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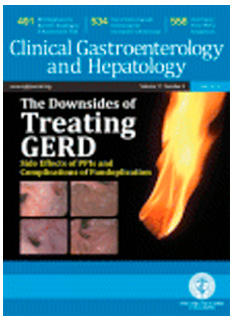

GREATER OVERLAP OF ROME IV DISORDERS OF GUT-BRAIN INTERACTIONS LEADS TO INCREASED DISEASE SEVERITY AND POORER QUALITY OF LIFE

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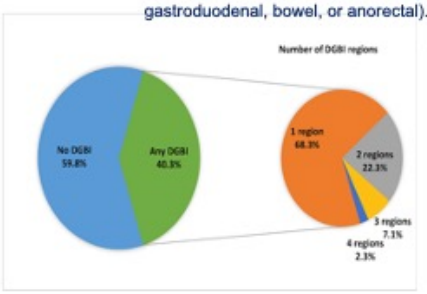
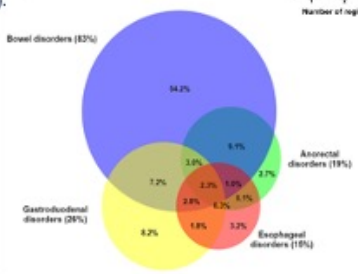
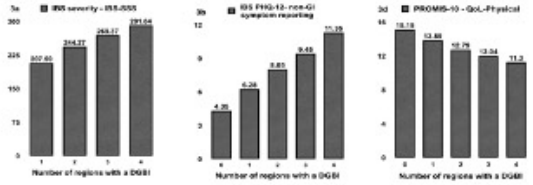
A global epidemiology study of the impact of overlapping Disorders of Gut-Brain Interactions (DGBI). 54,119 individuals in 26 countries from around the world participated in an Internet survey.
40.3% met criteria for at least 1 DGBI. Among those meeting Rome IV diagnostic criteria for Any DGBI, 32.7% met criteria for more than one GI region (esophageal, gastroduodenal, bowel, or anorectal).







Compared to individuals with only one DGBI, those with more that one region involved had lower quality of life, more psychosocial issues, and higher rates of doctor visits and other healthcare utilization. Overlapping DGBI have a negative impact on multiple illness parameters.

Clinical Gastroenterology and Hepatology

GREATER OVERLAP OF ROME IV DISORDERS OF GUT-BRAIN INTERACTIONS LEADS TO INCREASED DISEASE SEVERITY AND POORER QUALITY OF LIFE

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Short title: Overlapping Disorders of Gut-Brain Interaction

Abbreviations: DGBI-disorders of gut-brain interaction, GI-gastrointestinal; FGID-functional gastrointestinal disorder; IBS-irritable bowel syndrome; CI-confidence interval; QOL-quality of life; FD-functional dyspepsia; FC-functional constipation, OR-Odds ratio

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ADS contributed to the concept and design, the acquisition, analysis and interpretation of data, wrote the first draft and and subsequent drafts, and approved the final paper; **TF** contributed to the design, the acquisition, analysis and interpretation of data, the first and subsequent drafts, and the final paper; **IA** contributed to the design, the acquisition, analysis and interpretation of data , the first and subsequent drafts, and the final paper; **OSP** contributed to the concept and design, the acquisition, analysis and interpretation of data, was the database manager, contributed to the first draft and revised drafts, and approved the final paper; **DAD** contributed to the concept and design, the analysis and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **DLD** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **XF** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **SF** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **UCG** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **JK** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **RK** contributed to the design, the analysis and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **EO** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **EMMQ** contributed to the design, the interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **MS** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **MSim** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **JT** contributed to the design, the acquisition and

interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **WEW** contributed to the design, the analysis and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **PW** contributed to the design, the acquisition and interpretation of data, contributed to the first draft and revised drafts, and approved the final paper; **SIB** contributed to the design, the acquisition, analysis and interpretation of data, the first and subsequent drafts, and the final paper

Declaration of interests:

ADS has acted as consultant for Lapidot Israel and AbbVie-Israel outside the submitted work; **TF** has no conflict of interest; **IA** has no conflict of interest; **OSP** reports research contract from The Rome Foundation during the conduct of the study; and research contract from Glycom A/S and personal fees from metaMe Health, outside the submitted work; **DAD** reports personal fees from Olorinab, personal fees from Shire, personal fees from Ironwood, outside the submitted work; **DLD** speaker fee and/or advisory board fees from AlfaSigma, Abbott, Abbvie, Biocodex, Menarini, Pfizer, SECOM, Biessen, Sanofi, Terapia, R&B, outside the submitted work; **XF** has no conflict of interest; **SF** has no conflict of interest; **UCG** has no conflict of interest; **JK** has no conflict of interest; **RK** has no conflict of interest; **EO** has no conflict of interest; **EMMQ** has no conflict of interest; **MSch** reports grants, personal fees and other from Takeda Mexico, grants, personal fees and other from Alfasigma Mexico, personal fees from Carnot, personal fees from Gemelli Biotech Corp, other from Ferrer Mexico, outside the submitted work; **MSim** reports grants and personal fees from Gkycom, grants and personal fees from Danone Nutricia Research, personal fees from Ironwood, personal fees from Menarini, personal fees from Biocodex, grants from Genetic Analysis AS, personal fees from Arena, personal fees from Adnovate, personal fees from Tillotts, personal fees from Kyowa Kirin, personal fees from Takeda, personal fees from Alimentary Health, personal fees from AlfaSigma, personal fees from Falk Foundation, outside the submitted work; **JT** Jan Tack has given Scientific advice to Adare, AlfaWassermann, Allergan, Arena, Bayer, Christian Hansen, Clasado, Danone, Devintec, Falk, Grünenthal, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Neurogastrx, Neutec, Novartis, Noventure, Nutricia, Shionogi, Shire, Takeda, Theravance, Tramedico, Truvion, Tsumura, Zealand and Zeria pharmaceuticals, has received research support from Shire, Sofar and Tsumura, and has served on the Speaker bureau for Abbott, Allergan, AstraZeneca, Janssen, Kyowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda, Truvion and Zeria, all outside the submitted work; **WEW** reports receiving discounted equipment provided by Medspira Ltd for a research study, test kits for dextranomer injections to treat fecal incontinence from Palette Life Sciences, contribution from Glycom Ltc for a research fund to support an international collaborator outside the submitted work. None of these contributions come to the investigator directly; **PW** has acted as a consultant to or received research funding from Danone, Allergan Phazrma, Ironwood Pharma, Salix Pharma, 4D Pharma and Enteromed Ltd, all outside of the submitted work; **SIB** has no conflict of interest.

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What you need to know:

Background

- There is evidence for poorer outcomes among patients with overlapping DGBI, but mainly from small-scale studies using a small number of DGBI, primarily IBS and functional dyspepsia.

Findings

- In a population-based study with 54,127 participants in 26 countries we found a universal association between overlapping DGBI and a negative impact on quality of life, disease severity, psychological co-morbidity, and healthcare utilization.

Implications for patient care

- Physician awareness and identification of patients with overlapping DGBI could improve quality of care and patients' outcomes.

Abstract

Background and aims. Conditions such as irritable bowel syndrome (IBS), functional dyspepsia and functional constipation are among the prevalent gastrointestinal disorders classified as disorders of gut brain interaction (DGBI), which can adversely affect the lives of sufferers. This study aimed to assess the degree and consequences of overlapping DGBI in a large population-based global scale.

Methods. Internet survey data from 54,127 adults (49.1% females) in 26 countries were analyzed by 4 GI anatomic regions (esophageal, gastroduodenal, bowel, and anorectal). The number of DGBI-affected GI regions was assessed, including associations with sex, age, disease severity, quality of life (QoL), psychosocial variables, and healthcare utilization.

Results. 40.3% of surveyed individuals met Rome IV criteria for a DGBI. The percentages with 1-4 DGBI-affected GI regions were 68.3%, 22.3%, 7.1%, and 2.3%, respectively. IBS symptom severity (IBS-SSS) increased significantly from 1 (207.6) to 4 regions (291.6), as did non-GI symptom reporting (somatization), anxiety and depression, concerns and embarrassment about bowel function, doctor visits, medications and abdominal surgeries, (all $P<0.0001$). QoL decreased with increasing number of DGBI regions ($P< 0.0001$). In a logistic mixed model, non-GI symptoms (OR=1.09 1.08-1.10), being very vs. not concerned (OR=2.55, 2.27-2.90) very vs. not embarrassed about bowel function (OR=1.20, 1.08-1.33), and mean number of doctor visits (OR=1.23, 1.115-1.32) were most strongly associated with number of DGBI regions.

