

Epidemiology and Burden of Disorders of Gut-Brain Interaction in Romania: A Subgroup Analysis of the Rome Foundation Global Epidemiology Study

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ABSTRACT

Background & Aims: Disorders of gut-brain interaction (DGBI) are a group of chronic illnesses that are crucial to public health because they are widespread, influence patients' quality of life and functional level, and exert a major socioeconomic impact. We assessed the national prevalence of all 22 DGBI, the percentage of respondents satisfying diagnostic criteria for at least one DGBI, and the impact on the disease burden in Romania using data from the Rome Foundation Global Epidemiology Study.

Methods: Data were collected through an anonymous, nationwide, and secure online survey, which evaluated the prevalence of any DGBI as well as over 22 different DGBI. The Rome IV diagnostic questionnaire and an in-depth supplemental questionnaire were included in the survey, which was completed through the Internet with numerous built-in quality-assurance measures.

Results: The survey was completed by 2,049 participants (mean age 42.29±13.11 years) with a representative national distribution. Diagnostic criteria for any DGBI were met in 40.1% of the subjects, while 28.6% met criteria for only one DGBI (no overlap), and 11.5% met criteria for DGBIs in two, three, or four overlapping gastrointestinal anatomical regions. Females had a substantially higher predominance of DGBI than males. Psychosocial characteristics (such as quality of life, somatization, and concern about digestive problems) and healthcare utilization (such as physician visits and medication use) were associated with having any DGBI.

Conclusions: We provide the first comprehensive evaluation of the prevalence and burden of DGBI in Romania using the Rome IV criteria. The burden of DGBI in Romania is substantial, with 40.1% of the 2,049 participants meeting diagnostic criteria for any DGBI. These findings demonstrate the importance of patient care, and the need for training and future research.

Key words: disorders of gut-brain interaction (DGBI) - Rome IV diagnostic criteria - irritable bowel syndrome (IBS) – prevalence – epidemiology – Romania - health-related quality of life (HRQoL).

Abbreviations: CNS: central nervous system; DGBI: disorders of gut-brain interaction; FC: functional constipation; FD: functional dyspepsia; FGID: functional gastrointestinal diseases; GI: gastrointestinal; IBS: irritable bowel syndrome; PHQ: Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; QoL: quality of life; RFGES: Rome Foundation Global Epidemiology Study.

INTRODUCTION

The disorders of gut-brain interaction (DGBI) are defined as a diverse range of gastrointestinal (GI) symptoms caused by any combination of motility disturbance, visceral hypersensitivity, modified mucosal and immunological function, altered gut microbiota, and altered central nervous system (CNS) processing [1].

The term „functional gastrointestinal diseases” (FGID) has been replaced by DGBI, which better depicts the etiology of these disorders as it is understood today and eliminates the dichotomy of „organic” vs. „functional” involvement [2].

Irritable bowel syndrome (IBS), functional dyspepsia (FD), functional constipation (FC), functional diarrhea, and functional bloating/distention are conditions that fall within the DGBI spectrum [1]. Although DGBI have similar physiological properties, they can differ in terms of location in the GI tract, symptom duration, and vary among individuals or in the same individual over time. As a result, successful DGBI care necessitates a biopsychosocial approach that takes into account the diversity and complexity of people with these illnesses [3].

These disorders affect up to 30–40% of the general population in Western countries, and their prevalence decreases as people get older [4]. Eastern Europe is underrepresented in epidemiological data on the prevalence of DGBI and IBS [5, 6]. A small number of studies have been published on IBS in Romania. Dumitrascu et al. [7] investigated whether the stress caused by the dramatic events of December 1989 in Romania impacted the clinical condition of IBS patients. In 2002, Drug et al. [8] found that the prevalence of IBS symptoms in the general population of a city district in Eastern Romania was 14.4% (8.4% in males and 17.7% in females).

The Rome Foundation Global Epidemiology Study (RFGES) for 22 DGBI revealed that 40.3% of 54,127 participants in 26 countries, including Romania, met diagnostic criteria for at least one DGBI, implying the major global burden of these disorders [9]. Data were collected in an identical way by an Internet survey. The RFGES study in Romania included 2,049 respondents who met pre-determined age and gender criteria with a good geographical representation across the country, enabling the evaluation and diagnosis of 22 DGBI in the Romanian subgroup analysis [9].

