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ORIGINAL ARTICLE

Overlap of Irritable Bowel Syndrome and Functional Dyspepsia in the Clinical Setting: Prevalence and Risk Factors

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Abstract

Background According to Rome IV criteria, functional dyspepsia (FD) and irritable bowel syndrome (IBS) are distinct functional gastrointestinal disorders (FGID); however, overlap of these conditions is common in population-based studies, but clinical data are lacking.

Aims To determine the overlap of FD and IBS in the clinical setting and define risk factors for the overlap of FD/IBS.

Methods A total of 1127 consecutive gastroenterology outpatients of a tertiary center were recruited and symptoms assessed with a standardized validated questionnaire. Patients without evidence for structural or biochemical abnormalities as a cause of symptoms were then categorized based upon the symptom pattern as having FD, IBS or FD/IBS overlap. Additionally, this categorization was compared with the clinical diagnosis documented in the integrated electronic medical records system.

Results A total of 120 patients had a clinical diagnosis of a FGID. Based upon standardized assessment with a questionnaire, 64% of patients had FD/IBS overlap as compared to 23% based upon the routine clinical documentation. In patients with severe IBS or FD symptoms (defined as symptoms affecting quality of life), the likelihood of FD/IBS overlap was substantially increased (OR = 3.1; 95%CI 1.9–5.0) and (OR = 9.0; 95%CI 3.5–22.7), respectively. Thus, symptom severity for IBS- or FD symptoms were significantly higher for patients with FD/IBS overlap as compared to patients with FD or IBS alone (p all < 0.01). Age, gender and IBS-subtype were not associated with overlap.

Conclusion In the clinical setting, overlap of FD and IBS is the norm rather than the exception. FD/IBS overlap is associated with a more severe manifestation of a FGID.

Keywords Functional gastrointestinal disorders · Functional dyspepsia · Irritable bowel syndrome · Symptom severity

Introduction

Functional gastrointestinal disorders (FGIDs) are defined as distinct combinations of chronic or recurrent gastrointestinal symptoms not explained by obvious structural or biochemical abnormalities [1]. Among all FGIDs defined by the Rome Foundation, functional dyspepsia (FD) and irritable bowel syndrome (IBS) are common and the most broadly recognized [2, 3]. IBS and FD each affect roughly 5–20% of the general population, with numbers varying greatly according to diagnostic criteria, study design and geographic regions [4–8]. In population-based studies, overlap is well established, but limited data are available for patients seeking medical attention or being referred to specialists [9]. While overlap syndromes are not specifically mentioned in the Rome criteria (I–IV), they may represent a distinct cohort of patients. Although IBS and FD are both heterogeneous

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diseases, they appear to share similar underlying pathophysiological mechanisms including visceral hypersensitivity and potentially immune dysfunction, dysbiosis and increased mucosal permeability [10–13]. While FGIDs are not associated with a higher mortality rate, FGIDs have a major impact on quality of life, especially in those with greater symptom severity [14–21].

The aims of this study were to (a) determine and compare the overlap of FD and IBS in the clinical setting based upon standardized questionnaire assessment of symptoms and the routine clinical assessment and (b) identify risk factors for the overlap of FD and IBS.

We hypothesized that the overlap of FD and IBS will be seen more frequently when patients are assessed using a standardized questionnaire compared with the current routine clinical assessment and that patients with FD/IBS overlap will be characterized by more severe symptoms.