Conclusion. DGBI in multiple anatomic GI regions is associated with increased psychological co-morbidity, healthcare utilization, and IBS severity. Physician awareness of overlap could improve quality of care, prevent unnecessary interventions, and yield more positive health outcomes.

Keywords: DGBI; overlap; epidemiology; functional disorders; psychosocial

Introduction

The co-existence of multiple disorders of gut-brain interaction (DGBI), formerly known as functional GI disorders (FGIDs), is well known.[1] Comorbidity of DGBI with extra-intestinal functional disorders such as fibromyalgia, chronic fatigue syndrome, and chronic cystitis, is also recognized.[2] The presence in one individual of several DGBI[1] or a DGBI and another functional somatic syndrome,[2] commonly referred to as 'overlap,' is likely to have deleterious effects on disease severity and quality of life (QoL).

Earlier studies from the United Sates,[3] France,[4] and Canada,[5] confirmed the existence of relevant overlap groups. A study on the prevalence and impact of overlapping Rome IV DGBI with the same methodology as the present study, but conducted in a sample of three English speaking countries, the US, the UK, and Canada,[6] found that one third of the participants who met the diagnosis for any DGBI fulfilled criteria for more than one region with increased somatization, poorer QoL, and greater healthcare utilization.

These findings on overlapping DGBI and its impact on patients has important clinical, public health and research implications. However, relevant reports have been from small, local, or non-representative study populations and the majority have been on a limited number of DGBI, usually IBS and functional dyspepsia (FD). To evaluate this phenomenon on a larger representative global sample, we analyzed the database of the Rome Foundation Global Epidemiology Study (RFGES), which contains diagnoses for 22 DGBI in 54,127 individuals from 26 countries in 6 continents:[7] Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Egypt, France, Germany, Holland, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, South Africa, South Korea, Singapore, Spain, Sweden, Turkey, the US, and the UK.

The primary aims were to assess the prevalence and effects of co-existent DGBI in multiple GI regions by sex, age, and consistency among the 26 countries. The secondary aims

were to assess the association of multiple comorbid DGBI with QoL and psychosocial variables, including somatization, anxiety, depression, concerns and embarrassment related to bowel function, healthcare utilization, the use of medication (for GI symptoms, anxiety, depression, and sleep problems), and abdominal surgery. Also, the association between IBS disease severity and number of involved GI regions was assessed among participants meeting diagnostic criteria for IBS.

We hypothesized that the prevalence of multiple co-existing DGBI would be higher among women than men, and would decrease with increasing age, as was found in the RFGES,[7] and that these results would be consistent among the 26 countries. We also hypothesized that QoL would decrease directly with increasing numbers of DGBI regions, and that anxiety, depression, somatization, concern and embarrassment about bowel function, healthcare utilization, comorbidity with fibromyalgia, and IBS severity would increase directly with an increasing number of DGBI regions.

Methods

The following is an abridged summary of the RFGES methodology, as previously reported.[7] The full study was conducted by personal household interviews in seven countries where Internet surveys were not feasible and by Internet survey in 26 countries. Because the methodology and results differed in the two survey types, the present paper is based on the 26 Internet countries only. This survey was conducted through the Internet by the Rome Foundation with the help of a professional survey company (Qualtrics, LLC., Provo, Utah, USA). The participants were individuals in the general population, with a representative geographic distribution in each country. They were registered in panels to participate in various Internet surveys and selected for participation in this study exclusively based on demographic characteristics. The survey was anonymous, with a representative national geographic distribution, and had multiple built-in quality-assurance measures to exclude

poor-quality responders. Quota-based sampling was used to generate demographically balanced and population representative samples with pre-defined demographic parameters set as at least 2,000 participants per country, 50% females and 50% males, and 40% for 18-39 years, 40% for 40-64 years, and 20% for 65+ years. The Internet methodology used for data collection substantially reduced the risk of missing data or incorrect values.

Definitions of multi-region DGBI: The GI tract was divided into four anatomic regions (esophageal, gastroduodenal, bowel, and anorectal), based on the accepted Rome IV categorization.[7] For convenience, these anatomic GI regions are referred to as regions hereafter. Two other DGBI categories, centrally mediated abdominal pain and biliary pain, were not included due to the low number of diagnosed individuals meeting criteria for these diagnoses (below 0.1% of the population surveyed). The GI anatomic regions with their corresponding DGBI diagnoses appear in Supplementary Table 1.

Supplemental questionnaire: The survey included an 80-item supplemental questionnaire on sociodemographic characteristics, co-morbid symptoms and conditions, healthcare utilization, medications (for GI symptoms, anxiety/depression, sleep), psychosocial variables (anxiety, depression, non-GI symptoms), QoL, and IBS symptom severity, and validated questionnaires such as the PROMIS Global 10[8] for physical and mental QoL, Patient Health Questionnaire-12 (PHQ-12, non-GI symptoms as an approximation of somatization),[9] IBS symptom severity scale (IBS-SSS) (range 0-500),[10] and the Patient Health Questionnaire-4 (PHQ-4)[11] on anxiety/depression.

The questionnaire was translated by a professional company (TransPerfect, Inc. USA) into 21 languages, with linguistic and cultural validation.[7]

Statistical considerations

Categorical variables were summarized using frequencies and percentages, with comparisons between groups by either the chi-squared or Fisher's exact test. Continuous

variables were summarized using means and standard deviations, with differences between multiple independent groups assessed using analysis of variance. Statistical significance was set at the .05 level.

To estimate the prevalence of co-existent DGBI in multiple regions, overall and by sex and age groups, country prevalence data were pooled using the method of Yang,[12] where appropriate.

To examine the heterogeneity among the 26 countries, we calculated the meta-analytic overall prevalence estimate using both a fixed effects model and a random effects model, and calculated the I^2 and tau^2 indices of heterogeneity.

To address our secondary aim of the association of multiple comorbid DGBI regions with a variety of potential risk factors, we initially attempted an ordinal logistic mixed-effects regression with random intercept effects for country, of the number of regions with DGBI; however, the model did not satisfy the proportional odds assumption ($p<0.0001$). Since the main clinical question of interest was comparing the presence of DGBI in only 1 region with any DGBI in multiple GI regions (2, 3 or 4), we conducted instead a binary logistic mixed-effects regression with random intercept effects for country, with 1 DGBI region as the reference value and 2 or more DGBI-affected regions as the comparison group. This model addressed the secondary aims of associations of two or more comorbid DGBI with QoL and psychosocial variables. Models also considered associations with healthcare utilization, use of medication, and abdominal surgery. To assess the amount of correlation among observations within a country, we calculated the intraclass correlation coefficient (ICC) after fitting the models.

Finally, we assessed the association between IBS disease severity and overlap in the subset of subjects who met the diagnostic criteria for IBS (N=2,183), also using a binary logistic mixed-effects regression with random intercept effects for country.

Statistical analyses were carried out with SPSS software version 26.0 (SPSS Inc. Chicago, Illinois, US) and the Statistical Analysis System (SAS) software, version 9.4 (Cary, NC, US).

Ethical considerations

Ethical review was completed in each country and the study was approved or exempted from ethics board oversight, as subjects were anonymous to the investigators. All survey participants completed a written electronic informed consent form.

Results

The sample sizes and age and sex distributions for each of the 26 countries sampled have been detailed in a supplementary table in our previous paper from this study.[7] Of the total participants in the survey, 9.7% lived in rural communities (communities with less than 2500 inhabitants) and 25.5% had college-level education (more than 16 years of formal schooling).We achieved equal sex distribution and pre-planned age ranges and every country had at least 2,000 participants with a representative national geographic distribution. This survey was completed by 54,127 respondents with a mean age of 44.3 years (range 18-97); 49.1% women.

Eight participants fulfilling criteria for functional biliary pain were excluded from the analyses due to their small number, leaving 54,119. The final number of participants with any DGBI, after excluding individuals who also reported another GI diagnosis, was 21,788 (40.3%). There were missing PROMIS responses for 38 participants. They were included in all univariate analyses except for QoL, but excluded from multivariate analyses leaving a study population of 21,750 for those. The distribution of individuals with no DGBI or any DGBI and the distribution of individuals reporting DGBI in one to four multiple GI regions can be seen in Figure 1 and in the Venn diagram (Figure 2). The Rome IV IBS criteria were fulfilled by 2,195 (4.1%) individuals, but 12 did not have IBS-SSS scores, so the final IBS

subgroup population for analyses was 2,183 individuals (Supplementary Fig. 2 for a flow cart of the analysis samples(.