This study's objectives included providing descriptive data on the prevalence of all 22 DGBI in Romania, evaluating the percentage of respondents fulfilling the diagnostic criteria for „any DGBI” as an indicator of the burden of disease of these disorders, stratifying and comparing the prevalence rates by gender and age group, as well as examining characteristics such as sociodemographic variables, psychosocial variables, and healthcare utilization that are linked to having DGBI. Moreover, we also aimed to determine the degree of DGBI overlap by anatomic region (esophageal, gastroduodenal, bowel, and anorectal), and examine the relationship between this overlap and the parameters listed above.

METHODS

Study Participants

Romania was one of the 26 countries that used an anonymous Internet survey to collect data in the RFGES, whose methods have been detailed previously in full [9, 10].

In summary, a secure online survey that was available only to preselected invited participants was completed, utilizing population samples provided by a professional company, Qualtrics, LLC (Provo, Utah, USA) that specializes in internet surveys. The survey was anonymous, conducted throughout the country, and included built-in quality-assurance procedures such as two attention-check questions, a completion-speed check, and repeat questions to find inconsistent respondents. The software guaranteed that no mandatory questions were left unanswered, and featured automated skip patterns, resulting in complete and accurate symptom pattern data.

As defined by the pre-specified study parameters, the participants were chosen solely based on demographic characteristics, which included a minimum of 2,000 participants with an equal gender distribution, and a representative national geographic distribution. The participants completed a formal electronic consent form before answering the survey questions.

DGBI Case Definitions

To identify DGBI cases, the survey included the full Adult Rome IV Diagnostic Questionnaire [11] and a checklist to report organic disorders that the patients were diagnosed with, or surgical abdominal procedures that they underwent that could represent organic or structural causes for the symptoms. If they responded affirmative to these items, they were excluded from the DGBI case definition, despite satisfying the Rome IV DGBI criteria. Celiac disease, gastrointestinal cancer, and inflammatory bowel disease (Crohn's disease or ulcerative colitis), for example, were eliminated from all Rome IV DGBI diagnoses. Individuals that presented with peptic ulcer disease history were excluded from the esophageal, gastroduodenal, and biliary diagnoses.

An 80-item supplemental questionnaire on sociodemographic, medical and health history, comorbid symptoms and conditions, GI infections, health care utilization, medications, childhood and current living conditions, psychosocial variables, diet, quality of life (QoL), and culture and religion was also included in the survey. It contained validated questionnaires including the Patient Health Questionnaire-12 (PHQ-12), a screening tool for somatization, and the Patient Health Questionnaire-4 (PHQ-4) [13] on anxiety and depression.

To assess the burden of DGBI, we used two proxy variables: (1) health care utilization, which included a history of (a) physician consultation concerning bowel issues and (b) number of doctor visits each year for any medical issues, and (2) QoL scores on the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 questionnaire (range 4–20) [14]. This questionnaire, which is part of the PROMIS, is a freely accessible global health assessment tool that assesses symptoms, functioning, and QoL for a wide range of chronic diseases and disorders. Participants in Romania completed the online survey in the Romanian language.

Statistical Analysis

We conducted bivariate analyses on 17 independent variables to evaluate the relationship of sociodemographic and psychological characteristics with having any DGBI or specific DGBI. The chi-squared test or Fisher's exact test were used for categorical variables, and the t test or one-way ANOVA for continuous variables.

The Wald test for continuous and binary variables and the likelihood ratio test for categorical variables were used in a multiple logistic regression analysis of parameters associated with having any DGBI. Descriptive statistics of overlapping DGBI prevalence rates were performed, with additional stratification according to age group and gender. SPSS software version 26.0 (IBM, Armonk, NY) was used for all statistical analyses.

RESULTS

General Characteristics

The sociodemographic data are summarized in Table I. The study population included 2,049 participants in the Romanian sample with a mean age of 42.29 ± 13.11 years (standard deviation, SD), a range from 18 to 81 years, and an almost equal gender distribution (50.9% males and 49.1% females).

