Neurogastroenterology & Motility

Neurogastroenterol Motil (2016) **28,** 581–591 doi: 10.1111/nmo.12758

Bloating is associated with worse quality of life, treatment satisfaction, and treatment responsiveness among patients with constipation-predominant irritable bowel syndrome and functional constipation

L. NERI,* P. IOVINO† & THE LAXATIVE INADEQUATE RELIEF SURVEY (LIRS) GROUP[a]

*Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
†Department of Medicine and Surgery, University of Salerno, Salerno, Italy

Key Points

- We demonstrated that patients with non-organic chronic constipation regard the symptom of bloating as a key element in assessing clinical changes and treatments' efficacy irrespective of the intensity of other symptoms
- We sought to evaluate the association between bloating and quality of life, treatment satisfaction and treatment responsiveness among patients with constipation-predominant irritable bowel syndrome and functional constipation.
- We enrolled 2203 patients in a two-wave cross-sectional survey: quality of life data obtained through self-administered questionnaires were matched with reports of clinical examinations performed by gastroenterologists in 39 tertiary referral centers for the treatment of non-organic constipation.
- Bloating was associated with poorer health-related quality of life and treatment satisfaction after adjustment for potential confounders and other constipation-related symptoms.
- Bloating was associated with responsiveness to treatment after therapy switch independent of potential confounders.

Abstract

Background *The management of bloating is unclear and its relationship with patients' well-being and treatment satisfaction independent of other abdominal symptoms is uncharacterized. We evaluated the association of bloating with patient-reported outcomes.* ***Methods*** *Thirty-nine centers for functional gastrointestinal disorders joined the laxative inadequate relief survey. We enrolled 2203 consecutive outpatients with functional constipation (FC) or constipation-predominant irritable bowel syndrome (IBS-C) in two cross-sectional waves. Both wave 1 and 2 included the SF-12, the patient assessment of constipation-symptoms (PAC-SYM), and the treatment satisfaction questionnaire for medication (TSQM-2). Wave 2 only included a global rating of change (GRC) scale to assess patients' assessment of efficacy concerning treatment switches occurred in the 3 months prior to the interview. Bloating in the abdomen was defined on the basis of PAC-SYM item 3.* ***Key Results*** *The average age was 50.1 years (SD, 16.7) and 82.1% of patients were women. The prevalence of bloating was 91.6% (n = 1970). Bloating was associated with SF-12 Physical Composite Score ($p < 0.01$), SF-12 Mental Composite Score ($p < 0.01$), GRC ($p < 0.01$), Satisfaction with treatment effectiveness ($p < 0.01$), convenience of administration ($p < 0.01$), and side effects ($p < 0.01$) after adjustment*

Address for Correspondence
Luca Neri, MD, Post-Doctoral Fellow, Dipartimento di Scienze Cliniche e di Comunità, Università di Milano, Via San Barnaba, 8, Milano 20120, Italy.
Tel: +390236563473;
e-mail: luca_neri_4@hotmail.com
[a]Members of the LIRS Study Group are listed in Appendix and should be regarded as collaborators for indexing purposes.
Received: 18 June 2015
Accepted for publication: 19 November 2015

for possible confounders. ***Conclusions & Inferences*** *Our data suggest that patients regard bloating as a key element in assessing clinical changes and treatments' efficacy as this symptom exerts a strong influence on patient-reported outcomes independent of possible confounders and other symptoms of constipation. Our data provide the rationale to investigate the efficacy and tolerability of new treatments specifically addressing this important, yet disregarded, patients' complain.*

Keywords *bloating, chronic constipation, functional constipation, irritable bowel syndrome, patient-reported outcomes, quality of life, treatment satisfaction.*

Abbreviations: FC, functional constipation; FGID, functional gastrointestinal disorder; GRC, global rating of change; IBS – C, constipation-predominant irritable bowel syndrome; LIRS, laxative inadequate relief survey; PAC-SYM, patient assessment of constipation-symptoms; PRO, patients-reported outcomes; QoL, quality of life; TSQM-v2, treatment satisfaction questionnaire for medication.

BACKGROUND

Bloating is one of the most common and bothersome complaint in the general population.[1] This symptom has been described with various definitions, such as sensation of a distended abdomen or an abdominal tension or even excessive gas in the abdomen, although bloating should probably be defined as the feeling (e.g., a subjective sensation) of increased pressure within the abdomen.[2] Additionally, it is not clear to what extent patients' complaint of subjective bloating corresponds to the objective evidence of abdominal distension.[3] Bloating is frequently associated with functional gastrointestinal disorders (FGIDs) (i.e., functional dyspepsia, irritable bowel syndrome [IBS], and functional constipation [FC]). Up to 80% of patients with constipation complain of bloating and abdominal distension,[4–9] whereas 96% of patients with IBS report bloating, which is considered the most bothersome symptoms in 60% of them.[7]

There is evidence documenting a weak association between bloating and quality of life (QoL)[10,11] but no study comprehensively addressed the relationship of this common symptom with patients well-being and treatment satisfaction independent of other lower abdominal complains. Additionally, to our knowledge, no study has evaluated whether constipated patients are less responsive to constipation-related treatments in the presence of bloating.

Hence, we sought to assess the association of bloating with QoL and treatment satisfaction in patients with FC and IBS.

METHODS

Study sample and design

Thirty-nine Italian referral centers for gastrointestinal disorders joined the laxative inadequate relief study (LIRS),[12] a two-wave survey. In the first wave, LIRS 1, we enrolled 878 consecutive outpatients with chronic non-organic constipation from September through December 2011. In the second wave, LIRS 2, we enrolled 1325 outpatients in the same centers, from March 2012 and May 2013. Patients reporting at least two symptoms of FC according to Rome III criteria were evaluated by a gastroenterologist. The attending gastroenterologist recorded relevant clinical and demographic information in a standard data collection form. All participating gastroenterologists were experienced in the diagnosis and treatment of FGIDs and were instructed to exclude patients with secondary causes of constipation. Patients were classified in the FC or constipation-predominant IBS-C group, based on criteria listed in Table 1.

Patients willing to participate in the study and providing their informed consent were asked to fill in a self-administered survey. We matched the medical data collection form and the self-administered questionnaire for all study subjects.