Univariate analyses

Prevalence and effects of co-existent DGBI in multiple regions by sex and age, and country (Table 1). The rates for women were consistently higher than for men (Table 1) for "any DGBI" at 46.5% (95% CI 45.9, 47.1) vs. 34.2% (33.7, 34.8) and for each number of overlap (1-4 regions). The rates were highest in the 18-39 year age group, lower in the 40-64 year group, and lowest in the 65+ year age group for any DGBI and for all numbers of DGBI regions.

The prevalence of having DGBI in only a single GI region ranged from 22.1% (Holland) to 33.9% (Japan), for two DGBI-affected GI regions from 4.2% (Japan) to 11.6% (Brazil), for 3 DGBI regions from 1.0% (Singapore) to 5.2% (Brazil), and for four DGBI regions from 0% (Canada) to 1.9% (Spain). Despite the observed substantial variability among the 26 countries (Supplementary Figure 1), the risk of having a DGBI was not highly correlated among individuals within a country (ICC=0.02).

Association of multiple comorbid DGBI with IBS severity (IBS-SSS). Among the 2,183 with IBS, the mean IBS-SSS score increased incrementally with increasing overlap (Figure 3a) from 207.59 for IBS only to 291.64 for IBS with three overlapping GI regions.

Association of multiple comorbid DGBI with QoL and psychosocial variables. The percentage of participants who responded "not at all, somewhat, and very much" to the three questions on concern and embarrassment related to bowel function and the effect of stress and pressure on it, was significantly associated with the number of overlapping DGBI regions ($P<0.0001$ for all) (Table 2). The same was seen in the entire study population for the PHQ-12 score (Figure 3b), and PHQ-4 (Figure 3c). The PROMIS-10 physical score decreased incrementally with increasing numbers of DGBI regions (Figure 3d).

Association of multiple comorbid DGBI with healthcare utilization. The mean number of medications (Figure 3e), doctor visits for bowel problems (Figure 3f), and abdominal surgeries (not shown) increased incrementally. In regard to abdominal surgery, appendectomy was reported by 11.2% of participants without a DGBI, compared to 18.4% in individuals with DGBI in four GI regions, while the corresponding figures for cholecystectomy were 4.3% and 11.6%.

Multivariate analyses

We found that the factors significantly associated with overlapping DGBI were sex, age, doctor visits, concern and embarrassment about bowel function, stress, pressure or tension, anxiety, depression, non-GI symptoms, fibromyalgia, QoL-physical, and number of medications and surgeries (Table 3). The variables with the strongest association with DGBI in multiple regions were very vs. not at all concerned about bowel function (OR=2.55, 95% CI 2.26, 2.87), very vs. not embarrassed at all about talking about bowel problems (OR=1.21, 95% CI 1.09, 1.34), great vs. no effect of stress, pressure or tension on bowel function (OR=1.16, 95% CI 1.07, 1.27), having visited a doctor because of a bowel problem (OR=1.23, 95% CI 1.15, 1.32), and the number of different types of medications used regularly (OR=1.15, 1.13, 1.18). The final ICC value was: 0.05874 / (3.29+0.05874) = 0.0175.

Discussion

The results of this study demonstrate a universal association between overlapping DGBI and negative impact on a broad range of variables encompassing disease, quality of life, psychosocial variables, function, and healthcare utilization. In all of these, the negative effects increased incrementally with increasing degree of overlap. The results are in agreement with those found in the 3-country study, referenced above, which used the same questionnaire and data collection method in a smaller population of 6,000.[6] In that study the

rate of having any DGBI was 35% and a similar negative effect of overlap on psychosocial and healthcare utilization variables was reported.

The Rome IV consensus[13] subdivided DGBI according to the GI region where symptoms are thought to originate. DGBI are considered distinct diagnoses, and diagnoses within the same GI region are mutually exclusive; for example a single individual can have only one of the diagnoses of IBS, functional constipation, opioid-induced constipation, functional diarrhea, functional bloating/distention, and unspecified functional bowel disorder. However, an individual with one of these bowel disorders can also have an esophageal, and/or a gastroduodenal, and/or an anorectal disorder. This has raised the issue as to whether the various DGBI are distinctive entities, or different manifestations of the same underlying pathophysiology.[14, 15]

In the U.S. householder survey of FGIDs, an early epidemiology study using Rome I criteria,[3] 69% of the respondents had at least one persistent GI symptom with high rates for each surveyed region (esophageal, gastroduodenal, bowel and anorectal). Many reported symptoms in more than one region. Based on this study,[3] Drossman et al. proposed that the FGIDs may not be site-specific, but could reflect pathophysiological mechanisms that affect the entire GI tract and are augmented by sociocultural and behavioral factors.

Vakil et al. found that different FGIDs frequently co-exist in the same individual, a condition that is associated with greater symptom burden and increased physician consultations.[16] In the present study we found that the number of doctor visits for bowel problems increased with an incremental increase in involved regions. Longstreth and Yao[17] evaluated the rate of six surgeries among 4,587 health examinees in southern California who met physician-based criteria for IBS. IBS was associated with cholecystectomy at a 3-fold higher rate, and with appendectomy and hysterectomy at 2-fold higher rates than those without it. In the present study the rate of abdominal surgery was significantly higher in

individuals with one or more DGBI than those with no DGBI, and the percentage increased incrementally with increasing numbers of overlapping regions.

A common criticism of previous studies on DGBI overlap is that they were conducted on small, local, or non-representative populations, concentrated on a limited number of DGBI, and a large-scale multinational study was need to confirm that the findings are generalizable. The results of our study, conducted on a global scale and including all 22 DGBI from the RFGES database, provide strong evidence of the negative effects of multiple co-existing DGBI.

Although the negative effect of overlapping DGBI presented here increased incrementally with increasing overlap, the values were close enough to justify collapsing the four overlap categories into one "multiple DGBI regions" category for the logistic regression analysis. This binary logistic regression model identified variables that reflect multiple domains, as significant contributors. The finding on patients' concern and embarrassment and the effect of stress, pressure, and tension on their symptoms, has not been reported on this scale before. It speaks to the need for clinicians to address their patients' explanatory models of disease,[18] their concerns about illness, and their expectations from treatment.

Most of the associations identified in the logistic regression analysis are likely consequences of a higher symptom burden in the case of multiple conditions. Somatization, approximated by the PHQ-12 questionnaire on non-GI symptoms, was included in the logistic regression model. Defined as the reporting of multiple somatic (medically unexplained) symptoms, or as the expression of psychological distress as somatic symptoms,[19] somatization is associated with a process of symptom amplification, which may enhance the likelihood of reaching frequency thresholds for DGBI. Thus, somatization could amplify the finding of overlapping conditions in patients with a somatoform disorder.[20] On the other hand, somatization may be associated with numerous psychosocial disorders such as

anxiety, depression and post-traumatic stress, which have been associated with the presence of visceral hypersensitivity, impaired central processing and a generalized up-regulation of gut-brain signaling pathways conveying unpleasant or painful sensations.[21] Hence, somatization could be a marker for visceral hypersensitivity, a mechanism putatively affecting the whole gastrointestinal tract that may also enhance the likelihood of overlapping DGBI.

In another study,[22] the investigators compared the extent of overlap in their study with documentation in the patients' medical records. They found that the medical records had deficient documentation of comorbid DGBI, and that 64% of patients had FD/IBS overlap by study questionnaire compared to 23% based on routine clinical documentation. This could indicate that clinicians are not sufficiently aware of the existence and deleterious effect of DGBI overlap for their patients. This is of particular importance in light of our findings that overlap has a serious impact on the patient's illness experience, and that clinicians should weigh this in the doctor-patient therapeutic relationship.

This study, while methodologically rigorous, has several limitations. It was a cross-sectional study that captured a single point in time. The results could have been different in a longitudinal study such as a 12-year longitudinal study where changes in symptoms were observed over the study period, but the overall prevalence of DGBI remained relatively stable despite internal shifts.[23]

An additional limitation of our study is that participants could not be evaluated with procedures such as endoscopy, pH monitoring, or manometry, so in some cases their symptom could have been caused by an "organic" disease instead of DGBI. However, we believe that our inclusion of a checklist of history of organic diagnoses that might account for GI symptoms, and our exclusion of such cases from FGID prevalence counts compensated at least partially for this. Furthermore, since this was an anonymous population-based study, we

did not have access to medical records to compare our diagnostic prevalence rates to those documented for individual study participants.

In summary, the results of this large-scale multinational study of nationwide population samples in 26 countries on six continents show that multiple DGBI commonly co-exist and that this overlap has a substantial adverse impact. This is a consistent finding in all tested domains. While this phenomenon is prevalent and has been documented in previous studies, it is not sufficiently recognized by clinicians working with DGBI patients. This awareness in the clinical setting, manifested by identifying patients, explaining and acknowledging the impact of overlapping DGBI, eliciting and addressing the patients' concerns, and tailoring treatment strategies on an individual basis, could lead to more positive health outcomes. Furthermore, it might prevent some of the considerable number of unecessary investigations and interventions, sometimes of a surgical nature, to which these patients are frequently subjected.[24]

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Table 1. Distribution of involved anatomical regions, by sex, age group, and geographic region, pooled prevalence rate (% and 95% CI).