Materials and Methods

Study Population

Ethics approval for this study was obtained from Metro South Human Research Ethics Committee in Queensland, Australia on January 6, 2015, in accordance with the 1975 Declaration of Helsinki. A total of 1127 consecutive patients presenting to the gastroenterology outpatients clinic of the Princess Alexandra Hospital in Brisbane over a 2-month period were reviewed by staff of the Department of Gastroenterology and Hepatology. Individual written consent was not obtained as completion of the Structured Assessment of Gastrointestinal Symptoms Scale (SAGIS) is part of standard routine clinical practice, and only deidentified data are used for analyses. In total 9 consultants and 5 fellows or advanced trainees provided care for the patients. After 12 months, all available data were reviewed by two investigators. Patients with insufficient follow-up data (e.g. failure to attend any follow-up appointments), organic diseases, co-occurrence of functional and organic gastrointestinal (GI) diseases or patients referred for screening procedures were excluded. Of the 1127 reviewed consecutive patients, 989 had organic disease, were referred for screening procedures or had insufficient follow-up data. One hundred and thirty-eight patients were clinically identified as having (functional) symptoms unexplained by structural or biochemical abnormalities consistent with FD, IBS or FD/IBS overlap. Of these, 18 were excluded as their symptom intensities on the SAGIS form were rated too low (none of the symptoms rated at least 2 ("symptoms cannot be ignored")) and therefore not fulfilling criteria as outlined above. Overall 120 patients with FD and/or IBS without concomitant other structural or biochemical abnormality were included (Fig. 1).

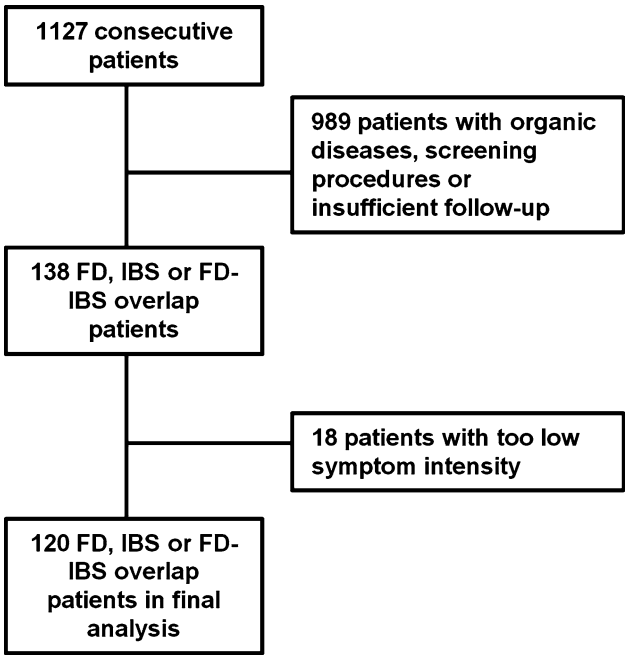

Fig. 1 CONSORT patient flow-diagram. From 1127 consecutive patient initially assessed, 989 had organic disease, were referred for screening procedures or had insufficient follow-up data. Another 18 patients had only very low symptom intensities not meeting inclusion criteria

Clinical Diagnosis

Clinically "working" diagnoses was documented by the treating physician (based upon routine clinical work-up and any clinical data including medical history, clinical assessment, endoscopy reports, histology and laboratory reports). This was done independently by two researchers who then agreed on a final clinical diagnosis. The diagnosis of a functional GI disorder was based upon the symptoms and the absence of structural or biochemical abnormalities.

Structured Assessment of Gastrointestinal Symptoms

During the initial presentation, symptoms were also assessed in all patients utilizing the previously validated SAGIS [22, 23]. The SAGIS instrument rates the severity/impact of 22 distinct gastrointestinal (GI) symptoms on a 5-point Likert scale.