Measures

Outcomes (see also Appendix S1) We assessed patients' health-related QoL with the SF-12,[13] the severity of constipation with the patient assessment of constipation-symptoms (PAC-SYM),[14] and treatment satisfaction with the treatment satisfaction questionnaire for medication (TSQM-v2).[15]

The PAC-SYM is a 12-item questionnaire assessing the presence and magnitude of constipation-related symptoms worded as follows: (1) discomfort in your abdomen; (2) pain in

Table 1 Classification of FC and IBS-C according to modified ROME III definition

Functional constipation	Lumpy/Hard Stools in at least 25% of defecations
At least two of the following symptoms for the last 3 months with symptom onset at least 6 months prior to diagnosis	Feeling of incomplete evacuation in at least 25% of defecations
	Sensation of anorectal obstruction/blockage for at least 25% of defecations
	Manual maneuvers to facilitate at least 25% of defecations
	Less than 3 defecations/week
	Straining during at least 25% of defecations
IBS-C	Fulfilling criteria for functional constipation
All criteria should be satisfied	Abdominal Pain or discomfort lasting at least 3 days/month in the past 3 months associated with relief of pain with a bowel movement
	Abdominal pain is the most bothersome symptom

your abdomen; (3) bloating in your abdomen; (4) stomach cramps; (5) painful bowel movements; (6) rectal burning during or after a bowel movement; (7) rectal tearing or bleeding after a bowel movement; (8) incomplete bowel movement, like you didn't 'finish'; (9) bowel movements that were too hard; (10) bowel movements that were too small; (11) straining or squeezing to try to pass bowel movements; (12) feeling like you had to pass a bowel movement you couldn't. Ratings occur along a 5-point likert scale (0 = absent; 4 = very severe). Items of the PAC-SYM questionnaire were identified through literature review and qualitative analysis of patient interviews (five focus groups of 8–10 patients per group, separated by sex and by two levels of self-reported constipation severity). Of note, to maximize the relevance of the symptom assessment to patients, items were constructed from the symptom description language used by focus-group patients. A recall period of 2 weeks was chosen for items to limit recall burden and to provide a relatively acute assessment. The instrument was designed for self-administration. Five pilot subjects completed the questionnaire to evaluate comprehensiveness and understandability. Furthermore, standard item reduction techniques were employed to select relevant items.[14]

The SF-12 is a 12-item questionnaire assessing patients' perception of their own mental and physical health. Response to the questionnaire yield two composite scores (the Mental Composite, MCS and the Physical Composite, PCS) ranging from 0 to 100, with higher scores indicating better QoL. The scoring system is norm based on the Italian general population (mean = 50; SD = 10).

The TSQM-v2 is an 11-item questionnaire assessing patients' satisfaction for the efficacy, safety, and convenience of use of their treatment. Patients response yield three subscales (efficacy, safety, and convenience) and an overall satisfaction rating. Scores occur on a 0–100 scale. Higher ratings indicate higher satisfaction with medication.

The LIRS II survey additionally inquired about therapy switching in the 3 months prior to the interview. We asked patients to rate their perceived overall clinical change after therapy switch with a bipolar Global Rating of Change Scale (GRC, 15 point, from −7 = extremely deteriorated to +7 = extremely improved).[16] As it has been previously suggested that the Minimal Clinically Important Change on a GRC scale is 2 points,[16] we classified patients ratings of clinical change as follows: −7 : −5 = very deteriorated; −4 : −2: deteriorated; −1 : 1 = unchanged; +2 : +4 = improved; +5 : +7 = very improved.

Definition of bloating Item 3 of the PAC-SYM was used to define patients with (score = 1–4) and without bloating (score = 0).

Covariates The covariates included in the model were patients' age, sex, employment, the diagnosis of IBS-C or FC based on ROME III criteria and the presence of abdominal pain and its characteristics, BMI, smoking habit, daily intake of water greater than 1 L (yes/no), duration of lower gastrointestinal symptoms (years since diagnosis), number of pregnancies and difficult deliveries, and the number of comorbidities and treatments (behavioral advice, bulking/osmotic, stimulant/herbal, enema/suppository, prucalopride, any association, or no therapy). Comorbidities included all diseases treated or diagnosed in the past 12 months and previous abdominal and extra-abdominal surgical interventions occurred in the same time frame as well.

Analysis

We defined questionnaire completers as all patients with no missing value in items relevant for questionnaire scoring. For each questionnaire item, the prevalence of missing values ranged from 1% to 7%. We tested differences in socio-demographic and clinical factors (see Measures, Covariates) among completers and non-completers with chi-squared and Wilcoxon test where appropriate. As we found no statistically significant differences between completers and non-completers in both LIRS I and LIRS II waves, we computed all questionnaire scores only for cases with complete answers.

Prevalence and magnitude of bloating The prevalence (PAC-SYM item $3 \geq 1$) and magnitude (PAC-SYM item 3 score) of bloating have been computed in patients with FC and IBS-C. We evaluated unadjusted differences in the prevalence and magnitude of bloating with chi-squared and Wilcoxon test. We adopted logistic regression and generalized linear models to evaluate correlates of the prevalence and magnitude of bloating, respectively.

Bloating and patient-reported outcomes To test whether bloating was associated with poorer patient-reported outcomes (PRO), we used Wilcoxon test to contrast QOL (SF12 summary scores), Treatment Satisfaction (TSQMv2 scales), and GRC scores between patients with and without bloating. We adopted generalized linear models to test the robustness of the results after adjustment for possible confounders and overlap-corrected PAC-SYM score (total score after deletion of the score reported in Item 3, the descriptor of bloating).

Sensitivity analysis Even though we advised all participating gastroenterologists to exclude any patient with alarm signs and any organic disease potentially associated with constipation, we relied on each center clinical practice rather than providing a standardized diagnostic algorithm for the study. As a consequence, a bias in patient enrollment cannot be completely ruled out. To evaluate the potential impact of selection bias we assessed differences in bloating prevalence, constipation characteristics (Rome III criteria), socio-demographic, and clinical characteristics between patients with and without organic diseases potentially associated with constipation (i.e., diabetes, anal fissures, previous history of abdominal surgery, clinical depression, chronic kidney disease, endometriosis, suspect heavy metals intoxication, cancers and neoplasms, hysterectomy, Alzheimer's disease or dementia, Parkinson's disease, multiple sclerosis, paraplegia or hemiparesis, diverticulosis, rectal prolapse; $n = 654$).

As a further check, we included the interaction term between bloating and an indicator variable denoting a medical history suggesting organic diseases potentially associated with constipation in all models evaluating the association between bloating and PRO (SF-12, TSQMv2, overlap-corrected PAC-SYM). A statistically significant interaction term would suggest possible selection bias. This procedure allows to estimate both the magnitude and the direction of possible selection bias. We report the difference-in-difference of the adjusted means calculated as follows:

$$\Delta_{p-s} = (aMean_{b1} - aMean_{b0})_p - (aMean_{b1} - aMean_{b0})_s$$

where $aMean_{b1}$ indicate the adjusted mean for patients reporting bloating; $aMean_{b0}$ indicate the adjusted mean for patients reporting no bloating. The suffix p indicates the group of patients with no previous history of organic diseases potentially associated with constipation. The suffix s indicates the group of patients with previous history organic diseases potentially associated with constipation. A statistically significant interaction and a positive $\Delta_{p\text{-}s}$ would suggest that the inclusion of patients with organic diseases potentially associated with constipation may lead to underestimating the association between bloating and PRO.