	Overall N=54119	Sex		Age group (years)		
		Male	Female	18-39	40-64	65+
		N=27548	N=26571	N=22998	N=22278	N=8843
Any DGBI	40.3 (39.8, 40.7)	34.2 (33.7, 34.8)	46.5 (45.9, 47.1)	44.3 (43.6, 44.9)	39.4 (38.8, 40.1)	31.9 (30.9, 32.8)
DGBI - 1 region	27.5 (27.1, 27.9)	23.8 (23.3, 24.3)	31.3 (30.8, 31.9)	30.1 (29.5, 30.7)	26.6 (26.0, 27.2)	23.0 (22.1, 23.9)
DGBI - 2 regions	9.0 (8.7, 9.2)	7.2 (6.9, 7.5)	10.8 (10.4, 11.2)	9.9 (9.5, 10.3)	9.0 (8.6, 9.3)	6.6 (6.1, 7.1)
DGBI - 3 regions	2.8 (2.7, 3.0)	2.3 (2.2, 2.5)	3.4 (3.1, 3.6)	3.2 (2.9, 3.4)	2.9 (2.7, 3.1)	1.8 (1.6, 2.1)
DGBI - 4 regions	0.9 (0.8, 1.0)	0.8 (0.7, 1.0)	1.0 (0.9, 1.1)	1.1 (0.9, 1.2)	1.0 (0.8, 1.1)	0.5 (0.3, 0.6)

	Overall N=50007*	Asia N=9487	Eastern Europe N=6106	Latin America N=8069	Middle East 6042	North America N=4052	Western Europe 16314
Any DGBI	39.5 (38.8, 40.3)	36.0 (35.1, 37.0)	43.6 (42.3, 44.8)	42.6 (41.5, 43.6)	41.2 (40.0, 42.5)	40.6 (39.1, 42.1)	39.6 (38.8, 40.3)
DGBI - 1 region	27.5 (27.1, 27.9)	26.9 (26.0, 27.8)	30.0 (28.8, 31.3)	27.7 (26.7, 28.7)	29.0 (27.9, 29.0)	25.2 (23.9, 26.6)	26.8 (26.1, 27.5)
DGBI - 2 regions	8.9 (8.7, 9.2)	6.8 (6.3, 7.3)	9.3 (8.6, 10.0)	10.1 (9.5, 10.8)	9.0 (8.3, 9.7)	10.1 (9.2, 11.0)	9.1 (8.7, 9.6)
DGBI - 3 regions	2.8 (2.7, 3.0)	1.8 (1.5, 2.1)	3.1 (2.6, 3.5)	3.7 (3.3, 4.1)	2.5 (2.1, 2.9)	3.7 (3.1, 4.3)	2.8 (2.5, 3.0)
DGBI - 4 regions	0.9 (0.8, 1.0)	0.5 (0.4, 0.7)	1.2 (1.0, 1.5)	1.0 (0.8, 1.2)	0.7 (0.5, 0.9)	1.5 (1.2, 1.9)	0.9 (0.8, 1.1)

*Excluding single country regions – South Africa and Australia

Asia = Japan, China, S. Korea, Singapore; Eastern Europe = Poland, Romania, Russia; Latin America = Argentina, Brazil, Colombia, Mexico; Middle East = Egypt, Israel, Turkey; North America = Canada, US; Western Europe = Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, UK

Table 2. The association between number of overlapping DGBI regions with concern about bowel function, embarrassment about discussing bowel functioning, and the effect of stress, pressure, or tension on bowel functioning.

How concerned are you about your bowel function?							
	% No DGBI (N=32,339)	% 1 region (N=14,889)	% 2 regions (N=4,861)	% 3 regions (N=1,537)	% 4 regions (N=501)	N	P
Not at all concerned	67.0	40.4	24.3	15.2	5.8	29,128	<0.0001
Somewhat concerned	28.4	52.9	61.5	61.1	58.7	21,299	
Very much concerned	4.5	6.7	14.2	23.7	35.5	3,700	
Are you embarrassed to discuss your bowel functioning with others (families, friends?)							
Not at all embarrassed	68.7	55.3	47.7	41.3	30.9	33,571	<0.0001
Somewhat embarrassed	26.4	35.4	39.7	40.6	43.9	16,585	
Very much embarrassed	4.9	9.3	12.5	18.1	25.1	3,971	
Does stress, pressure, or tension affect your bowel functioning?							
Does not affect at all	54.6	30.6	18.9	14.1	8.6	23,409	<0.0001
Affects somewhat	37.4	49.2	49.4	46.7	44.5	22,758	
Affects very much	8.0	20.2	31.7	39.2	46.9	7,960	

* chi-squared (8 d.f.) test of association

Table 3. A Logistic Mixed-Effects Model with dependent binary variable (1 DGBI=0; 2+3+4 DGBI =1) and with country as a random intercept effect (N=21,750).

Effect	*aOR (95% CI)
Sex (Female vs. Male as reference)	0.92 (0.86, 0.98)
Age	
(18 to 39 vs. ≥65 as reference)	1.12 (1.00, 1.24)
(40 to 64 vs. ≥65 as reference)	1.13 (1.02, 1.25)
Have you ever visited a doctor because of a bowel problem? (Yes vs. No as reference)	1.23 (1.15, 1.32)
How concerned are you about your bowel functioning?	
(Somewhat vs. Not at all as reference)	1.56 (1.44, 1.68)
(Very concerned vs. Not at all as reference)	2.55 (2.26, 2.87)
Are you embarrassed to discuss your bowel functioning with others (family, friends)?	
(Somewhat vs. Not at all as reference)	1.06 (0.99. 1.13)
(Very embarrassed vs. Not at all as reference)	1.21 (1.09, 1.34)
Does stress, pressure or tension affect your bowel functioning?	
(Somewhat vs. Not at all as reference)	1.42 (1.28, 1.57)
(Greatly affects it vs. Not at all as reference)	1.16 (1.07, 1.27)
PROMIS-10 Global Physical Health score	0.93 (0.91, 0.94)
PROMIS-10 Global Mental Health score	0.96 (0.80, 1.14)
PHQ-4	1.03 (1.02, 1.05)
PHQ-12	1.09 (1.08, 1.10)
Fibromyalgia	1.02 (1.01, 1.03)
Number of surgeries	1.05 (0.99, 1.11)
Number of medications	1.15 (1.13, 1.18)

* aOR = adjusted Odds Ratio

Titles for figures

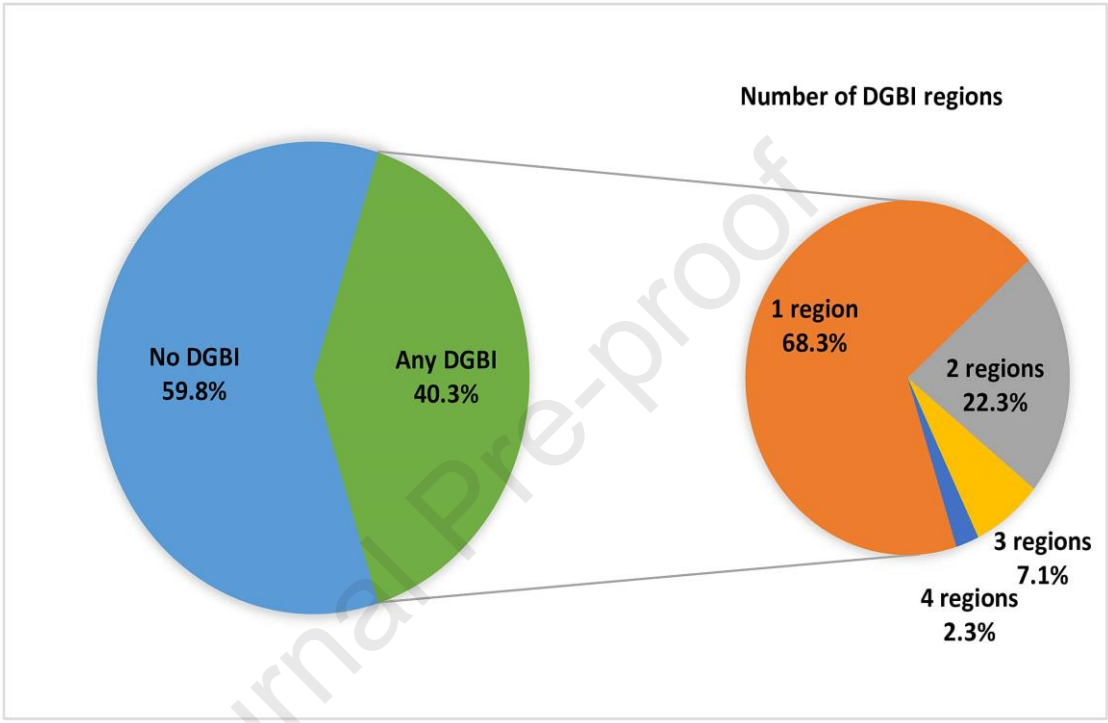
Figure 1. The distribution of individuals with no DGBI or any DGBI (left panel) and the distribution of individuals reporting DGBI in one to four multiple GI regions (right panel).