Table I. Sociodemographic data of study population

Variable	n	%
Age (years) (n=2049)		
18-39	830	40.5
40-64	1125	54.9
65+	94	4.6
Mean $\pm$ SD	42.29 $\pm$ 13.11	
Median	43	
Range	18-81	
Gender		
Male	1043	50.9
Female	1006	49.1
Education (years) (n=2042*)		
Mean $\pm$ SD	14.77 $\pm$ 3.69	
Median	15	
Range	0-30	
Do you live in a: (n=2049)		
City (more than 50,000 inhabitants)	1364	66.6
Town (2,500 to 50,000 inhabitants)	457	22.3
Village or small town (less than 2,500 inhabitants)	213	10.4
Place in the countryside that is not a part of any city, town or village	15	0.7
Living area (n=2049)		
Urban	1821	88.9
Rural	228	11.1
Current relationship status (n=2049)		
Single	420	20.5
Married	1168	57.0
Divorced	159	7.8
Widowed	45	2.2
Co-habiting (not married but living with an adult partner)	257	12.5
Religious identity (n=2049)		
Buddhism	2	0.1
Catholicism	96	4.7
Islam	5	0.2
Mormonism	1	0.0
Orthodox Christianity (Eastern Orthodox)	1551	75.7
Protestantism	55	2.7
Sikhism	1	0
Taoism or traditional Chinese religion	1	0
Other religion not listed above	44	2.1
No particular religion, but I believe in God or a higher power	142	6.9
No religion, and I do not believe in God or a higher power	86	4.2
I do not wish to answer this question	65	3.2

* 7 missing participant responses

The age group distribution was 40.5% of ages 18-39 years (n=830), 54.9% ages 40-64 years (n=1125), and 4.6% age 65+ (n=94). A total of 1,821 participants lived in urban

areas (88.9%) and 228 participants in rural areas (11.1%). The distribution of participants throughout the country's geographic districts was similar to the national population distribution, as outlined in Fig. 1.

Descriptive Prevalence Analyses for DGBIs

We assessed the extent of DGBI involvement by anatomical GI area including esophageal, gastroduodenal, bowel, CNS related GI pain, biliary, and anorectal disorders. Table II summarizes the prevalence rates for 22 Rome IV functional GI diagnoses according to gender, age group and size of community (urban vs. rural). Regarding gastroduodenal disorders, their prevalence differed by age groups in FD, being most frequently seen between 18-39 years, and in rumination syndrome, with the highest frequency in the 40-64 years age group. IBS was more frequently reported in females compared to males. Moreover, FC was significantly more frequent in females, in the age group 18-39 years, and in participants living in urban areas. A higher frequency for functional diarrhea was reported in males, while functional bloating/distention was more frequent in females. Furthermore, female participants had a higher frequency of any bowel disorder compared to male participants.

Factors Associated with DGBI

Univariate Analyses

Participants with and without DGBI were compared in terms of sociodemographic and psychological characteristics, as reported in Table III. Meeting diagnostic criteria for any DGBI was strongly associated with female gender, but not with age group, years of education, or current relationship status. It was associated also with community size, psychosocial variables such as physical and mental quality of life (PROMIS Global-10), somatization (PHQ-12), anxiety and depression (PHQ-4), concerns regarding bowel function, embarrassment about discussing bowel function with family and friends, effect of stress, pressure, and tension on bowel function, in addition to health utilization variables such as mean number of medications, mean number of abdominal surgeries and doctor visits for any problem or bowel problems.

Multivariable Analyses

Being very concerned about bowel function, a great effect of stress, pressure, or tension on bowel function, higher mean number of medications, living in an urban area, higher mean PHQ-12 score, and lower PROMIS-10 QoL-physical component scores were the variables with the strongest association with DGBI, as demonstrated in Table IV. On the other hand, no significant association was observed between age group or gender and the presence of any DGBI.

DGBI Overlap and Associations with Healthcare Utilization, QoL, Disease Severity, and Other Psychosocial Variables

In Table V, we show the distribution of the number of involved anatomical regions and overlapping DGBI, by gender, age group and region.

Meeting diagnostic criteria for any DGBI was found in 40.1% of the participants, with 28.6% meeting the diagnostic