A $p < 0.05$ was considered statistically significant. We carried out all analysis with SAS 9.2® (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study sample

Patients' characteristics are described in Table 2. LIRS 1 and LIRS 2 were substantially similar relative to key patients' characteristics. About 55% ($n = 1212$) received dietary prescriptions alone or in associations with other treatments. Additionally, 512 patients (23.2%) received fiber supplementation alone or in associations with other treatments. There was no difference across bloating groups in the proportion of patients receiving dietary prescriptions or fiber supplementation (data not shown). Most patients received associations of constipation-related treatments in the month prior to the interview (i.e., schemes including a combination of more than one drug with or without dietary recommendation). Overall patients receiving dietary recommendations or fiber supplementation alone or in association with other treatments were 208 (12.7%) and there was no difference in the proportion of fiber supplementation prescription across bloating strata. During LIRS I, fielding prucalopride was not available in Italy. During LIRS II, 151 (11.4%) patients received a prescription for prucalopride alone and 167 (12.6%) patients in association with other treatments. Most common prucalopride associations were dietary (16.4%), bulking/osmotic (14.8%), enema/suppository (13.5%), and stimulant/herbal (7.9%) treatments. Prescription of prucalopride was a switch from previous treatments in the majority of patients (94%). Mean overlap-corrected PAC-SYM score (i.e., total score after deletion of the score reported in Item 3, the PAC-SYM descriptor of bloating) was 1.46 ± 0.77.

Table 2 Characteristics of sample study

Characteristics	Whole sample	LIRS I	LIRS II
n	2203	878	1325
	Mean (SD), *n* (%)		
Age	50.1 (16.7)	50.3 (16.6)	49.9 (16.9)
Women	1808 (82.1)	706 (80.4)	1102 (83.2)
Employed	1090 (49.5)	370 (42.1)	720 (54.3)
IBS-C	369 (16.8)	149 (17.0)	220 (16.6)
FC	1834 (83.3)	729 (83.0)	1105 (83.4)
Rome III criteria			
Lumpy/Hard stools	1638 (74.4)	659 (75.1)	979 (73.9)
Incomplete evacuation	1604 (72.8)	650 (74.0)	954 (72.1)
Sensation of obstruction	346 (40.4)	346 (40.4)	507 (38.3)
Manual maneuvers	539 (24.5)	220 (25.1)	319 (24.1)
<3 defecations/week	1501 (68.2)	565 (64.4)	936 (70.7)
Straining	1812 (82.3)	723 (82.4)	1089 (82.3)
Bloating prevalence	1970 (91.6)	778 (92.4)	1192 (91.1)
Time since constipation onset	11.9 (13.7)	17.3 (15.0)	7.0 (10.2)
Therapy (mutually exclusive classes)*			
Behavioral advice	266 (12.2)	125 (14.6)	141 (10.7)
Bulking/osmotic	157 (7.2)	43 (5.0)	114 (8.6)
Stimulant/herbal	113 (5.2)	52 (6.1)	61 (4.6)
Enema	58 (2.7)	23 (2.7)	35 (2.6)
Prucalopride	–	N/A	151 (11.4)
Any association†	1352 (62.0)	563 (65.7)	789 (59.6)
None	107 (4.9)	51 (5.9)	56 (4.2)
Water >1 L/day	1325 (60.3)	537 (61.7)	788 (59.5)
Current smoker (Y)	806 (36.6)	325 (38.1)	477 (36.0)
Number of comorbidities	2.4 (2.0)	2.5 (2.1)	2.3 (1.9)
BMI	23.6 (4.1)	23.8 (4.0)	23.5 (4.3)
Cesarean birth or prolonged labor‡	605 (33.5)	224 (31.7)	381 (34.6)

*Missing information concerning treatment: $n = 150$. †Any Association entails a combination of multiple treatments. ‡Statistics based on 1808 women.

Prevalence and magnitude of bloating

The prevalence of bloating was 91.6% ($n = 1970$). Patients with IBS-C reported slightly more bloating than patients with FC (95.9%, $n = 347$ *vs* 90.8%, $n = 1623$ in IBS-C and FC, respectively; $p < 0.01$). After adjustment for possible confounders (covariates in the methods section), IBS-C (OR = 2.80, $p < 0.01$), women (OR = 2.36, $p < 0.01$), obese subjects (BMI >30) (OR = 3.51, $p < 0.01$) and patients with more comorbidities (>3: OR = 2.04; 1–3: OR = 1.96; 0: ref.; $p < 0.01$) were more likely to report any bloating. The magnitude of bloating (PAC-SYM item 3) was greater in patients with IBS-C compared to FC (2.69 ± 0.93 *vs* 2.38 ± 0.98, $p < 0.01$, respectively). After adjustment for possible confounders, patients with a diagnosis of IBS-C ($\beta = 0.32$, $p < 0.01$), women ($\beta = 0.56$, $p < 0.01$), those with a paid job ($\beta = 0.15$, $p < 0.01$), older subjects (less than 33 years: reference; 33–67 years: $\beta = -0{,}14$; older than 67 years: −0.34; $p < 0{,}01$), those currently smoking ($\beta = 0.14$, $p < 0.01$), and those with more comorbidities (0 medical conditions: $\beta = -0.59$; 1–3 medical conditions: $\beta = -0.20$; >3 medical conditions: reference; $p < 0.01$) reported higher bloating magnitude. A diagnosis or treatment for depression/anxiety in the past 12 months ($\beta = 0.12$, $p < 0.053$) was marginally associated with bloating magnitude.

Bloating and quality of life

Patients with bloating reported lower QOL scores independently of the diagnosis of FC or IBS-C (Fig. 1, Panel A). Additionally, we observed that the relationship between bloating and HRQOL was not different in patients with FC or IBS-C (p for interaction >0.1). This pattern of association was robust to adjustment for