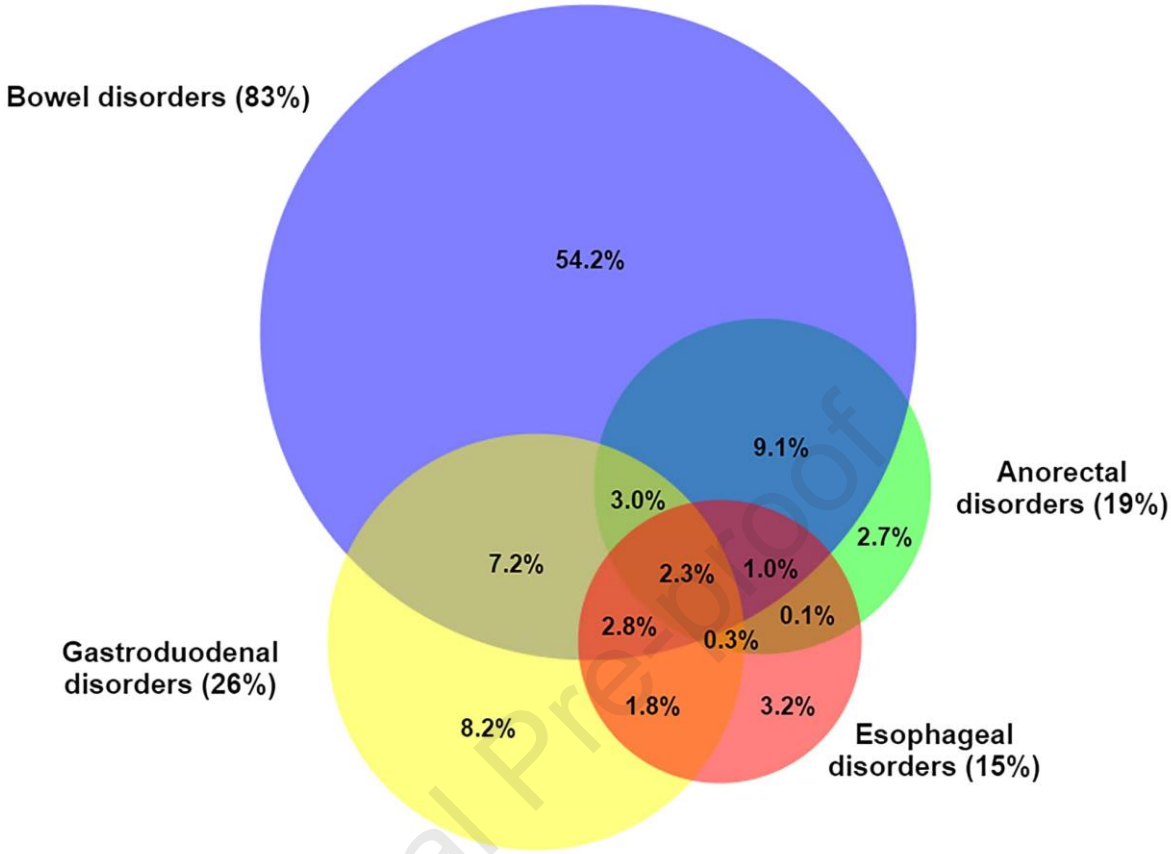
Figure 2. Venn diagram showing the overlap between DGBI (N=27,188). The figure in parenthesis for each region is the cumulative percentage of all combinations involving that region. Due to technical limitations, the overlap between esophageal and bowel (3.3 %) and between gastroduodenal and anorectal (0.7%) do not appear in the diagram, so the percentages inside the circles add up to less than 100%.

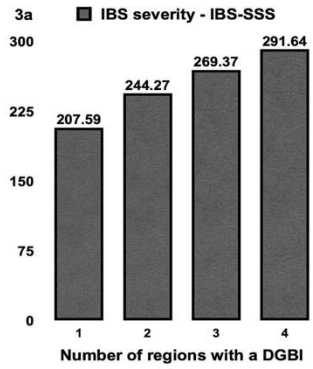
Figure 3. Bivariate analyses: relationship between number of overlapping GI regions affected with DGBI and: (3a) IBS-SSS; (3b) non-GI symptoms (PHQ-12); (3c) anxiety and depression (PHQ-4); (3d) quality of life (PROMIS-10-physical); (3e) mean number of medications; and (3f) doctor visits. IBS-SSS (3a) has 4 columns compared to 5 for the others because, per definition, if a patient has IBS, which is a DGBI, there cannot be a "no DGBI" column.

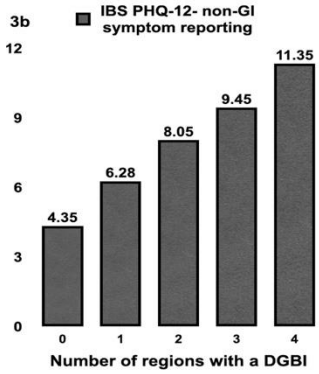
Supplementary Figure 1. Forest plot of the proportion reporting DGBI in multiple GI regions among those reporting any DGBI, by country. The proportion and 95% CIs of 2+3+4 DGBI for each country and overall were calculated using Yang's method [12].

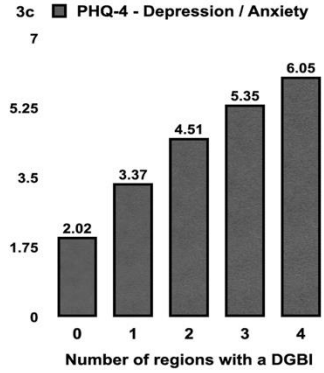
Supplementary Figure 2. Flow chart of the study samples in terms of aims and analyses. Top panel is the selection of overlap groups, middle panel is for IBS-SSS analysis in sub-group of individuals meeting criteria for Rome IV IBS, and bottom panel is for PROMIS-10 analysis.

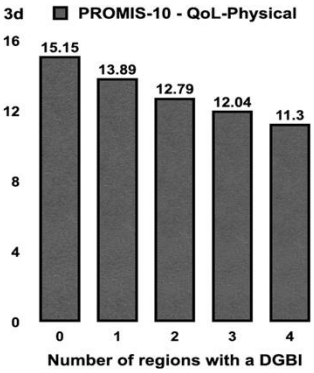


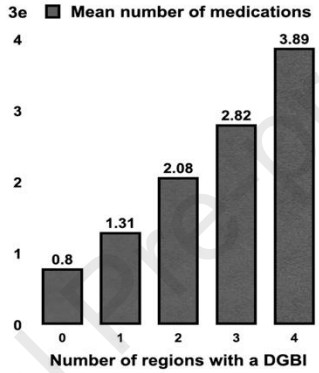


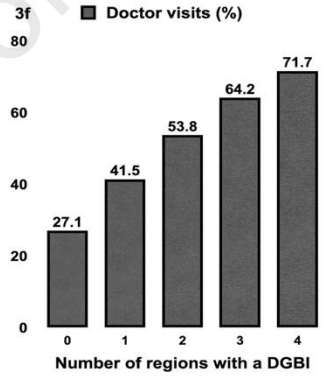












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DGBI - 2 regions	9.0 (8.7, 9.2)	7.2 (6.9, 7.5)	10.8 (10.4, 11.2)	9.9 (9.5, 10.3)	9.0 (8.6, 9.3)	6.6 (6.1, 7.1)
DGBI - 3 regions	2.8 (2.7, 3.0)	2.3 (2.2, 2.5)	3.4 (3.1, 3.6)	3.2 (2.9, 3.4)	2.9 (2.7, 3.1)	1.8 (1.6, 2.1)
DGBI - 4 regions	0.9 (0.8, 1.0)	0.8 (0.7, 1.0)	1.0 (0.9, 1.1)	1.1 (0.9, 1.2)	1.0 (0.8, 1.1)	0.5 (0.3, 0.6)

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DGBI - 4 regions	0.9 (0.8, 1.0)	0.5 (0.4, 0.7)	1.2 (1.0, 1.5)	1.0 (0.8, 1.2)	0.7 (0.5, 0.9)	1.5 (1.2, 1.9)	0.9 (0.8, 1.1)

*Excluding single country regions – South Africa and Australia

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* chi-squared (8 d.f.) test of association

Table 3. Logistic Mixed-Effects Model of 2-3-4 DGBI regions (1 DGBI region as reference), with country as a random intercept effect (N=21,750).