Patient Categorization

For the diagnosis of IBS based on the SAGIS, one of the following symptoms had to be at least moderate ("2 = cannot be

ignored") and a cumulative severity score of these symptoms had to be equal or greater than 4. The symptoms that were considered to define IBS were: "diarrhea," "loose stools," "urgency to defecate," "pain/discomfort prior to defecation," "abdominal cramps," "constipation," "bloating" and "difficulty defecating." IBS was further subtyped into diarrhea predominant IBS (IBS-D), constipation predominant IBS (IBS-C) and mixed IBS (IBS-M). Criteria for IBS-D were "diarrhea" greater or equal to 2 ("cannot be ignored") and "constipation" smaller or equal to 1 ("can be ignored"). Criteria for IBS-C were "constipation" greater or equal to 2 and "diarrhea" smaller or equal to 1. If both symptoms "diarrhea" and "constipation" were equal or greater than 2, patients were categorized as IBS-M. For the diagnosis of FD, at least one of the following symptoms had to be moderate and a cumulative severity score of these symptoms had to be equal or greater than 3. The symptoms that were considered to define FD were: "fullness" (feeling of congestion of food without relation to prior food intake), "early satiety" (disproportional to the quantity of food), "postprandial pain or discomfort" and "epigastric pain." FD was further subtyped into epigastric pain syndrome (EPS), postprandial distress syndrome (PDS) and FD unspecified (FD-U). Criteria for PDS were "postprandial pain or discomfort" greater or equal to 2 and "epigastric pain" smaller or equal to 1. Criteria for EPS were "epigastric pain" greater or equal to 2 and "postprandial pain or discomfort" smaller or equal to 1. If both symptoms "epigastric pain" and "postprandial pain" were greater or equal to 2, patients were categorized as FD-EPS/PDS overlap. For the diagnosis of FD/IBS overlap both of the outlined criteria (for IBS and FD) had to be fulfilled.

Statistical Analysis

Frequencies of patients clinically diagnosed as FD, IBS and FD/IBS overlap were calculated as percentages and compared with the frequencies of patients based on the outlined criteria utilizing SAGIS. All subsequent tests (IBS subtyping, FD subtyping and assessment of risk factors) utilized patient categorization based upon the standardized questionnaire. Demographic factors (gender, age) were assessed and compared for the different groups of patients utilizing Pearson Chi-square tests and Mann–Whitney-*U*-tests. For all patients an IBS and a FD symptom intensity score based on the symptoms outlined above was derived by summing the severity scores of the individual symptoms. Furthermore, the number of severe and very severe FD and IBS symptoms was tallied for each patient. Based on the mean intensity scores for FD and IBS symptoms, patients were divided into three groups (a) low, (b) medium and (c) high symptom intensity group depending on their individual symptom score. The cutoff values between groups were chosen such that each group represented around one-third of patients.

The frequency (and 95% confidence intervals) for each group (IBS, FD and FD/IBS overlap) and subgroups based upon symptom intensities was calculated and compared utilizing Pearson Chi-square tests and relative risks (RR). Relative risk values > 1.0 indicate increased risk, while values < 1.0 indicate reduced risk, and values close to 1.0 indicate similar risk between groups. In addition, mean symptoms scores for dyspeptic symptoms and IBS symptoms for patients with and without FD/IBS overlap were calculated and compared utilizing nonparametric tests.

All statistical tests were two-sided, and p values < 0.05 were considered significant.

Results

Study Population

The mean age of the patients in the study was 49.0 years, and 64.2% (95%CI 55.6–72.8) of the patients were female.

Clinical and Questionnaire-Based Categorization

Based on the clinical documentation provided by the treating physician, 71 (59.2%, 95%CI [50.4–68.0]) patients were diagnosed as having IBS, 21 (17.5%, 95%CI [10.7–24.3]) had FD and in 28 (23.3%, 95%CI [15.7–30.9]) overlap of FD and IBS was documented. However, based upon the SAGIS questionnaire data, 35 (29.2%, 95%CI [21.1–37.3]) were classified as IBS, 8 (6.7%, 95%CI [2.211.2]) as FD and 77 (64.2%, 95%CI [55.6–72.8]) as FD/IBS overlap patients (Fig. 2).