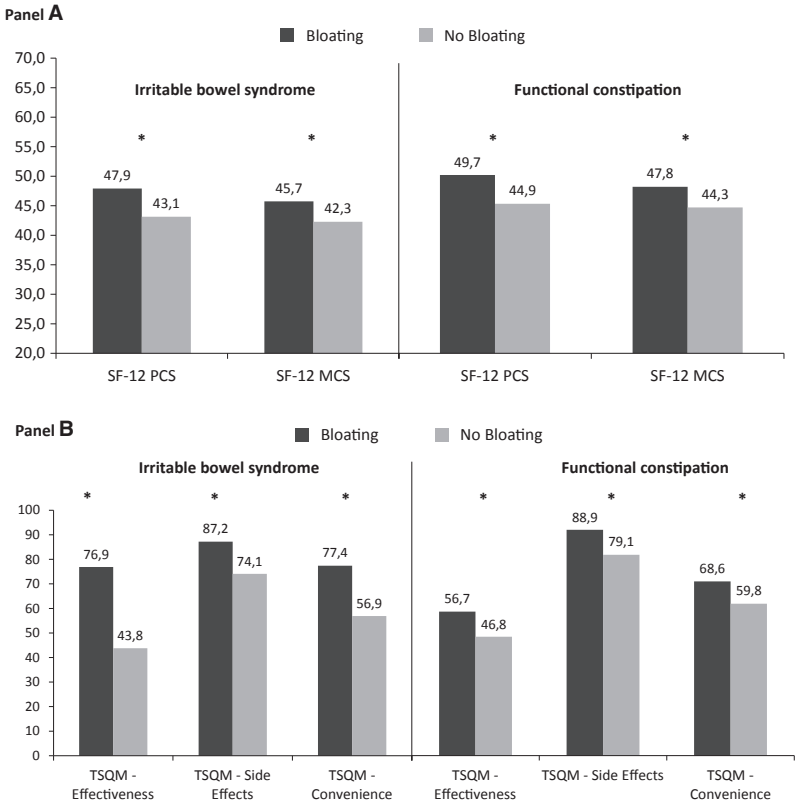

Figure 1 Bloating, quality of life, and treatment satisfaction. Association between bloating SF-12 (A) and TSQMv2 (B) scores based on estimated scores from general linear models. Higher scores indicate higher quality of life (A) or patients' satisfaction with medications (B). The model included an indicator variable denoting the presence/absence of bloating and the diagnosis of IBS-C/FC. The interaction term between bloating and diagnosis of IBS-C/FC was not statistically significant.

possible confounders (Table 3). The association between bloating and SF-12 physical composite (Bloating: $\beta = -2.34$, $p < 0.01$) was independent of other constipation-related symptoms (overlap-corrected PAC-SYM scores: $\beta = -3.83$, $p < 0.01$). On the contrary the association between bloating and SF-12 mental composite (Bloating: $\beta = -0.64$, $p = 0.46$) was not independent of other constipation-related symptoms (overlap-corrected PAC-SYM score: $\beta = -4.69$, $p < 0.01$).

Bloating and treatment satisfaction

Among patients without bloating, 78% ($n = 112$) reported to be partially or completely satisfied with the effectiveness, 96% ($n = 136$) with the safety and 91% ($n = 127$) with the convenience of administration of their treatment. Patients with bloating reported lower satisfaction on all dimensions (59%, 87%, and 82% respectively, $p < 0.01$). Additionally, patients with bloating reported lower treatment satisfaction scores independent of the diagnosis of FC or IBS-C (Fig. 1, Panel B). Bloating was associated with treatment satisfaction independent of possible confounders (Table 3). After adjustment for overlap-corrected PAC-SYM scores, bloating was still associated with TSQM Effectiveness ($\beta = -4.79$, $p < 0.01$) and TSQM Convenience ($\beta = -4.63$, $p = 0.02$), while the association with TSQM Safety was strongly attenuated and lost statistical significance ($\beta = -2.82$, $p = 0.23$).

Bloating and clinical change after therapy switch

A minority ($n = 413$, 30%) of LIRS II patients initiated a new therapy in the 3 months prior to the interview. Most patients (66%) reported subjective clinical improvement after switch or initiation of therapy, 27% reported no clinical change and only 7% reported worsening symptoms. Bloating was strongly associated with patients' rating of change after therapy switch independent of treatment and adjustment for possible confounders (Table 4).

Sensitivity analysis

Patients with a medical history of conditions possibly associated with secondary constipation were older

Table 3 Correlates of patient-reported outcomes

	PAC-SYM[†]	SF-12: PCS	SF-12: MCS	Effectiveness	Side effects	Convenience
Characteristics	Unstandardized regression coefficient estimates					
Intercept	1.17	52.71	42.61	65.71	85.15	76.40
Bloating	0.59**	−4.71**	−3.54**	−11.53**	−9.21**	−10.15**
IBS-C (reference: FC)	0.19**	−1.07*	−1.40**	−1.29	−1.40**	−0.41
Age[‡]	−0.06**	−1.01**	0.07	0.28	1.28*	0.51
Women	0.09	−0.60	−1.42*	0.44	0.60	2.15
Employed	−0.06	2.10**	0.96	1.56	4.39**	2.62*
Time since disease onset[§]	0.04*	0.11	0.005	−0.41	−0.49	−0.24
Current smoker (Y)	0.02	−0.30	−0.78	1.05	0.43	0.69
Water >1 L/day	−0.01	0.17	0.40	0.41	0.06	1.73
Number of comorbidities	0.08**	−1.09**	−0.90**	−0.94**	−2.00**	−0.41
BMI[¶]	−0.02	−0.47	−0.20	0.65	0.34	−0.10
Diabetes	0.01	−1.14	0.96	1.07	2.46	−3.69
Depression/anxiety	−0.05	−0.47	−5.94**	1.74	−3.47	1.77
Therapy						
Diet/other	0.53**	−1.49	−1.14	−18.33**	−7.46**	−16.44**
Bulking/osmotic	0.64**	−1.52	−3.49**	−13.14**	−3.27**	−17.99**
Stimulant/herbal	0.78**	−1.25	−2.34	−17.70**	−8.33**	−18.80**
Enema	0.68**	−2.01	−1.72	−16.80**	−7.31**	−22.26**
Any association	0.63**	−2.25**	−2.79**	−16.19**	−7.00**	−18.91**
None	0.62**	−0.65	−1.16	−25.57**	−21.90**	−23.46**
Prucalopride	Reference	Reference	Reference	Reference	Reference	Reference

Unstandardized regression coefficient estimates represent the change in the dependent variable for a 1-unit change in the independent variable. For categorical variables (e.g., presence/absence of bloating), the parameter represent the change in the dependent variable when the condition is present. The intercept estimates represent the baseline value of the dependent variable when all covariates in the model are set to their reference category (i.e., patients reporting no bloating, men, with FC, 18 years old, unemployed, with a first diagnosis of chronic non-organic constipation in the past month, non-smoking, with BMI = 23.6, with no comorbidities and treated with prucalopride). Comparisons across treatment groups are contrasted against the reference group 'prucalopride': hence, each parameter estimate represents the change in score occurring with a treatment option compared to the reference category after adjustment for covariates and confounders. Higher scores of the SF-12 and TSQM II questionnaire represent higher quality of life and treatment satisfaction, respectively. [†]PAC-SYM score corrected for overlap; [‡]10-year intervals; [§]5-year intervals; [¶]5-unit intervals; *$p < 0.05$; **$p < 0.01$.

(56.7 *vs* 47.4, $p = 0.02$) and more likely to report a feeling of incomplete evacuation in at least 25% of defecations (78% *vs* 71%, $p < 0.05$), a sensation of anorectal obstruction/blockage for at least 25% of defecations (48% *vs* 36%, $p < 0.05$), the need to adopt manual maneuvers to facilitate at least 25% of defecations (22% *vs* 30%, $p < 0.05$). We observed no differences in bloating prevalence, IBS prevalence, gender, fluid intake >1 L/day, smoking habit, treatment, time since constipation onset across patients with/without previous history of organic diseases potentially associated with constipation (data not shown). The relationship between bloating and health-related QoL (SF-12) was not moderated by the inclusion/exclusion of patients with medical history of conditions possibly associated with secondary constipation (SF-12, PCS: p for interaction = 0.79; SF-12, MCS: p for interaction = 0.20). On the contrary, moderation analysis revealed that the association between bloating, treatment satisfaction, and other constipation-related symptoms was weaker in patients with a medical history of conditions possibly associated with secondary constipation. As such, the inclusion of patients with organic constipation in the analysis may lead to underestimating the association between patients' report of bloating and constipation severity (overlap-corrected PAC-SYM: $\Delta_{p\text{-}s} = 0.49$, $p < 0.01$), satisfaction with treatment effectiveness (TSQMv2-Effectiveness: $\Delta_{p\text{-}s} = 12.38$, $p < 0.01$), and satisfaction with treatment convenience of administration (TSQMv2-Convenience: $\Delta_{p\text{-}s} = 14.39$, $p < 0.01$).