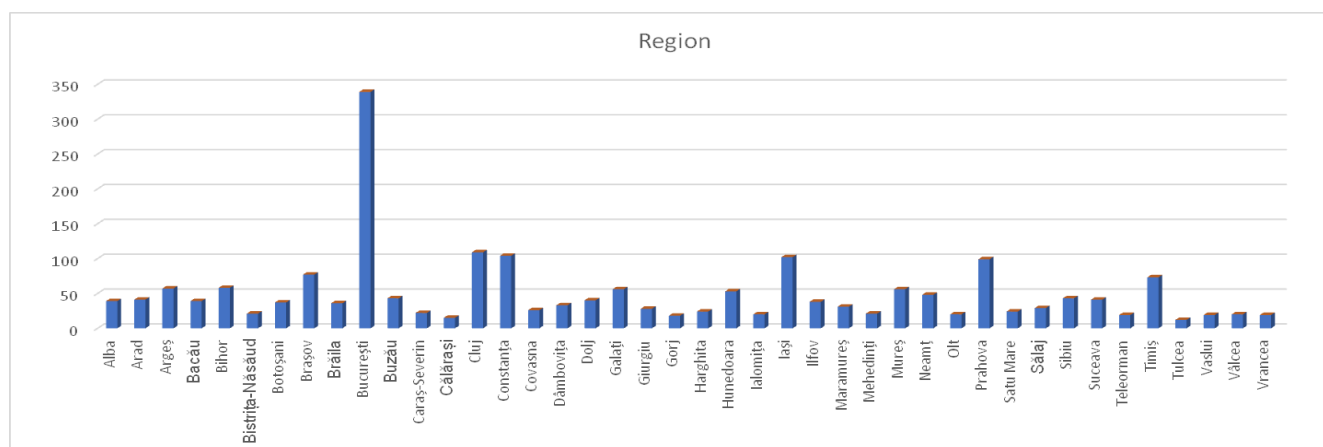


Fig. 1. Distribution of participants according to districts in Romania

criteria for only one DGBI (no overlap) and 11.5% meeting criteria for 2+ overlapping DGBI (Fig. 2), with a significantly higher rate for females compared to males ($p < 0.0001$). Moreover, the age group of 18-39 years had the highest prevalence of fulfilling criteria for at least one DGBI (40.8%), followed by people 40-64 years (39.7%), and 65+ years (37.2%). Participants living in urban areas had a higher prevalence of DGBI (41%) compared to rural areas (32.5%).

In Table VI, we present QoL scores by the number of overlapping GI regions. Due to the small number of participants with 4 overlapping GI regions, we combined the data for participants with 3 or 4 overlapping regions. There was incrementally worsening QoL, increased healthcare utilization, increased anxiety and depression, and increased somatization as the number of involved GI regions increased from 1 to 3 or 4. However, no significant difference was observed regarding DGBI overlap with the number of abdominal surgeries.

DISCUSSION

While there is a considerable amount of epidemiological data on DGBI, most of it centered on IBS. Moreover, the majority of reported studies did not use a representative national sample, and only a few covered all of the DGBI. The very limited number of DGBI epidemiological studies conducted in Romania focused on the prevalence of IBS, the latest using the now-antiquated Rome II diagnostic criteria [8, 15]. The RFGES was created to address these issues to the greatest extent possible. As a result of Romania's participation in this study, we have now a better grasp of the disease burden and associated variables related with all of the evaluated DGBI.

Epidemiological data on IBS is scarce in East European countries [5, 6]. Most countries have modest, local research and/or studies that were not published in international journals. A report from the Neurogastro 2019 meeting, which took place in Romania, summarized the recent data on IBS from some Central and East European countries, according to 12 specialists who took part in this report [16].

Prior to RFGES, the results of a limited number of studies from Romania were available. Of these, one reported that general physicians in Romania seem to be well trained

in recognizing IBS, most of them (66%) estimating the prevalence at about 10% for this disease in their practice [15]. Another study, published only in abstract form, reported the prevalence of diagnosed IBS among the patients of family physicians [17]. The prevalence rate for IBS was 2% in a sample of over 25,000 patients from the rosters of 28 general practitioners (GPs), with a 1:1 gender ratio.

Another study conducted by Drug et al. [8] reported that in an urban population in East Europe, 14.4% of individuals suffered from IBS symptoms with a gender ratio of 1:2. No significant difference in positive psychiatric history was found between the general population (6.2%) and IBS patients (6.1%). In contrast, psychiatric disorders were found to be significantly more common in IBS patients who sought medical help (18%) than in subjects with similar symptoms in the general population (6.2%).

In the RFGES study in Romania, psychosocial variables such as somatization (PHQ-12), quality of life (PROMIS-10 physical), concern about bowel function, and the effect of stress, pressure, and tension on the bowel, and healthcare utilization were all significantly associated with having any DGBI. These results are similar to the recently published subgroup analysis of the RFGES in Israel [10]. These findings highlight the necessity of understanding the patient's explanatory model of illness when developing a patient-centered treatment strategy [18], as well as the impact of psychological determinants on disease experience.