Of the 35 patients which were categorized based upon the questionnaire data as IBS, 28 (80.0%, 95%CI [63.1–91.6]) had clinically been diagnosed with IBS, 3 (8.6%, 95%CI [1.8–23.1]) also had clinically been diagnosed with FD and 4

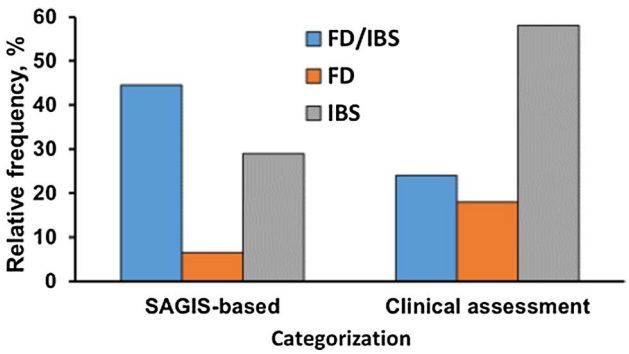

Fig. 2 Proportion of patients (%) with Functional Dyspepsia (FD), Irritable Bowel Syndrome (IBS) or FD/IBS overlap (FD/IBS) based upon the routine clinical assessment (right) versus categorization based upon the structured assessment of gastrointestinal symptoms (SAGIS) instrument (left), $N = 120$

(11.4%, 95%CI [3.2–26.7]) with FD/IBS overlap. Similarly, of the 8 patients which were categorized based upon the questionnaire data as FD, 5 (62.5%, 95%CI [24.5–91.5]) also had clinically been diagnosed with FD, 3 (37.5%, 95%CI [8.5–75.5]) had clinically been diagnosed with FD/IBS overlap and none with IBS.

Of the 77 patients which were categorized based upon the questionnaire data as FD/IBS overlap, 21 (27.3%, 95%CI [17.7–38.6]) also had clinically been diagnosed with FD/IBS overlap, 43 (55.8%, 95%CI [44.1–67.2]) had clinically been diagnosed with IBS, and 13 (16.9%, 95%CI [9.3–27.1%]) had clinically been diagnosed with FD.

Of the 112 patients which were categorized based upon the questionnaire data as IBS and FD/IBS overlap, 33.9% (95%CI [25.1–42.7]) had diarrhea predominant IBS (IBS-D), 27.7% (95%CI [19.4–36.0]) had constipation predominant IBS (IBS-C), and 38.4% (95%CI [29.4–47.4]) had a mixed IBS (IBS-M, Fig. 3). Of the 85 patients with FD or FD/IBS overlap, 70.6% (95%CI [60.9–80.3]) had FD-EPS/PDS overlap while 19.3% (95%CI [10.9–27.7]) had isolated symptoms consistent with postprandial pain syndrome and 9.4% (95%CI [3.2–15.6]) had only dyspepsia symptoms consistent with epigastric pain syndrome.

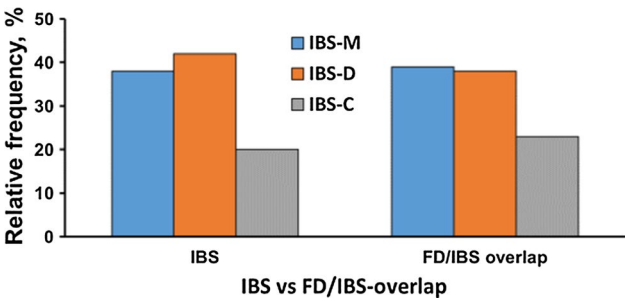

Fig. 3 Proportion of patients (%) with mixed IBS (IBS-M), diarrhea-dominant IBS (IBS-D) and constipation dominant IBS (IBS-C) in patients with IBS or FD/IBS overlap, $N = 120$, n.s

Intensity of FD and IBS Symptoms in Subjects With and Without Overlap

In patients with functional dyspepsia or IBS alone, the symptom intensities of dyspepsia- and IBS symptoms were significantly lower as compared to patients with overlap of FD and IBS (6.4 ± 0.6 and 11.1 ± 0.9 vs. 16.8 ± 0.8 and 19.4 ± 0.8, p all < 0.01, Fig. 3).