DISCUSSION

In this large cross-sectional study, we observed a strong association between bloating, health-related QoL, and treatment satisfaction independent of the diagnosis of IBS-C or FC, other constipation-related symptoms and possible confounders. Finally, we found that patients with bloating were less responsive to treatment and that the intensity of bloating was strongly related to the subjective clinical rating of change after therapy switch.

Given its widespread prevalence, bloating has been considered a supportive symptom rather than part of the diagnostic criteria for most FGIDs so far; however, when bloating is not part of another functional bowel or gastrointestinal disorder it is classified as an

Table 4 Correlates of global rating of change after therapy switch

	Model 1	Model 2	Model 3
Unstandardized regression coefficient estimates			
Intercept	3.34	4.52	6.61
Bloating	−1.15**	−1.48**	−0.64
IBS-C	–	−0.09	−0.03
Women	–	−0.40	−0.77
Unemployed	–	−0.29	−0.37
Non-smoker	–	−0.17	−0.26
Diabetes	–	−0.65	−0.23
Depression	–	0.28	−0.60
Fluid intake <1 L	–	−0.45	−0.22
Time since symptoms onset	–	−0.01	−0.01
Number of comorbidities	–	−0.37**	−0.31**
BMI	–	−0.02	−0.01
PAC-SYM (overlap corrected)	–	–	−1.38**
Treatment after switch			
Prucalopride – monotherapy	Ref.	Ref.	Ref.
Other monotherapies*	−1.15**	−1.28**	−0.56
Prucalopride – associations	−0.84**	−0.69	−0.55
Other associations	−1.46**	−1.30**	−0.58

General linear models. Variables included in Model 1: bloating, treatment after switch; Model 2: Model 1+ IBS-Like pain, gender, employment, smoke, diabetes, depression, fluid intake, time since disease onset, number of comorbidities, BMI; Model 3: Model 2+ Overlap corrected Pac-Sym score. *Monotherapies include dietary prescription, bulking/osmotics, herbal/stimulants, enema/suppository alone. Unstandardized regression coefficient estimates represent the change in the dependent variable for a 1-unit change in the independent variable. For categorical variables (e.g., presence/absence of bloating), the parameter represent the change in the dependent variable when the condition is present.
**denotes statistically significant associations at $P < 0.05$.

independent entity named functional bloating[17] by the Rome III consensus. In our sample bloating was more prevalent in women, obese subjects and those with IBS-C. Even though the odds ratios for these factors indicated a strong association, bloating prevalence in men without these conditions was still very high. Our sensitivity analysis further showed that inclusion of patients with any organic disease potentially associated with constipation had little impact on the prevalence estimates of bloating. Taken together, these results suggest that bloating is a widespread problem in all patients with constipation independent of their clinical diagnosis.

A key finding of our study was that bloating was associated with reduced physical functioning (SF12-Physical Composite Score) independent of possible confounders (including abdominal pain and diagnosis of FC/IBS-C). This difference approached clinical significance according to common minimal clinically important difference standards for QoL measures[18] indicating that the difference observed may be appreciated by patients as a real difference in QoL. This finding is in contrast with previous reports showing that only abdominal pain and diarrhea, but not bloating and other IBS-related symptoms, were independently associated with reduced QoL.[10] One difficulty in assessing the association of bloating and QoL independent of abdominal pain in previous studies might be that such symptoms are strongly related. Our large sample size allowed greater precision and extensive adjustment, thus reducing confounding bias.

Paired with HRQOL data, we observed greater treatment satisfaction in patients without bloating after adjustment for other constipation-related symptoms. Consistent with our observation, relief from bloating was the most difficult endpoint to achieve for all common therapies, in a recent European survey.[19] A further important finding of our study was that patients with bloating were less responsive to various constipation-related treatments independent of socio-demographic factors, general health, therapy, and the diagnosis of IBS-C or FC. Overall, this evidence suggests that bloating might be a relevant independent target of therapy despite it currently remains without a proper clinical classification, a clear pathophysiology, and an effective treatment. Our study highlights the importance of bloating as an independent clinical feature in patients with FC and IBS-C. In theory, a pharmaceutical agent that can stimulate intestinal gas flow might have beneficial effects on this symptom. There is experimental evidence that prokinetic drugs such as 5-HT_4 receptor agonists could effectively address bloating.[20–28] Additionally, patients treated with linaclotide, a minimally absorbed 14 amino acid peptide enhancing luminal fluid secretion and bowel motility, reported improvements of bloating sensations during a 12-week follow-up randomized controlled parallel group clinical trial against placebo.[29] However, the sensation of abdominal distension is often reported by patients with somatization disorders, a condition associated with a propensity to amplify the intensity and significance of bodily sensations, which in turn may be associated with greater healthcare-seeking behavior,[30] reduced treatment satisfaction, and worse responsiveness to treatment of somatic symptoms. Our study was not designed to shed light on the pathophysiological mechanisms underlying bloating, other lower GI symptoms, and PRO. Hopefully, further research would evaluate the inter-play between abdominal distension, sensation of bloating, and other constipation-related symptoms thus helping to manage these difficult patients.

Our study has several strengths. Firstly, we were able to provide a comprehensive picture of PRO (i.e., QoL, treatment satisfaction and clinical rating of change after therapy) thus allowing to inspect patients' perspective concerning bloating burden on several

dimensions of well-being and health. Secondly, our large sample size and extensive data collection allowed adjustment for potentially important confounders. Thirdly, clinical data and patients' screening for inclusion was conducted by expert gastroenterologists thus reducing information and classification bias. Additionally, our sensitivity analysis showed that the association between bloating and PRO was stronger in patients with FC or IBS-C compared to subjects with medical conditions associated with secondary constipation. Thus, including patients with secondary constipation in the sample might lead to underestimating the association between bloating and PRO. Finally, the association of bloating on PRO observed in the cross-sectional analysis was confirmed in the longitudinal section of our study.

