Article:
Veldman, F., Innocenti, F., Aziz, I. et al. (2026) Prevalence and burden of fatigue across disorders of gut–brain interaction: results from the Rome foundation global epidemiology study. Alimentary Pharmacology & Therapeutics. ISSN: 0269-2813

https://doi.org/10.1111/apt.70756

Alimentary Pharmacology & Therapeutics

WILEY

AP&T Alimentary Pharmacology & Therapeutics

ORIGINAL ARTICLE OPEN ACCESS

Prevalence and Burden of Fatigue Across Disorders of Gut–Brain Interaction: Results From the Rome Foundation Global Epidemiology Study

Fleur Veldman[1] | Francesco Innocenti[2] | Imran Aziz[3,4] | Asma Fikree[5,6] | Shrikant I. Bangdiwala[7] | Olafur Palsson[8] | Ami D. Sperber[9] | Daniel Keszthelyi[1]

[1]Department of Gastroenterology-Hepatology, NUTRIM Research Institute of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, the Netherlands | [2]Department of Methodology and Statistics, Care and Public Health Research Institute (CAPHRI), Faculty of Health Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands | [3]Academic Unit of Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK | [4]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK | [5]GI Physiology Unit, University College London Hospital NHS Foundation Trust, London, UK | [6]Division of Surgery & Interventional Science, Research Department of Targeted Intervention, University College London, London, UK | [7]Department of Health Research Methods, Evidence and Impact, Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada | [8]Center for Functional GI & Motility Disorders, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, USA | [9]Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel

Correspondence: Fleur Veldman (fleur.veldman@maastrichtuniversity.nl)

Received: 13 March 2026 | **Revised:** 13 May 2026 | **Accepted:** 20 May 2026

Keywords: disorders of gut–brain interaction | epidemiology | fatigue | illness burden

ABSTRACT

Background: Overlap among disorders of gut-brain interaction (DGBI) is common, with many patients experiencing concomitant non-gastrointestinal symptoms. Fatigue is frequently reported, yet population-based prevalence estimates across DGBI are limited.

Aims: To examine the prevalence and burden of fatigue among DGBI.

Methods: Data were derived from the Rome Foundation Global Epidemiology Study's internet-based survey, conducted in 26 countries using the Rome IV Adult Diagnostic Questionnaire. Fatigue was assessed with single items from the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 and the Patient Health Questionnaire-12 (PHQ-12). Prevalence of fatigue was compared across three groups, including no DGBI, one DGBI and multiple DGBI, with potential associated factors examined using logistic regression.

Results: Among 54,127 participants (49% female; mean age 44 years), 59.9% had no DGBI, 26.6% had one DGBI and 13.5% had multiple DGBI. Fatigue prevalence was higher with more DGBI overlap: PROMIS 7.7% (95% CI:7.46–8.04), 16.4% (95% CI: 15.79–17.00), 30.2% (95% CI: 29.16–31.26); PHQ-12 12.6% (95% CI: 12.24–12.96), 25.8% (95% CI: 25.06–26.49), 42.0% (95% CI: 40.83–43.09) for no, one, and multiple DGBI. Fatigue was most common in reflux hypersensitivity (PROMIS 46%, PHQ-12 58%) and irritable bowel syndrome (PROMIS 39%, PHQ-12 53%). Among individuals with DGBI, fatigue was consistently associated across both definitions with female sex, age, BMI, sleep disturbance, higher anxiety and depression scores, greater somatic symptom burden, lower psychological well-being, antidepressant use, and satiety, abdominal pain, and bloating.

Conclusions: Fatigue is common and burdensome in DGBI, particularly with overlapping diagnoses. Given the cross-sectional design, directionality between fatigue and DGBI symptom burden remains unclear. Future research should employ longitudinal fatigue assessments to inform targeted management.