Several limitations need to be further discussed. Participants from urban areas made up a substantially larger percentage of this study sample compared to those from rural areas (88.9% vs 11.1%, respectively). This is a substantially higher urban percentage than for the Romanian national population overall, which is only about 54% urban [19]. This difference is likely mainly due to the recruitment process that was performed by a company that specializes in Internet surveying. Thus, individuals from rural areas with less access to the Internet were less likely to participate. Another drawback of our study is that participants were not assessed with investigational methods including endoscopy or manometry because the study used a nonclinical questionnaire of the general population.

Table II. Prevalence rate n(%) for 22 Rome IV functional gastrointestinal diagnoses by gender, age and region

Anatomical GI areas for DGBIs	Overall n=2,049			Sex			Age group (years)						Living area									
				Male n=1,043			Female n=1,006			p	18-39 n=830		40-64 n=1,125		65+ n=94		p	Urban n=1,821 Rural n=228				
	n	%		n	%		n	%			n	%	n	%	n	%		n	%	n	%	
A. Esophageal Disorders																						
Functional chest pain	22	1.1		8	0.8	14	1.4	0.247	6	0.7	15	1.3	1	1.1		0.433	17	1.7	5	0.5	0.177	
Functional heartburn	11	0.5		6	0.6	5	0.5	0.999	4	0.5	7	0.6	0	0		-	11	1.1	0	0	-	
Reflux hypersensitivity	11	0.5		3	0.3	8	0.8	0.203	5	0.6	4	0.4	2	2.1		-	9	0.9	2	0.2	0.465	
Globus	10	0.5		4	0.4	6	0.6	0.709	6	0.7	4	0.4	0	0.0		-	9	0.9	1	0.1	0.999	
Functional dysphagia	55	2.7		24	2.3	31	3.1	0.339	27	3.3	26	2.3	2	2.1		0.419	52	5.2	3	0.3	0.245	
Any esophageal disorder	95	4.6		41	3.9	54	5.4	0.149	41	4.9	50	4.4	4	4.3		0.862	85	8.4	10	1.0	0.999	
B. Gastrooduodenal Disorders																						
Functional dyspepsia	152	7.4		74	7.1	78	7.8	0.628	76	9.2	69	6.1	7	7.4		0.040	139	13.8	13	1.2	0.362	
PDS	126	6.1		63	6.0	63	6.3	0.906	62	7.5	59	5.2	5	5.3		0.121	117	11.6	9	0.9	0.176	
EPS	53	2.6		25	2.4	28	2.8	0.582	29	3.5	20	1.8	4	4.3		0.035	48	4.8	5	0.5	0.904	
Belching disorder	23	1.1		12	1.2	11	1.1	0.999	7	0.8	16	1.4	0	0		0.278	23	2.3	0	0	-	
Rumination syndrome	45	2.2		16	1.5	29	2.9	0.052	11	1.3	33	2.9	1	1.1		0.042	38	3.8	7	0.7	0.456	
Chronic nausea vomiting syndrome	18	0.9		9	0.9	9	0.9	0.999	10	1.2	7	0.6	1	1.1		-	18	1.8	0	0	-	
Cyclic vomiting syndrome	24	1.2		15	1.4	9	0.9	0.349	12	1.4	11	1.0	1	1.1		0.633	22	2.2	2	0.2	0.981	
Cannabinoid hyperemesis syndrome	0	0.0		0	0	0	0	-	0	0	0	0	0	0		-	0	0	0	0	-	
Any gastroduodenal disorder	217	10.6		104	10.0	113	11.2	0.392	100	12.0	108	9.6	9	9.6		0.209	198	19.7	19	1.8	0.287	
C. Bowel Disorders																						
Rome-IV IBS	71	3.5		26	2.5	45	4.5	0.019	29	3.5	40	3.6	2	2.1		0.766	64	6.4	7	0.7	0.915	
IBS-C	23	1.1		7	0.7	16	1.6	0.075	11	1.3	12	1.1	0	0		0.495	19	1.9	4	0.4	0.497	
IBS-D	18	0.9		9	0.9	9	0.9	0.999	8	1.0	9	0.8	1	1.1		0.911	16	1.6	2	0.2	0.999	
IBS-U	6	0.3		2	0.2	4	0.4	0.653	0	0	6	0.5	0	0		-	6	0.6	0	0	-	
IBS-M	25	1.2		8	0.8	17	1.7	0.087	10	1.2	13	1.2	2	2.1		0.711	24	2.4	1	0.1	0.429	
Functional Constipation	240	11.7		83	8.0	157	15.6	<0.0001	117	14.1	111	9.9	12	12.8		0.015	224	22.3	16	1.5	0.020	
Opioid-induced constipation	29	1.4		10	1.0	19	1.9	0.109	10	1.2	17	1.5	2	2.1		0.712	25	2.5	4	0.4	0.813	
Functional diarrhea	54	2.6		37	3.5	17	1.7	0.012	22	2.7	28	2.5	4	4.3		0.589	48	4.8	6	0.6	0.999	
Functional bloating/distention	137	6.7		56	5.4	81	8.1	0.019	48	5.8	83	7.4	6	6.4		0.375	124	12.3	13	1.2	0.641	