Nevertheless, we should acknowledge some limitations. Firstly, observational studies cannot prove causality as residual confounding by unmeasured variable can never be completely ruled out. Secondly, even though a gastroenterologist compiled a standardized form on patients' clinical characteristics, we lacked information on physiological tests of bowel function, which may have helped classify patients in functional sub-types. Thirdly, patients included in our study were referred to a 3rd level center and our findings may not be generalizable to all patients with FC or IBS-C. It should be noted however that the average PAC-SYM score in our sample was as low as that reported in the PAC-SYM validation study, a research which recruited patients from the general population by advertisement.[14] Overall our results support the internal validity of our study. Prevalence estimates and risk factors for bloating are consistent with several previous reports in the same source population thus reducing the likelihood of selection bias and information bias.[7] Fourthly, we lacked detailed information allowing us differentiating between subjective bloating and objective abdominal distension, thus limiting our ability to further inspect the differential impact of these distinct conditions on PRO. Finally, we could not collect detailed dietary information in this study. Fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP)-restricted diet have recently shown promising outcomes in the management of FC and IBS-C.[31] Additionally, dietary intake of alimentary fibers might be associated with increased bloating.[32] As a consequence we could not evaluate the impact of different diets on bloating prevalence and magnitude.

In conclusion, we found that bloating is a highly prevalent and bothersome symptom which is partially independent of other lower gastrointestinal complaints in patients' with FC and IBS-C. Our data suggest that patients regard bloating as a key element in assessing treatments' efficacy as this symptom exerts a strong influence on QoL independent of other constipation-related symptoms. Paired with its prevalence among constipated patients and the lack of established management options, our data provide the rationale to investigate the efficacy and tolerability of new treatments specifically addressing this important, yet often disregarded, patients' complaint.

FUNDING

The LIRS study has been partially funded by Shire Pharmaceutical Inc. Data collection have been carried out by DoxaPharma SRL. Shire Pharmaceuticals did not have access to the raw data.

CONFLICTS OF INTEREST

Dr Neri has received an unrestricted research grant by DoxaPharma SRL to support the production of this manuscript.

AUTHOR CONTRIBUTION

LN participated in study concept and design, data analysis, interpretation of results, manuscript drafting, and approved the final version of the manuscript; PI participated in study concept and design, data collection, interpretation of results, provided critical revisions to manuscript drafts, and approved the final version of the manuscript. All members of the LIRS study group participated in study concept and design, data collection, provided critical revisions to manuscript drafts, and approved the final version of the manuscript.

REFERENCES

1 Jiang X, Locke GR 3rd, Choung RS, Zinsmeister AR, Schleck CD, Talley NJ. Knill-Jones Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. *Gut* 2008; **57**: 756–63.

2 Iovino P, Bucci C, Tremolaterra F, Santonicola A, Chiarioni G. Bloating and functional gastro-intestinal disorders: where are we and where are we going? *World J Gastroenterol* 2014; **20**: 14407–19.

3 Schmulson M, Chang L. Review article: the treatment of functional abdominal bloating and distension. *Aliment Pharmacol Ther* 2011; **33**: 1071–86. doi:10.1111/j.1365-2036.2011.04637.x.

4 Talley NJ, Phillips SF, Melton J 3rd, Wiltgen C, Zinsmeister AR A patient questionnaire to identify bowel disease. *Ann Intern Med* 1989; **111**: 671–4.

5 Lembo T, Naliboff B, Munakata J, Fullerton S, Saba L, Tung S, Schmulson M, Mayer EA. Symptoms and visceral perception in patients with pain-predominant irritable bowel syndrome. *Am J Gastroenterol* 1999; **94**: 1320–6.

6 Sach J, Bolus R, Fitzgerald L, Naliboff B, Chang L, Mayer E. Is there a difference between abdominal pain and discomfort in moderate to severe IBS patients? *Am J Gastroenterol* 2002; **12**: 3131–8.

7 Wiklund IK, Fullerton S, Hawkey CJ, Jones RH, Longstreth GF, Mayer EA, Peacock RA, Wilson IK *et al.* An irritable bowel syndrome-specific symptom questionnaire: development and validation. *Scand J Gastroenterol* 2003; **38**: 947–54.

8 Thompson WG, Longstreth G, Drossman DA, Heaton K, Irvine EJ, Muller-Lissner SC. Functional bowel disorders in functional abdominal pain. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *The Functional Gastrointestinal Disorders*, 2nd edn. McLean, VA: Degnon Associates, 2000: 351–432.

9 Hernando-Harder AC, Serra J, Azpiroz F, Milà M, Aguadé S, Malagelada C, Tremolaterra F, Villoria A *et al.* Colonic responses to gas loads in subgroups of patients with abdominal bloating. *Am J Gastroenterol* 2010; **105**: 876–82.

10 Koloski NA, Boyce PM, Jones MP, Talley NJ. What level of IBS symptoms drives impairment in health-related quality of life in community subjects with irritable bowel syndrome? Are current IBS symptom thresholds clinically meaningful? *Qual Life Res* 2012; **21**: 829–36. doi:10.1007/s11136-011-9985-5.

11 Ringel Y, Williams RE, Kalilani L, Cook SF. Prevalence, characteristics, and impact of bloating symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009; **7**: 68–72. doi:10.1016/j.cgh.2008.07.008; quiz 3.

12 Neri L, Basilisco G, Corazziari E, Stanghellini V, Bassotti G, Bellini M, Perelli I, Cuomo R *et al.* Constipation severity is associated with productivity losses and healthcare utilization in patients with chronic constipation. *United European Gastroenterol J* 2014; **2**: 138–47.

13 Apolone G, Mosconi P, Quattrocchi L. *Questionario sullo stato di salute SF-12*. Versione italiana. Ed. Guerini e Associati, published on January 2005. ISBN: 8883352017

14 Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999; **34**: 870–7.

15 Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health* 2005; **8** (Suppl. 1): S9–24.

16 Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther* 2009; **17**: 163–70.

17 Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480–91.

18 Copay AG, Subach BR, Glassman SD, Polly DW Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J* 2007; **7**: 541–6.

19 Emmanuel A, Quigley EM, Simrén M, Feng Y, Müller-Lissner S, Urbain D, Tack J, Bredenoord AJ *et al.* Factors affecting satisfaction with treatment in European women with chronic constipation: an internet survey. *United European Gastroenterol J* 2013; **1**: 375–84.

20 Azpiroz F, Serra J. Treatment of excessive intestinal gas. *Curr Treat Opin Gastroenterol* 2004; **7**: 299–305.

21 Müller-Lissner SA, Fumagalli I, Bardhan KD, Pace F, Pecher E, Nault B, Rüegg P *et al.* Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001; **15**: 1655–66.

22 Grider JR, Kuemmerle JF, Jin JG. 5-HT released by mucosal stimuli initiates peristalsis by activating 5-HT4/5-HT1P receptors on sensory CGRP neurons. *Am J Physiol* 1996; **270**: G778–82.

23 Coleski R, Owyang C, Hasler WL. Modulation of intestinal gas dynamics in healthy human volunteers by the 5-HT receptor agonist tegaserod. *Am J Gastroenterol* 2006; **101**: 1858–65.

24 Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation predominant irritable bowel syndrome. *Gastroenterology* 2000; **118**: 463–8.

