorder 7-item scale, IBS: Irritable Bowel Syndrome, IBS-SSS: IBS Severity Scoring System, MFI: Multidimensional Fatigue Inventory, MINI: Mini International Neuropsychiatric Interview, PHQ-9: Patient Health Questionnaire 9 item scale, PHQ-12: Patient Health Questionnaire 12 item scale.

according to a diagnostic interview (MINI). This highlights the interaction among these conditions in determining the overall disease burden in IBS. These findings are expected and in agreement with other studies, which have explored how different factors are associated with symptom severity and quality of life in IBS, including interaction among pathophysiological factors, [33] psychological symptoms, [34] and central sensitization conditions (including psychiatric disorders, functional somatic disorders and chronic pain disorders). [35] Hence, findings from our current and previous studies strongly support a holistic and multidimensional view when managing patients with IBS, since a multitude of factors influence the overall disease burden.

Like all studies, our study has strengths and limitations. One strength was that diagnoses were based on current diagnostic criteria and standardized interviews for psychiatric diagnoses, instead of relying on symptom severity questionnaires. The participants were thoroughly characterized regarding a large number of factors potentially relevant for the disease using validated outcome measures. Furthermore, the inclusion of nine different European centers increases the generalizability of the findings across Europe, but this also came with challenges when applying uniform methodology across sites. This potential problem was overcome through regular online meetings, where consensus was reached on diagnostic uncertainties. A limitation of the study was that it was not population-based, but the group sizes were decided before the study started. Hence, prevalence rates of comorbid conditions in IBS in the general population cannot be obtained from this study. Another limitation was that the COVID-19 pandemic restricted or paused inclusion at the centers at different time periods, prolonging the planned inclusion time.

To conclude, in this large pan-European study, we have demonstrated that comorbid conditions are associated with more severe symptoms and thus more suffering among IBS patients. The findings from this study affirm the need to consider and systematically screen for comorbidities when managing IBS, and to use a multidisciplinary treatment focus for this large and complex group of patients.

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Ethics Statement

The study protocol was elaborated under DISCOvERIE and implemented by 9 recruiting centers by the principles of the ethical guidelines of the revised Declaration of Helsinki after approval by the Medical Ethics Committees at: Hospital Vall d'Hebron (PR(AG)26–2020 A), Goeteborgs Universitet (20–939), Universiteit Maastricht (043–3876009), Semmelweis Egyetem (19461–5/2021/EUIG), Stichting Radboud Universitair Medisch Centrum (2021–1049), Johann Wolfgang Goethe—Universität Frankfurt am Main (20–939), Alma Mater Studiorum—Università di Bologna (632/2020), KU Leuven (B3222021000445, S64753), Universitatea de Medicina Si Farmacie Iuliu (294/15/09/2020). Ethics approval was obtained in all participating centers, including Material and Data Transfer agreements for joint analyses. All study participants received written and oral study information and gave oral and written consent to participate in the study before inclusion.

Conflicts of Interest

Inês A. Trindade receives consultancy fees from Pfizer and speaker fees from the Portuguese Study Group for IBD (GEDII). Hans Törnblom served as a consultant for Cinclus Pharma, Dr Falk GmbH, Galapagos, Medifactia, Mylan, PRO.MED.CS, Purpose Pharma and Vipun Medical. Javier Santos serves/has served as a medical consultant for Noventure, Devintecpharma, Reckitt, Hipra, Ipsen, Viatris, Ordesa and Sequentia and discloses present or past recent scientific collaborations with Ordesa, Salvat, Norgine, Alfa-Sigma, Cosmo, Adare, Pileje, Danone, Farmasierra, Italfarmaco, Venter, Takeda, and Menarini. Beatriz Lobo has past/present scientific collaborations with Alfa-Sigma, Venter, Devintecpharma, GE HealthCare, Schwabe Farma Ibérica and is a consultant/Advisory Board member in Schwabe Farma Ibérica and VenterPharm. Andreas Reif has received honoraria for lectures and/or advisory boards from Janssen/Johnson & Johnson, Boehringer Ingelheim, Compass, GH Research, SAGE/Biogen, LivaNova, Medice, Shire/Takeda, Newron, MSD, AbbVie, cyclerion and received research grants from Medice and Janssen. Mareike Aichholzer received honoraria for scientific advice and travel funds from Janssen and speaker honoraria from UCB Pharma. Lukas Van Oudenhove has served as a consultant and advisory board member and collaborated scientifically with Danone and Nestlé. Giovanni Barbara receives consultancies, business interests or sources of honoraria payments from Aboca, AB Biotics, Agave, Alfa Sigma, AGPharma, Bayer, Biocodex, Boeringer, Bromatech, Cadigroup, Danone, Diadema, Falk Pharma, GE Healthcare, Giuliani, Mayoly, Malesci, Sanofy, Sofar and Yakult. Josep Antoni Ramos-Quiroga was on the speakers' bureau and/or acted as consultant for Biogen, Idorsia, Casen-Recordati, Johnson&Johnson, Novartis, Takeda, Bial, Sincrolab, Neuraxpharm, Novartis, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3 years; received travel fees from Idorsia, Johnson&-Johnson, Rubió, Takeda, Bial and Medice and received unrestricted educational and research support from the following companies in the last 3 years: Exeltis, Idorsia, Casen-Recordati, Takeda, Neuraxpharm, Oryzon, Roche, Probitas and Rubió. István Bitter received speaker or consultancy fees from Gedeon Richter, Janssen/Janssen Cilag/Johnson@&Johnson, KRKA, Lundbeck, Medichem Pharmaceuticals, Mitsubishi Tanabe Pharma Singapore Inc. by Unilab, Medscape and Newron outside of this work in the past 3 years and received royalties from Oxford University Press. Dan Lucian Dumitrascu is a speaker and advisory board member in, and/or receiving grants from: Abbot, Abvie, Alfasigma, Biocodex, ES Vida, Ewopharma, Gilead, Ipsen, Menarini, Merz, Prisum, Sanofi, Terapia, Vedra and Zentiva. Carmen Alonso-Cotoner has past/present scientific collaborations with Alfa-Sigma, Venter, Norgine, Menarini, Noventure, Bioproject, Devintecpharma and is a consultant/Advisory Board member in Alfasigma and VenterPharma. Amanda Rodríguez-Urrutia has served as a consultant for Danone, and she has collaborated scientifically with Janssen-Cilag, Danone, Pileje, Farmasierra, Aboca and Organon. Magnus Simrén receives unrestricted research grants from: BioGaia; is a Consultant/Advisory Board member in Biocodex, Tillotts, BioGaia, Renapharma, and AlfaSigma and is in the Speakers' bureau for Tillotts, Takeda, Biocodex, Sanofi, Abbvie, Janssen Immunology, Pfizer, BioGaia, Renapharma, Mayoly and Bromatech. Irina Midenfjord, Mahrukh Khadija, Elias Sundelin, Danique Mulder, Alejandro Arias Vasquez, Georgy Ruesing, Maaike Van Den Houte, Maria Chiara Matteucci, Michelle Bosman, Daisy Jonkers, Eva Jekkel and Andrei-Vasile Pop declare no conflicts of interest.

Data Availability Statement

Data are available on request from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Table S1: Inclusion at the different study centers. **Table S2**: Additional characteristics of subjects – surgery, work life, allergy. **Table S3**: Psychiatric diagnoses according to the MINI interview. **Table S4**: Symptom severity in IBS patients with and without a history of trauma.