1 | Introduction

Disorders of gut-brain interaction (DGBI) are highly prevalent conditions, with a global prevalence of 40.3% among adults [1]. These disorders are primarily characterized by gastrointestinal (GI) symptoms and can be categorized into anatomical groups based on the presumed origin of symptoms [1, 2]. Overlap between DGBI categories is frequently observed, with the number of affected gastrointestinal regions being related to greater symptom severity, psychological comorbidity, and reduced quality of life [2]. Many patients also report concomitant non-GI complaints, underscoring the complex and multidimensional impact of DGBI [2, 3].

Fatigue is one such symptom, defined as a persistent feeling of mental or physical tiredness or weakness that is disproportionate to or independent of activity, and that is not alleviated by rest [4, 5]. It has been reported as one of the most bothersome non-GI symptoms in patients with irritable bowel syndrome (IBS), a prototypical DGBI [4, 6]. In some cases, it is perceived as equally distressing as the GI symptoms themselves [4, 7]. Furthermore, fatigue has been shown to exert a multidimensional impact on patient outcomes, including increased symptom severity, impaired quality of life, reduced work productivity, and greater healthcare utilization and costs, underscoring the importance of recognizing and addressing this symptom [4, 6, 8, 9]. Importantly, although fatigue is recognized as a distressing and highly prevalent symptom in IBS, robust prevalence estimates for the broader DGBI population are lacking. Consequently, it remains unclear whether fatigue is underrecognized across DGBI as a whole and to what extent it contributes to overall patient burden.

Efforts to effectively recognize and manage fatigue in DGBI are hindered by a limited understanding of its underlying mechanisms. The overlap with GI symptoms may be partially explained by shared pathophysiological pathways, including dysregulation of the hypothalamic–pituitary–adrenal axis, abnormalities in serotonin neurotransmission and alterations in immune activation with low-grade inflammation [7, 10, 11]. Similar mechanisms have been implicated in fatigue among patients with inflammatory bowel disease (IBD) in remission, suggesting a role for altered gut-brain signalling [5]. Multiple individual and health-related factors may influence the occurrence of fatigue, including sex, BMI, sleep disturbance and psychological comorbidity [4, 6, 7, 12]. Furthermore, it remains uncertain whether fatigue represents a distinct non-GI symptom or is secondary to comorbid conditions, such as depression, in which fatigue and loss of energy are central features [8]. Notably, many patients with IBS and functional dyspepsia (FD), another DGBI, meet the criteria for chronic fatigue syndrome, yet the mechanisms driving this overlap remain to be elucidated [2, 12].

Together, these uncertainties underscore the unmet need for a comprehensive understanding of fatigue in DGBI to improve clinical recognition and management. The Rome Foundation Global Epidemiology Study (RFGES), a multinational investigation assessing the prevalence and determinants of 22 distinct DGBI in the global population, provides a unique opportunity to reliably assess the prevalence and burden of fatigue across three groups: (I) individuals without any DGBI; (II) individuals with one Rome-IV defined DGBI diagnosis; and (III) individuals with two or more Rome IV-defined DGBI diagnoses.

Therefore, the present study aimed to examine fatigue in DGBI and its contribution to overall patient burden. It was hypothesized that fatigue prevalence would increase progressively across these three groups, reflecting the greater disease burden among patients with overlapping DGBI [2, 3].

2 | Materials and Methods

This study was conducted under the auspices of the Rome Foundation Research Institute and forms part of the RFGES. Data in the RFGES were obtained from 33 countries across six continents using internet-based surveys, face-to-face interviews, or both approaches. A full account of the RFGES methodology has been published previously [1].

2.1 | Participants

This study includes respondents from the 26 countries within the RFGES that used internet-based survey methods. Participants were recruited through a professional survey panel provider (Qualtrics LLC, Provo, Utah, USA) who provided respondents with points redeemable for gifts. Prespecified demographic criteria ensured a minimum of 2000 respondents per country, with 50% male and 50% female, and an age distribution of 40% aged 18–39 years, 40% aged 40–64 years and 20% aged 65 or older [1].