Risk Factors for FD/IBS Overlap

When patients were stratified based upon the intensity of IBS or FD symptoms (as low, moderate or severe), proportions of FD, IBS and FD/IBS overlap differed significantly ($p < 0.01$, Table 1). Patients with severe FD (SAGIS score ≥ 8) or severe IBS symptoms (SAGIS score ≥ 18) were significantly more likely to have FD/IBS overlap as compared to other groups. Patients with moderate (SAGIS score 12–17) or severe IBS symptom intensity (SAGIS score ≥ 18) were significantly more likely to have FD/IBS overlap compared to the low intensity (SAGIS score 0–11) or moderate group (RR = 2.6, 95%CI [1.6–4.3], $p < 0.05$ and RR = 3.1, 95%CI [1.9–5.0], $p < 0.05$, respectively).There were no significant differences in the frequency of IBS subtypes between IBS and FD/IBS overlap patients (all $p > 0.3$).

The proportions of IBS and FD/IBS overlap differed significantly (p all < 0.01) between the low (SAGIS score 0–3), the medium (SAGIS score 4–7) and the high intensity (SAGIS score 8–16) FD symptom groups (see Fig. 4 and Table 2). Patients with a moderate or severe FD symptom intensity were significantly more likely to have an FD/IBS overlap compared to the low intensity group (RR = 7.9, 95%CI [3.1–20], $p < 0.05$ and RR = 9.0, 95%CI [3.5–22.7], $p < 0.05$, respectively). There were no significant differences in the frequency of FD subtypes between FD and FD/IBS overlap patients (all $p > 0.3$).

Table 1 Proportion of patients with Functional Dyspepsia (FD), Irritable Bowel Syndrome (IBS) or FD/IBS overlap (FD/IBS) and intensity of IBS symptoms as measured with the Structured Assessment of Gastrointestinal Symptoms (SAGIS) instrument

IBS symptom intensity	Proportion with IBS or FD/IBS overlap, % (95% CI)		
	IBS	FD/IBS	FD
Low ($n = 41$)	51.2 (35.1–67.1)	29.3 (16.1–45.5)	19.5 (8.8–34.9)
Moderate ($n = 39$)	25.6* (13–42.1)	74.4$^{@}$ (57.9–87)	0$^{@@}$ (0–9)
Severe ($n = 40$)	10** (2.8–23.7)	90$^{\#}$ (76.3–97.2)	0$^{\#\#}$ (0–8.8)

*$\text{chi}^2(1) = 5.5$, $p < 0.05$, versus low intensity

**$\text{chi}^2(1) = 16.1$, $p < 0.05$ versus low intensity

$^{@}\text{chi}^2(1) = 17.5$, $p < 0.05$, versus low intensity

$^{@@}\text{chi}^2(1) = 30.9$, $p < 0.05$ versus low intensity

$^{\#}\text{chi}^2(1) = 8.5$, $p < 0.05$

$^{\#\#}\text{chi}^2(1) = 8.7$, $p < 0.05$, versus low intensity

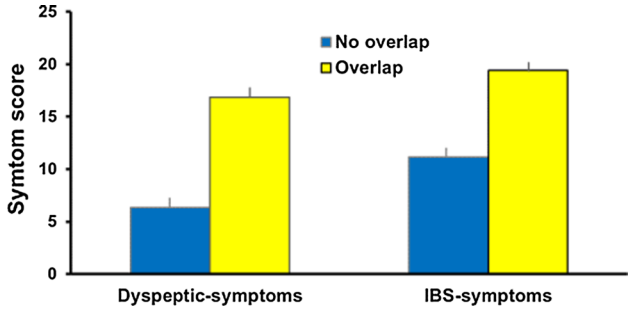

Fig. 4 Severity of dyspeptic- and IBS symptoms as measured by SAGIS symptom score (mean ± SEM) in patients with and without FD/IBS overlap (p all < 0.01 overlap vs. no overlap)

Overall, 66.2% of FD/IBS overlap patients were female. There was no significant ($p > 0.3$) gender difference for overlap versus non-overlap patients (60.5% females in non-overlap patients). Similarly, age was not associated with overlap ($p > 0.9$).