25 Anderson JL, May HT, Blair TL, Muhlestein JB, Horne BD, Carlquist JF. Association of tegaserod with cardiovascular outcomes in a matched study of 18,221 treated and untreated patients. *Eur Heart J* 2008; **29** (Suppl.): 755.

26 Tack J, Stanghellini V, Dubois D, Joseph A, Vandeplassche L, Kerstens R. Effect of prucalopride on symptoms of chronic constipation. *Neurogastroenterol Motil* 2014; **26**: 21–7. doi:10.1111/nmo.12217.

27 De Schryver AM, Andriesse GI, Samsom M, Smout AJ, Gooszen HG, Akkermans LM. The effects of the specific 5HT(4) receptor agonist, prucalopride, on colonic motility in healthy volunteers. *Aliment Pharmacol Ther* 2002; **16**: 603–12.

28 Wong BS, Manabe N, Camilleri M. Role of prucalopride, a serotonin (5-HT4) receptor agonist, for the treatment of chronic constipation. *Clin Exp Gastroenterol* 2010; **3**: 49–56.

29 Lacy BE, Schey R, Shiff SJ, Lavins BJ, Fox SM, Jia XD, Blakesley RE, Hao X *et al.* Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. *PLoS ONE* 2015; **10**: e0134349.

30 Spiegel BM, Kanwal F, Naliboff B, Mayer E. The impact of somatization on the use of gastrointestinal healthcare resources in patients with irritable bowel syndrome. *Am J Gastroenterol* 2005; **100**: 2262–73.

31 Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther* 2015; **41**: 1256–70.

32 Hebden JM, Blackshaw E, D'Amato M, Perkins AC, Spiller RC. Abnormalities of GI transit in bloated irritable bowel syndrome: effect of bran on transit and symptoms. *Am J Gastroenterol* 2002; **97**: 2315–20.

APPENDIX
LIRS STUDY GROUP MEMBERS

Last Name, First Name, Degree	Affiliation	Role
Altomare, Donato Francesco, MD	D.E.T.O. Sezione Chirurgia generale e trapianto di fegato – Policlinico Consorzile, Bari, Italy	Co-investigator
Annese, Vito, MD	Gastroenterologia - AOUC Careggi, Firenze, Italy	Co-investigator
Badiali, Danilo, MD	Dipartimento di Medicina Interna e Specialità Mediche - Gastroenterologia A - Università Sapienza - Policlinico Umberto I - Roma	Co-investigator
Basilisco, Guido, MD	U.O. di Gastroenterologia 2 - IRCCS Ca' Granda - Ospedale Maggiore Policlinico - Milano	Co-investigator
Bassotti, Gabrio, MD	Sezione di Gastroenterologia - Dipartimento di Medicina- Università di Perugia - Ospedale S. Maria della Misericordia - Perugia	Co-investigator
Battaglia, Edda, MD	S.O.C. Gastroenterologia - Ospedale Cardinal Massaia, Asti, Italy	Co-investigator
Bazzocchi, Gabriele, MD	U.O. Riabilitazione Gastroenterologia Montecatone Rehabilitation Institute, Bologna, Italy	Co-investigator
Bellini, Massimo, MD	U.O. Gastroenterologia Universitaria - AOUP Pisana	Co-investigator
Bendia, Emanuele, MD	UO Gastroenterologia Clinica - Ospedali Riuniti, Ancona, Italy	Co-investigator
Benini, Luigi, MD	U.O. di Gastroeneterologia - Policlinico G.B. Rossi - Università di Verona - Verona	Co-investigator
Biscaglia, Giuseppe, MD	S.C. di Gastroenterologia ed Endoscopia Digestiva Ospedale 'Casa Sollievo della Sofferenza' – IRCCS, San Giovanni Rotondo (FG)	Co-investigator
Biviano, Ivano, MD	Dipartimento di Medicina Interna e Specialità Mediche, Gastroenterologia A - Università Sapienza, Roma – Italy	Co-investigator
Bocchini, Renato, MD	Fisiopatologia ed Endoscopia Digestiva. Gastroenterologia ed Endoscopia Digestiva, Casa di Cura Malatesta Novello, Cesena, Italy	Co-investigator
Bonventre, Sebastiano, MD	Ambulatorio fisiopatologia digestiva AOU Paolo Giaccone, Palermo, Italy	Co-investigator
Bossa, Fabrizio, MD	IRCCS Ospedale Casa Sollievo della Sofferenza San Giovanni Rotondo, Foggia, Italy	Co-investigator
Brandimarte, Giovanni, MD	U.O. Gastroenterologia, Ospedale Cristo Re, Roma, Italy	Co-investigator
Cannizzaro, Renato, MD	S.O.C. Gastroenterologia Centro di riferimento oncologico Aviano, Pordenone, Italy	Co-investigator
Cicala, Michele, MD	UO Gastroenterologia ed endoscopia digestive, Policlinico Universitario Campus Biomedico, Roma, Italy	Co-investigator
Cipolletta, Livio, MD	UO di Gastroenterologia P.O. 'A. Maresca' ASL Napoli 3 Sud, Napoli, Italy	Co-investigator
Clara, Virgilio, MD	U.O.C. Gastroenterologia ARNAS Garibaldi Nesima, Catania, Italy	Co-investigator
Cogliandro, Rosanna, MD	Dipartimento di Medicina clinica Policlinico S. Orsola Malpighi, Bologna, Italy	Co-investigator
Comandini, Giulia, MD	U.O. Gastroenterologia A.O. Bufalini, Forli-Cesena, Italy	Co-investigator
Corazziari, Enrico, MD	Dipartimento di Medicina Interna e Specialità Mediche, Gastroenterologia A - Università Sapienza, Roma – Italy	Co-investigator
Crotta, Sergio, MD	U.B. Gastroenterologia ed endoscopia digestiva Ospedale Beuregard, Aosta, Italy	Co-investigator
Cuomo, Rosario, MD	Department of Clinical & Experimental Medicine, Federico II University Hospital School of Medicine, Napoli - Italy	Co-investigator
D'Alba, Lucia, MD	UOC/UOSD Gastroenterologia ed endoscopia digestiva – A.O. S.Giovanni Addolorata	Co-investigator
De Giorgi, Francesco, MD	U.O. di Gastroenterologia - Settore di Diagnosi e Terapia - Malattie Motorie Digestive - A.O.U. Federico II - Napoli	Co-investigator
Del Piano, Mario, MD	U.O. di Gastroenterologia - Az. Ospedaliera Universitaria 'Maggiore Della Carità', Novara, Italy	Co-investigator
Di Fonzo, Michela, MD	U.O. Gastroenterologia, Ospedale Cristo Re, Roma, Italy	Co-investigator
Di Mario, Francesco, MD	S.C. Gastroenterologia Ospedale Regionale Ca' Foncello, Treviso, Italy	Co-investigator
Di Stefano, Michele, MD	UO Clinica Medica 1 - Università di Pavia - Fondazione IRCCS - Policlinico S. Matteo - Pavia	Co-investigator
D'Onofrio, Vittorio , MD	UOC Gastroenterologia AOS San G. Moscati, Avellino, Italy	Co-investigator
Efthymakis, Kostantinos, MD	U.O.D. Gastroenterologia ed endoscopia digestiva P.O. SS. Annunziata, Chieti, Italy	Co-investigator
Fiore, Pierluigi, MD	U.O. Gastroenterologia, Casa di Cura 'Di Lorenzo', Avezzano L'Aquila, Italy	Co-investigator
Fortuna, Manuela, MD	Servizio di Endoscopia Digestiva, Ospedale San Camillo, Trento, Italy	Co-investigator
Fries, Walter, MD	U.O.S. Malattie Intestinali Croniche - Dipartimento di Medicina Interna - Policlinico G. Martino - Messina	Co-investigator
Gaetani, Eleonora, MD	Dipartimento di Scienze Mediche, Medicina Interna e Gastroenterologia, Ospedale Policlinico Gemelli, Roma, Italy	Co-investigator
Galeazzi, Francesca, MD	UOC Gastroenterologia AO Università di Padova, Padova, Italy	Co-investigator
Gasbarrini, Antonio, MD	UOC Medicina Interna e Gastroenterologia, Policlinico Universitario 'A. Gemelli', Roma, Italy	Co-investigator
Geccherle', Andrea, MD	Centro Multispecialistico Malattie Retto-Perineale, Ospedale Del Sacro Cuore 'Don Calabria', Negrar, Italy	Co-investigator
Giangregorio, Francesco, MD	U.O. di Gastroenterologia, Epatologia ed Endoscopia Digestiva – Ospedale Guglielmo da Saliceto, Piacenza, Italy	Co-investigator
Girardi, Lisa, MD	UOC Di Gastroenterologia, Ospedale dell'Angelo, Mestre, Italy	Co-investigator
Grassini, Mario, MD	S.O.C. Gastroenterologia - Ospedale Cardinal Massaia, Asti, Italy	Co-investigator
Groppo, Marzia, MD	UOC Gastroenterologia, ASL 9 Regione Veneto, Treviso, Italy	Co-investigator
Guarnieri, Giovanni, MD	S.C. Gastroenterologia Ospedale Regionale Ca' Foncello, Treviso, Italy	Co-investigator