Effect	*aOR (95% CI)
Sex (Female vs. Male as reference)	0.92 (0.86, 0.98)
Age	
(18 to 39 vs. ≥65 as reference)	1.12 (1.00, 1.24)
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Are you embarrassed to discuss your bowel functioning with others (family, friends)?	
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Does stress, pressure or tension affect your bowel functioning?	
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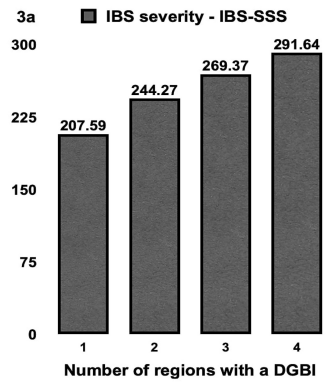
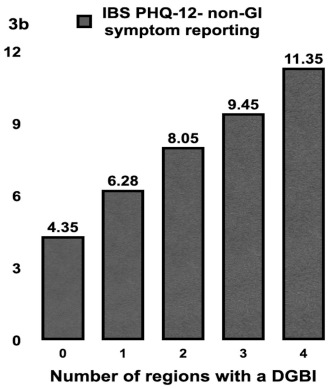
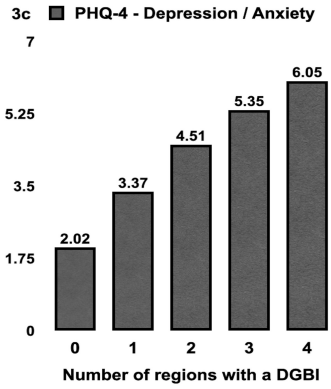
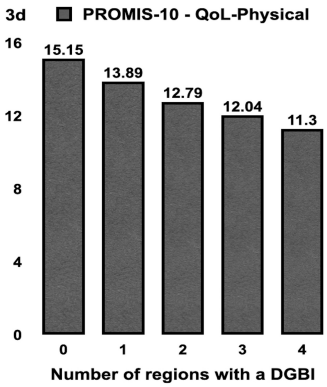
(Greatly affects it vs. Not at all as reference)	1.16 (1.07, 1.27)
PROMIS-10 Global Physical Health score	0.93 (0.91, 0.94)
PROMIS-10 Global Mental Health score	0.96 (0.80, 1.14)
PHQ-4 Anxiety/depression	1.03 (1.02, 1.05)
PHQ-12 - somatization	1.09 (1.08, 1.10)
Fibromyalgia	1.02 (1.01, 1.03)
Number of surgeries	1.05 (0.99, 1.11)
Number of medications	1.15 (1.13, 1.18)