Tabel II (continued)

Unspecified functional bowel disorder	171	8.3	89	8.5	82	8.2	0.816	67	8.1	99	8.8	5	5.3	0.469	152	15.1	19	1.8	0.999
Any bowel disorder	674	32.9	290	27.8	384	38.2	<0.0001	283	34.1	362	32.2	29	30.9	0.612	611	60.7	63	6.0	0.083
D. Central Nervous System Disorders of GI Pain																			
Centrally mediated abdominal pain syndrome	0	0	0	0	0	0	-	0	0	0	0	0	0	-	0	0	0	0	-
E. Biliary Disorders																			
Functional biliary pain	1	0	1	0.1	0	0.0	-	1	0.1	0	0	0	0	-	1	0.1	0	0	-
F. Anorectal Disorders																			
Fecal incontinence	15	0.7	9	0.9	6	0.6	0.656	4	0.5	11	1.0	0	0	0.310	13	1.3	2	0.2	0.999
Levator ani syndrome	8	0.4	3	0.3	5	0.5	0.687	3	0.4	4	0.4	1	1.1	-	7	0.7	1	0.1	0.999
Proctalgia fugax	141	6.9	71	6.8	70	7.0	0.961	55	6.6	77	6.8	9	9.6	0.523	130	12.9	11	1.1	0.239
Any anorectal disorder	161	7.9	81	7.8	80	8.0	0.962	61	7.3	90	8.0	10	10.6	<0.0001	148	14.7	13	1.2	0.244

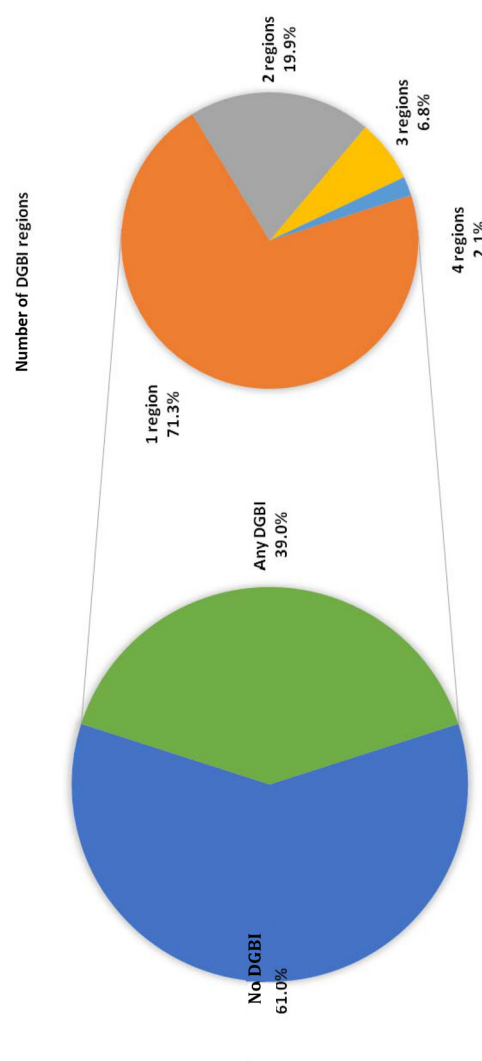


Fig. 2. Overlapping DGBIs in Romania. Distribution of included participants without DGBI and with any DGBI (left panel) and distribution of participants who met the diagnostic criteria according to the number of involved anatomical gastrointestinal regions (right panel).