Discussion

The key findings of this study are: (1) when an assessment of gastrointestinal symptoms is done with a standardized questionnaire, 64.2% of patients with FD and/or IBS suffer from an FD/IBS overlap compared to 23.3% FD/IBS overlap based upon the routine clinical assessment and (2) in patients with an FD/IBS overlap the severity of dyspepsia and IBS symptoms is significantly higher as compared to patients with either FD or IBS. Thus, patients with severe FGID manifestations are more likely to have an overlap of symptoms.

Patients with gastrointestinal symptoms without identifiable structural or biochemical abnormalities are classified as having a functional gastrointestinal disorder [1]. These patients are categorized into different groups based upon the symptom pattern as proposed by the Rome Foundation and other groups [1, 24, 25]. It is well recognized that FD and IBS are the most prevalent subgroups [2]. While overlap of these conditions is mentioned as a possibility in the Rome IV Criteria [25, 26] we found a considerable overlap of 64.2%. However, in patients with "severe" symptoms, overlap appears to be the norm rather than the exception. In addition, overlap is not explained by two independent conditions that will randomly coexist in a small number of patients. This finding is consistent with population-based studies which have revealed substantial overlap of patients with IBS and FD [8, 9, 27–29]. Our data are also consistent with data from the Leuven group who assessed IBS symptoms in a cohort of subjects with meal-related epigastric symptoms undergoing barostat studies; 46% of these patients also had IBS symptoms based upon the Rome II Criteria [28].

The cohort of consecutive patients has been recruited in a tertiary hospital setting. Compared to the population or primary care setting, symptoms might be on average more severe. However, all patients have undergone comprehensive diagnostic work-up. Thus, from the initial cohort of 1127 consecutive patients we were able to focus on 120 patients without any relevant organic confounders. All patient data were reviewed 12 months after the initial presentation. This ensures that no organic cause has emerged in the interim and provides confidence with regard to the absence of potential confounding structural or organic causes of symptoms. Only 11% of the patients of our study cohort had functional dyspepsia or IBS. This is most likely due to the fact that very strict criteria were applied and our protocol included a review of the patient records 12 months after the initial presentation. This gives confidence that our results have not been confounded by coexisting organic disease. However, this approach may have excluded some patients with FGIDs who had coexisting organic disease (e.g., GORD).

Standard clinical assessment of patients with FGIDs underestimated the prevalence of FD/IBS overlap when

Table 2 Proportion of patients with Functional Dyspepsia (FD), Irritable Bowel Syndrome (IBS) or FD/IBS overlap (FD/IBS) and intensity of FD symptoms as measured with the Structured Assessment of Gastrointestinal Symptoms (SAGIS) Instrument

FD symptom intensity	Proportion with IBS or FD/IBS overlap, % (95% CI)		
	IBS	FD/IBS	FD
Low ($n = 38$)	84.2 (68.7–94)	10.5 (2.9–24.8)	5.3 (0.6–17.7)
Moderate ($n = 42$)	7.1* (1.5–19.5)	83.3[@] (68.6–93)	9.5[#] (2.7–22.6)
Severe ($n = 40$)	0** (0–8.8)	95[@@] (83.1–99.4)	5[##] (0.6–16.9)

*$\text{chi}^2(1) = 48.1$, $p < 0.05$ versus low intensity

**$\text{chi}^2(1) = 57.1$, $p < 0.05$ versus low intensity

[@] $\text{chi}^2(1) = 47.3$, $p < 0.05$ versus low intensity

[@@] $\text{chi}^2(1) = 56.0$, $p < 0.05$ versus low intensity

[#] no significant difference ($p > 0.3$) versus low intensity group

compared with a standardized symptom assessment (23.3 vs. 64.2%) utilizing a questionnaire. While it might be argued that this finding requires independent verification, our data suggest that there is at least a risk that the clinical categorization does not match the categorization that is based upon a standardized symptom assessment utilizing a questionnaire. Another strength of the study is the follow-up of the patients.