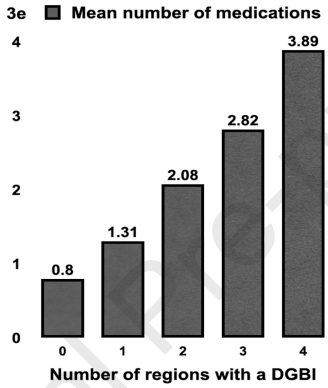
* aOR = adjusted Odds Ratio

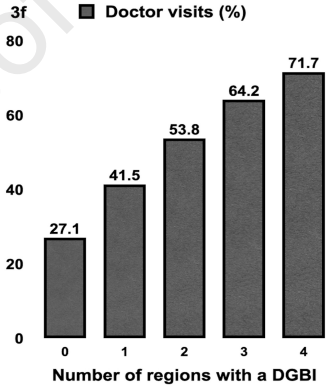


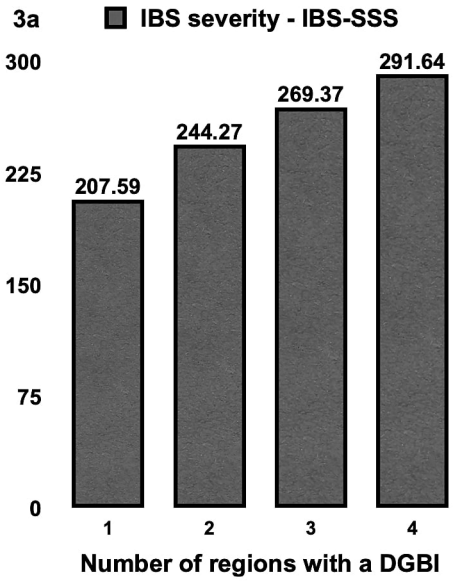


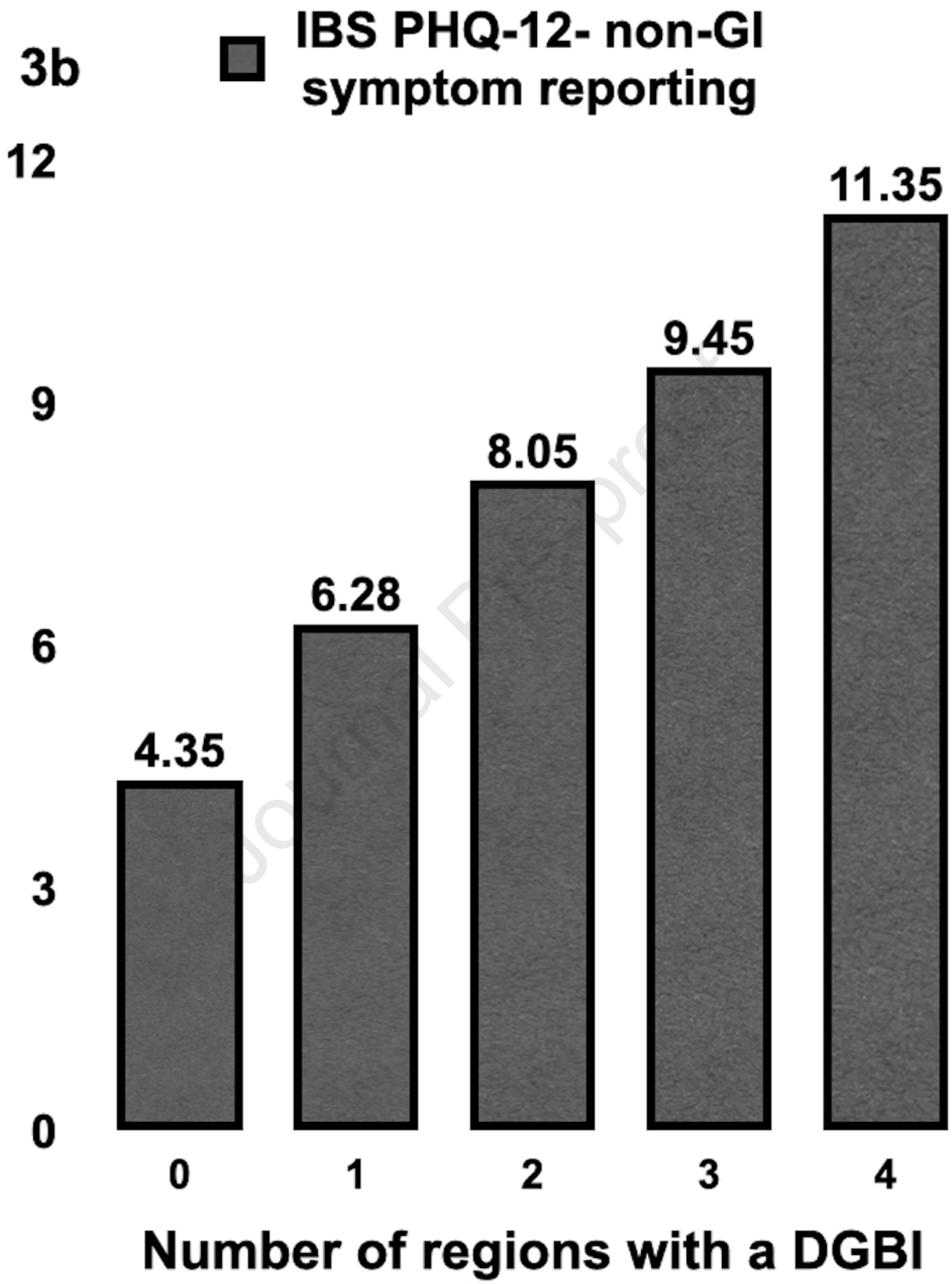


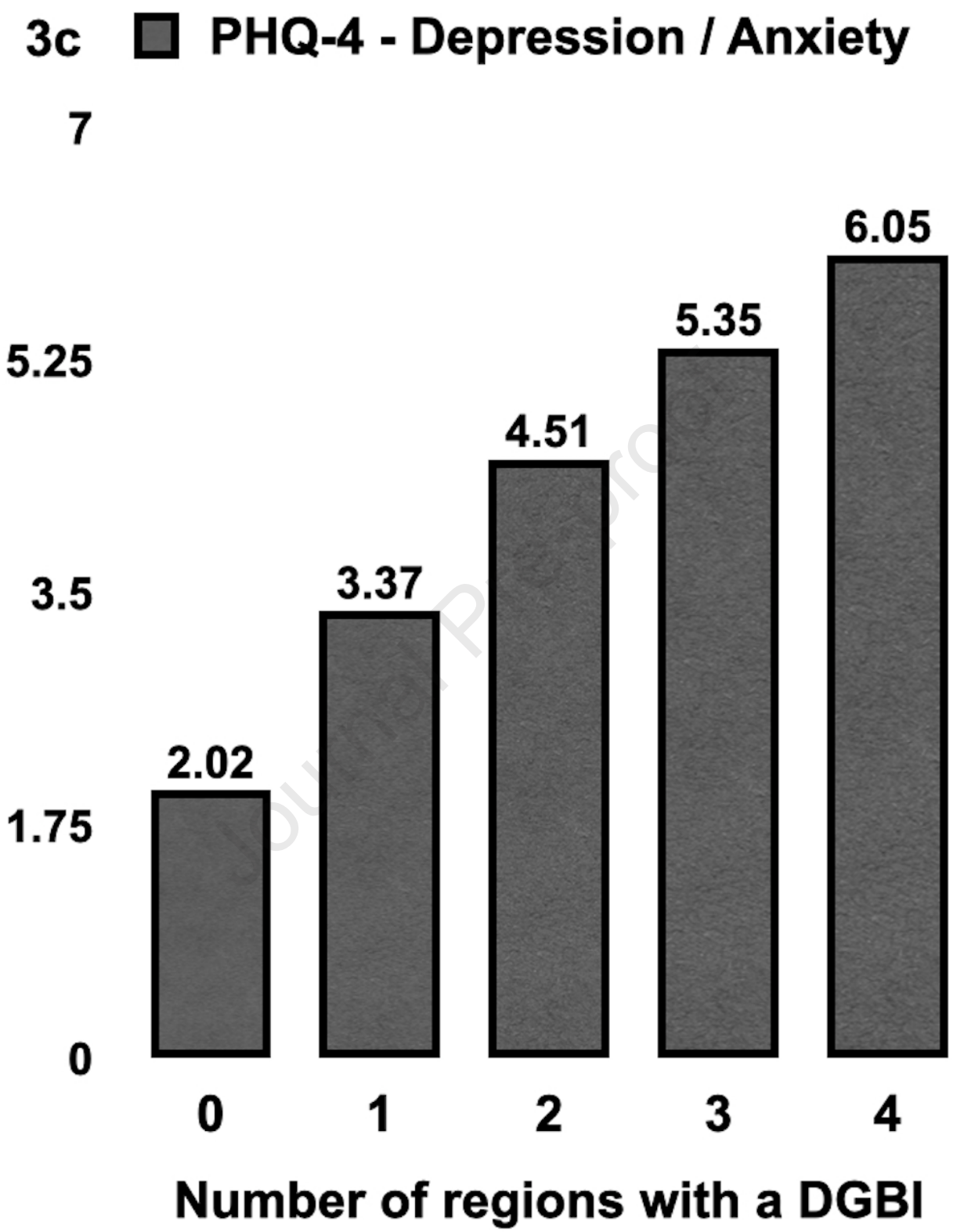


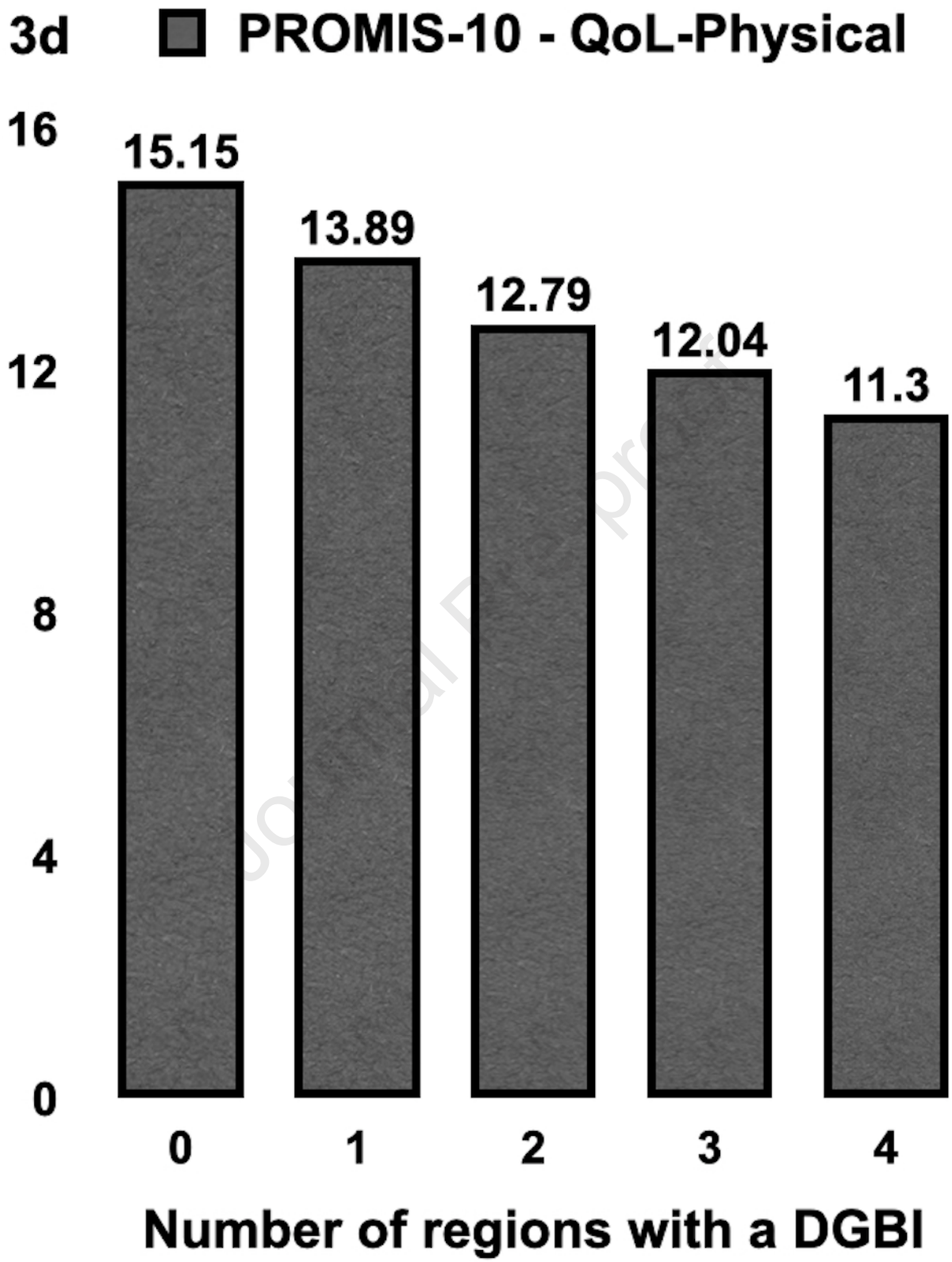


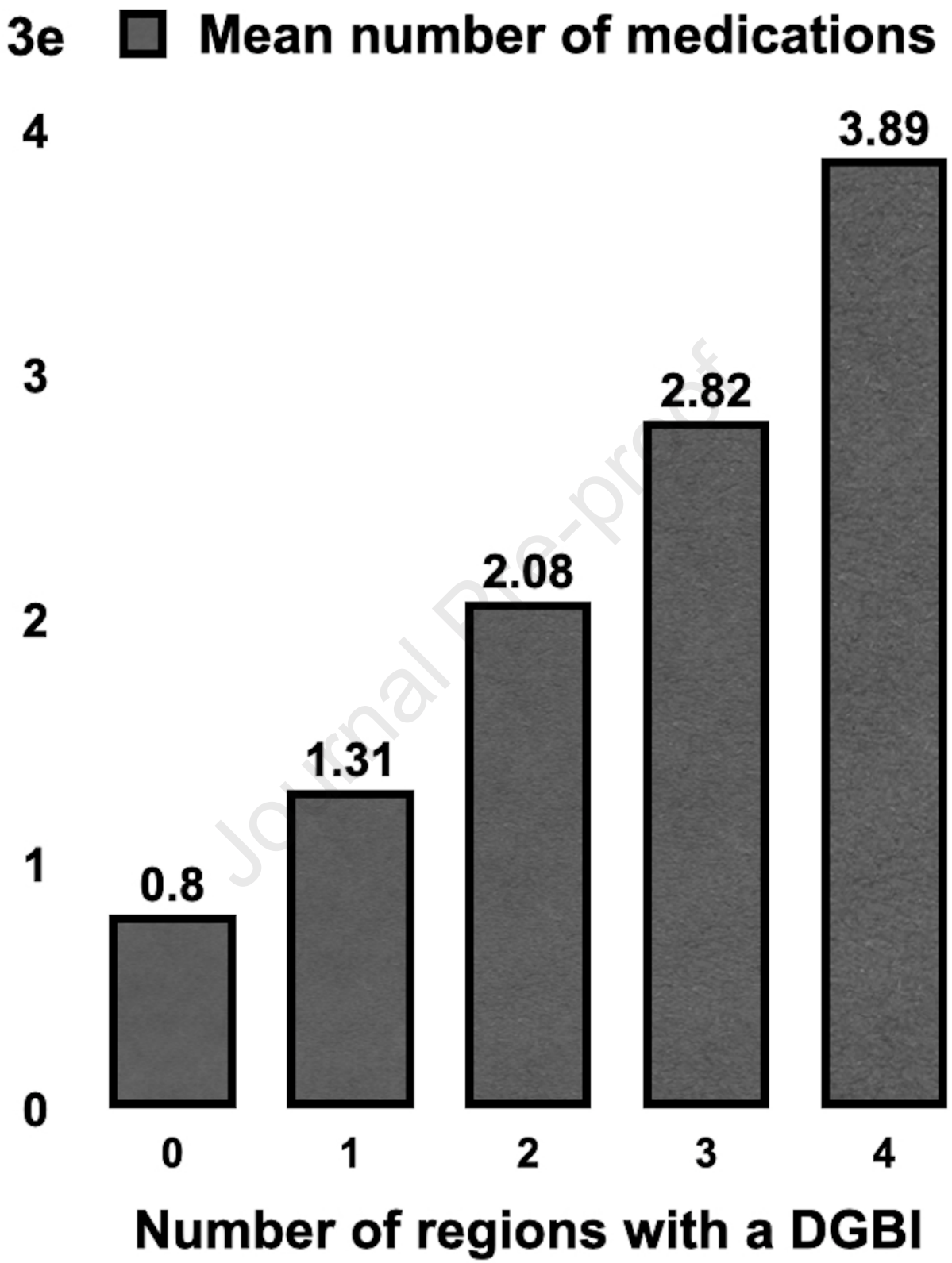


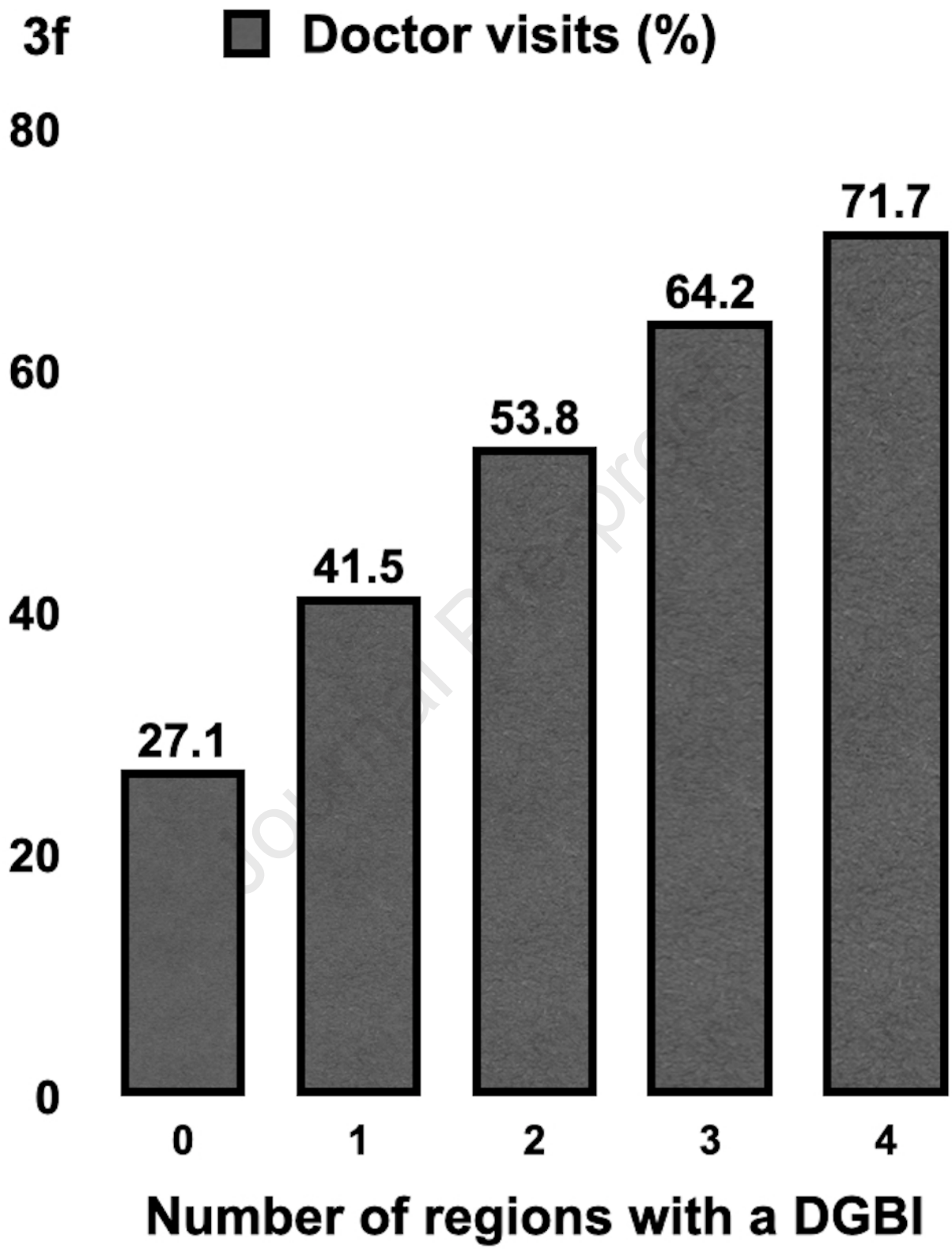


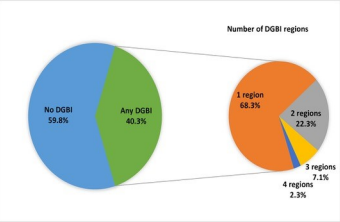

3b
IBS PHQ-12- non-GI symptom reporting
12
9
6
3
0
4.35
6.28
8.05
9.45
11.35
0
1
2
3
4
Number of regions with a DGBI

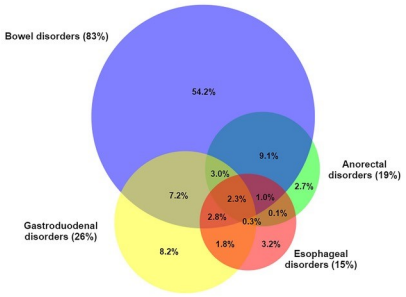

3c
PHQ-4 - Depression / Anxiety
7
5.25
3.5
1.75
0
2.02
3.37
4.51
5.35
6.05
0
1
2
3
4
Number of regions with a DGBI


3d
PROMIS-10 - QoL-Physical
16
12
8
4
0
15.15
13.89
12.79
12.04
11.3
0
1
2
3
4
Number of regions with a DGBI




3f
Doctor visits (%)
80
60
40
20
0
27.1
41.5
53.8
64.2
71.7
0
1
2
3
4
Number of regions with a DGBI





What you need to know:

Background

- There is evidence for poorer outcomes among patients with overlapping DGBI, but mainly from small-scale studies using a small number of DGBI, primarily IBS and functional dyspepsia.

Findings

- In a population-based study with 54,127 participants in 26 countries we found a universal association between overlapping DGBI and a negative impact on quality of life, disease severity, psychological co-morbidity, and healthcare utilization.

Implications for patient care

- Physician awareness and identification of patients with overlapping DGBI could improve quality of care and patients' outcomes.