Table III. Comparison of the association of sociodemographic and psychosocial variables among participants with and without any disorders of gut-brain interaction (DGBI) in Romania

Variable	No DGBI (n=1,228)		Any DGBIs (n=821)		p
	n	%	n	%	
Gender					
Male	670	54.6	373	45.4	<0.0001
Female	558	45.4	448	54.6	
Total	1,228		821		
Age					
18-39	491	40.0%	339	41.3%	0.750
40-64	678	55.2%	447	54.4%	
65+	59	4.8%	35	4.3%	
Total	1,228		821		
Education (years)					
Mean ± SD	14.9±3.8	14.7±3.6	0.103		
Total	1,222*		820**		
Do you live in a:					
City (more than 50,000 inhabitants)	794	64.7	570	69.4	0.057
Town (2,500 to 50,000 inhabitants)	280	22.8	177	21.6	
Village or small town (less than 2,500 inhabitants)	144	11.7	69	8.4	
Place in the countryside that is not a part of any city, town or village	10	0.8	5	0.6	
Total	1,228		821		
Living area					
Urban	1074	87.5	747	91.0	0.015
Rural	154	12.5	74	9.0	
Total	1,228		821		
Current relationship status					
Single	264	21.5	156	19.0	0.571
Married	698	56.8	470	57.2	
Divorced	95	7.7	64	7.8	
Widowed	26	2.1	19	2.3	
Co-habiting	145	11.8	112	13.6	
Total	1,228		821		
PROMIS-10 physical mean score					
Mean ± SD	13.4±2.3	14.9±2.1	<0.0001		
Total	1,222*		819**		
PROMIS-10 mental mean score					
Mean ± SD	14.7±2.5	13.4±2.3	<0.0001		
Total	1,228		821		
PHQ-12 mean score					
Mean ± SD	5.3±3.5	7.7±3.8	<0.0001		
Total	1,228		821		
PHQ-4 mean score					
Mean ± SD	2.0±2.2	3.5±2.9	<0.0001		
Total	1,228		821		
Mean number of medications					
Mean ± SD	0.9±1.3	1.7±1.7	<0.0001		
Total	1,228		821		
Mean number of abdominal surgeries					
Mean ± SD	0.4±0.6	0.4±0.7	0.001		
Total	1,228		821		

Table III (continued)

How concerned are you about your bowel functioning?					
Not at all	192	15.6	75	9.1	<0.0001
Somewhat	688	56.0	494	60.2	
Very concerned	348	28.3	252	30.7	
Total	1,228		821		
Are you embarrassed to discuss your bowel functioning with others (family, friends)?					
Not at all	846	68.9	494	60.2	<0.0001
Somewhat	338	27.5	287	35.0	
Very embarrassed	44	3.6	40	4.9	
Total	1,228		821		
Does stress, pressure or tension affect your bowel functioning?					
Not at all	588	47.9	169	20.6	<0.0001
Somewhat	525	42.8	446	54.3	
Greatly affects it	115	9.4	206	25.1	
Total	1,228		821		
Have you ever visited a doctor because of a bowel problem?					
Yes	300	24.4	308	37.5	<0.0001
No	928	75.6	513	62.5	
Total	1,228		821		
How often do you go to a doctor for your health?					
Once a month or more	131	10.7	129	15.7	0.001
A few times a year	545	44.4	377	45.9	
Once a year	266	21.7	130	15.8	
Less than once a year	268	21.8	177	21.6	
Never	18	1.5	8	1.0	
Total	1,228		821		

* 6 missing participant responses; ** 2 missing participant responses; SD: standard deviation; PHQ: Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System.

Table IV. Multivariate Logistic Regression Analysis for DGBIs

Variable	OR	95% CI		p*
		Lower	Upper	
Age (Years)	0.998	0.990	1.005	0.562
Gender (Male)	1.009	0.824	1.234	0.933
PROMIS-10 physical mean score	0.850	0.808	0.894	<0.0001
PHQ-12 mean score	1.091	1.057	1.126	<0.0001
Mean number of medications	1.127	1.048	1.212	0.001
Does stress, pressure or tension affect your bowel functioning-not at all	Reference			-
Does stress, pressure or tension affect your bowel functioning-somewhat	2.046	1.631	2.566	<0.0001
Does stress, pressure or tension affect your bowel functioning-very	3.010	2.193	4.131	
Area (Urban)	1.415	1.024	1.955	0.035

* p-values for continuous and binary variables based on the Wald test; and for categorical variables based on the Likelihood Ratio Test.

Therefore, some of the participants' digestive complaints could have been caused by an „organic” etiology. Nevertheless, we consider that the inclusion of a checklist of organic diseases that could explain GI symptoms, as well as the removal of such cases from DGBI prevalence counts in our analyses partially adjusted for this potential problem and may have led to a negative bias, reducing the prevalence rates of the DGBI compared to previous studies that did not use this strategy.