(Continued.)

APPENDIX *(continued)*

Last Name, First Name, Degree	Affiliation	Role
Iovino, Paola, MD	Department of Medicine and Surgery, University of Salerno, Salerno, Italy	Writing Committee Member
Lo Cascio, Massimiliano, MD	UO Gastroenterologia - Ospedale di Fermo, Fermo, Italy	Co-investigator
Lolli, Roberto, MD	UOC Gastroenterologia e Endoscopia digestiva, Ospedale Regionale Valle d'Aosta, Aosta, Italy	Co-investigator
Luzza, Francesco, MD	U.O. di Fisiopaologia Digestiva, Dipartimento di Scienze della Salute, Università di Catanzaro 'Magna Graecia', Catanzaro, Italy	Co-investigator
Macarri, Giampiero, MD	UO Gastroenterologia - Ospedale di Fermo, Fermo, Italy	Co-investigator
Marino, Maria, MD	Servizio Di Endoscopia, Ospedale Di Ortona, Ortona, Italy	Co-investigator
Miraglia, Stefania, MD	U.O.C. Gastroenterologia ARNAS Garibaldi Nesima, Catania, Italy	Co-investigator
Monastra, Santo, MD	UO Gastroenterologia ed Endoscopia Digestiva, Ospedale San Gennaro, Asl Napoli 1 Centro, Napoli, Italy	Co-investigator
Neri, Luca, MD, PhD	Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italy	Writing Committee Member
Neri, Maria Cristina, MD	UO Gastroenterologia ed endoscopia digestiva – Pio Albergo Trivulzio, Milano, Italy	Co-investigator
Neri, Matteo, MD	U.O.D. Gastroenterologia ed endoscopia digestiva P.O. SS. Annunziata, Chieti, Italy	Co-investigator
Noris, Roberto Antonio, MD	U.O.C. di Gastroenterologia ed Endoscopia Digestiva - A.O. Bolognini - Seriate (BG)	Co-investigator
Orselli, Silvia, MD	UO Gastroenterologia - AOUC Careggi, Firenze, Italy	Co-investigator
Passaretti, Sandro, MD	U.O. Gastroenterologia Ospedale Universitario San Raffaele, Milano, Italy	Co-investigator
Paviotti, Alberto, MD	SOSD di Gastroenterologia ed Endoscopia Digestiva ASS5- Palmanova, Italy	Co-investigator
Pazzi, Paolo, MD	U.O. Gastroenterologia A.O. Bufalini, Forlì-Cesena, Italy	Co-investigator
Pilotto, Alberto, MD	U.O.C. Geriatria AZ. ULSS 16 OSP. S. Antonio, Padova, Italy	Co-investigator
Portincasa, Piero, MD	UO di Semeiotica Funzionale e Strumentale, Clinica Medica 'A. Murri' - Università degli Studi di Bari, Bari, Italy	Co-investigator
Ranaldo, Nunzio, MD	Istituto Gastroenterologia Universitaria, Policlinico Di Bari, Bari, Italy	Co-investigator
Ravelli, Paolo, MD	UO Gastroenterologia ed Endoscopia Digestiva, Ospedali Riuniti, Bergamo, Italy	Co-investigator
Rogai, Francesca, MD	UO Gastroenterologia sod. 2, AOU Careggi, Firenze, Italy	Co-investigator
Sablich, Renato, MD	UO Gastroenterologia AZ. Ospedaliera S. Maria Degli Angeli, Pordenone, Italy	Co-investigator
Savarino, Vincenzo, MD	U.O. Clinica gastroenterologia con endoscopia - IRCCS Azienda Ospedaliera Universitaria San Martino - IST - Genova	Co-investigator
Spinzi, Giancarlo, MD	UO Gastroenterologia, Ospedale Valduce, Como, Italy	Co-investigator
Stanghellini, Vincenzo, MD	Dipartimento di Medicina Clinica, Università Alma Mater Studiorum, Bologna, Italy	Co-investigator
Tammaro, Leonardo, MD	UOC/UOSD Gastroenterologia ed endoscopia digestiva - AO S. Giovanni Addolorata, Roma, Italy	Co-investigator
Torresan, Francesco, MD	UO Gastroenterologia, Ambulatorio Motilità, Ospedale S.Orsola Malpighi, Bologna, Italy	Co-investigator
Usai Satta, Paolo, MD	Società Complessa di Gastroenterologia - Azienda Ospedaliera G. Brotzu - Cagliari	Co-investigator
Valle, Claudio, MD	ASL 1 Imperiese – S.S. Cure domiciliari Imperia, Imperia, Italy	Co-investigator

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Description of psychometric instruments.