Based upon our data, the frequency of FD/IBS overlap is closely associated with the intensity of FD and IBS symptoms. In the medium and high intensity groups, the frequency of FD/IBS overlap was significantly higher compared to the low intensity group. 90% of patients in the high IBS symptom intensity group, and 95% of patients in the high FD symptom intensity group had an overlap of both disorders. This finding is supported by the results from a recent internet-based cross-sectional health survey that showed that the overlap of multiple FGIDs is associated with greater health impairment including increasing somatization, poorer mental and physical functioning, more medical therapies, and a higher prevalence of abdominal surgeries [30].

For clinical trials, the Rome criteria are the established standard. The fact that many if not most patients have an overlap of FD and IBS or IBS and symptoms of reflux disease [31] and the fact that overlap is actually associated with more severe symptoms, may have important implications for the design of clinical trials or may explain why some trials have failed. If patients with "pure" IBS or FD are recruited and patients with an overlap of symptoms are excluded, this may result in a bias toward patients with less severe symptoms. As a consequence, significant treatment effects might be difficult to demonstrate due to ceiling effects. On the other hand, effective treatments are particularly needed for patients with severe symptom manifestations and these patients are currently excluded from studies. Therefore, including FD/IBS overlap might be beneficial to demonstrate efficacy of therapies in clinical studies. Rome IV now at least mentions inclusion of patients with overlapping conditions but has also recognized this as a challenge for clinical trials [32]. For our study we used the routine clinical assessment and compared this with data we obtained during the clinical presentation utilizing the validated SAGIS instrument. This instrument does not simply assess severity or frequency of symptoms but the impact of specific symptoms on daily life [22, 23]. This recently developed instrument has good psychometric properties and symptom scores are well correlated with other established instruments such as the Rome III Questionnaire [22, 23]. For example we have found patients with moderate symptoms on the SAGIS, 18/22 (81.8%) meet Rome III and 17/22 (71.3%) meet Rome IV criteria. According to Rome IV, the threshold for FD should be that the symptoms are "bothersome," which is defined as "severe enough to impact on usual activities" [26]. While it seems likely that this feature helps to discriminate between real-world patients and non-patients, this criterion is lacking for the definition of IBS. The SAGIS instrument, however, rates symptoms on the basis of symptom interference with daily activities and therefore, as outlined above, reflects quality of life (QoL) probably better than frequency or form of bowel motions. It is well recognized that quality of life is severely affected in patients with FGIDs [33–36]. Based upon our data, quality of life might be particularly affected in patients with an FD/IBS overlap. Future studies should also assess whether the diagnosis of IBS/FD varies over time and whether this is related to the intensity of symptoms experienced over time.

In summary, our data, based upon a cohort of consecutive patients referred to a tertiary center demonstrate that in the routine clinical practice the majority of patients with functional GI disorders have an overlap of FD and IBS. Patients having either FD or IBS overall have less severe symptoms, and patients with overlap may represent the more severe end of the spectrum of patients with FD or IBS. The implications of overlap of FD and IBS for the long-term outcome of patients and the response to therapies—including the response in clinical trials—need to be explored.

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Author's contribution MvW and GH were involved in planning and conducting the study, data collection, analyzing and interpretation of data, drafting of manuscript, and final review of manuscript. JH contributed to the concept and design, data collection, important intellectual input, and critical review of manuscript. MJ was involved in data analysis and critical review of the manuscript. JM, GR, AS, NK, BK and NT contributed to important intellectual input, important contribution to study planning, and critical review of manuscript.

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Compliance with ethical standards

Conflict of interest None.

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