Our study contains several strengths. The methodology was robust. Pre-determined sample size, gender, and age distribution characteristics were fulfilled, and the national distribution closely matched the actual geographic population distribution of Romania. The Internet-based data collection strategy is one of the study's strengths. This system ensured the highest quality control with no missing data, automatic skip patterns, repeat questions to identify

Table V. Distribution of number of involved anatomical regions, by sex, age and region prevalence rate n (%)

DGBI	Overall n=2049		Gender				p	Age group (years)						p	Living area				p
			Male n=1043		Female n=1006			18-39 n=830		40-64 n=1125		65+ n=94			Urban n=1821		Rural n=228		
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	
Any DGBI	821	40.1	373	35.8	448	44.5	<0.0001	339	40.8	447	39.7	35	37.2	0.750	747	41.0	74	32.5	0.015
# of DGBIs																			
0	1228	59.9	670	64.2	558	55.5	<0.0001	491	59.2	678	60.3	59	62.8	0.720	1074	59.0	154	67.5	0.074
1	585	28.6	272	26.1	313	31.1		234	28.2	329	29.2	22	23.4		536	29.4	49	21.5	
2	163	8.0	64	6.1	99	9.8		73	8.8	80	7.1	10	10.6		143	7.9	20	8.8	
3	56	2.7	32	3.1	24	2.4		23	2.8	31	2.8	2	2.1		52	2.9	4	1.8	
4	17	0.8	5	0.5	12	1.2		9	1.1	7	0.6	1	1.1		16	0.9	1	0.4	

DGBI: disorders of gut-brain interaction.

Table VI. Anxiety, depression, and HRQoL scores according to the number of GI anatomical region numbers in DGBI

GI Anatomical region numbers	DGBI region numbers		IBS-SSS score		PROMIS-10 physical score		PROMIS-10 mental score		PHQ-12 score		PHQ-4 score		Mean number of medications		Mean number of abdominal surgeries	
	n	%	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
No DGBI	1228	61.0			1222	14.93	1228	14.69	1228	5.29	1228	2.00	1228	0.90	1228	0.36
One region	585	71.3	16	175.63	583	13.81	583	13.73	583	6.98	583	3.05	583	1.39	583	0.43
Two regions	163	19.9	19	235.79	163	12.84	163	12.59	163	8.70	163	4.15	163	2.09	163	0.46
Three/Four regions	73	8.8	34	246.18	73	11.73	73	12.45	73	10.7	73	5.32	73	2.89	73	0.59
ANOVA (p-value)	–		0.095		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		0.164	

DGBI: disorders of gut-brain interaction; GI: gastrointestinal; HRQoL: healthcare-related quality of life; IBS-SSS: irritable bowel syndrome symptom severity scale; PHQ: Patient Health Questionnaires; PROMIS-10: Patient-Reported Outcomes Measurement Information System-10.

and delete extremely inconsistent survey respondents, and automatic attention and speed checks, as described previously in full in the initial RFGES paper [9]. Additionally, there was no need to key in data because the data were imported straight from the participants' electronic responses into the online database, reducing errors related to data entry and processing.

CONCLUSIONS

The study population had a 40% prevalence of DGBI, leading to an important impact on quality of life and the burden of healthcare utilization. A higher prevalence of DGBI was associated with an increased effect of self-reported pressure, stress, or tension on bowel function, residing in an urban area and consuming more medications. The PROMIS-10 physical component score, reflecting the physical aspects of general quality of life, was found to be inversely related to DGBI, whereas age, education and relationship status were not associated with DGBI. Higher levels of anxiety and depression (PHQ-4, PHQ-1), higher somatization scores (PHQ-12), and lower HRQoL (PROMIS-10 mental and physical) were associated with an increasing number of overlapping DGBI region. These findings highlight the significance of identifying

patients with overlapping DGBI in Romanian clinical practice and treating all elements of their condition.

Future research based on the obtained results will facilitate investigation of the impact of factors such as nutrition, hygiene, economic status, education level, and psychological comorbidity on the prevalence of DGBI. These are expected to lead to hypotheses for future research, which could result in novel findings regarding the pathophysiology of DGBI.

Conflicts of interest: None to declare.

Authors' contribution: D.L.D. suggested the study, translated the questionnaires into Romanian and contributed to the writing of the paper. T.F. performed statistics and contributed to the writing. A.I. wrote the first draft. S.B., O.P., A.D.S. initiated and conducted the Rome Global Epidemiology Study, performed the analysis of data and contributed to the writing of the text; ADS in addition organized the team working to this paper.

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