2.2 | Internet Survey

A secure, anonymous online survey was conducted in each of the 26 countries. Surveys underwent translatability assessment by a professional company (TransPerfect Inc., New York, NY) and were translated into 21 languages, ensuring both linguistic validation and cultural adaptation [1, 13]. Quality-assurance procedures were implemented to exclude unreliable responders, including attention-check items, completion time thresholds, and repeated questions to identify inconsistent responses. The survey guaranteed that all mandatory questions were answered and incorporated automated skip patterns, resulting in comprehensive and accurate data on participants' symptom profiles [1]. Institutional Review Boards (IRBs) and ethics committees in each participating country reviewed the study and deemed it exempt from ethics oversight due to anonymous data collection. Electronic informed consent was nonetheless obtained from all respondents.

2.3 | Study Questionnaires

The internet survey comprised up to 160 questions, including the Rome IV Adult Diagnostic Questionnaire, the Rome III IBS Questionnaire for comparison with Rome IV, and an additional 80 items to identify DGBI-related associations. The exact number of questions varied based on participants' responses. The Rome IV Adult Diagnostic Questionnaire included 86 items assessing

gastrointestinal symptoms to identify participants with a DGBI. Symptoms were classified into 22 distinct DGBI types within six Rome classification categories: oesophageal disorders, gastroduodenal disorders, bowel disorders, anorectal disorders, biliary disorders and centrally mediated abdominal pain syndrome (CAPS). Individuals with self-reported organic diseases potentially explaining their symptoms (e.g., celiac disease, inflammatory bowel disease) were excluded from DGBI classification, but remained in the denominator. Additional survey items assessed sociodemographic characteristics and factors potentially associated with DGBI, including psychosocial determinants, healthcare access, medication use, and quality of life, utilizing validated instruments (e.g., the PHQ-4 for anxiety and depression and the PHQ-12 for somatic symptom burden). In accordance with the Rome Foundation scoring algorithm, the gastrointestinal and menstruation-related items were excluded from the PHQ-15 total score, leaving 11 items representing PHQ-12. The fatigue item was additionally omitted in this study, as fatigue was analysed as the primary outcome. The IBS Severity Scoring System (IBS-SSS) was used to assess the severity of IBS symptoms. Scores were categorized as none/minimal symptoms (0–74), mild (75–174), moderate (175–299) and severe ($\geq$300), consistent with established cut-offs [14].

2.4 | Fatigue Assessment

Fatigue was assessed using individual items from the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 and the Patient Health Questionnaire-12 (PHQ-12). Although these individual items have not been formally validated as standalone measures of fatigue, the survey was pre-specified and a validated fatigue instrument could not be incorporated; these items were therefore used as a pragmatic estimate of fatigue and to allow sensitivity analyses. On the PROMIS Global-10, a patient-reported outcome measure assessing overall health and quality of life, fatigue was defined as reporting 'severe' or 'very severe' on the item 'How would you rate your fatigue on average?' [15]. On the PHQ-12, which evaluates somatic symptom severity over the past 4 weeks, fatigue was defined as being 'bothered a lot' by the item 'feeling tired or having low energy' [16]. Cut-offs were chosen pragmatically based on response options.

2.5 | Statistical Analyses

Given that the primary objective was to estimate the global prevalence of fatigue in patients with DGBI, the sample size was expected to yield a prevalence estimate with an acceptably narrow 95% confidence interval (CI). Based on the RFGES, 40.3% of participants who completed the internet survey ($n = 54{,}127$) had at least one DGBI diagnosis, corresponding to an estimated 21,813 individuals across the 26 participating countries [1]. Assuming a fatigue prevalence of 50%, the 95% CI around the global prevalence estimate among individuals with a DGBI had a margin of error of approximately 0.7%. For prevalence estimates lower or higher than 50%, the margin of error would be smaller.

Data analyses were conducted using R (Version 4.4.3) [17]. Baseline characteristics are reported as means with standard deviation for continuous variables, while categorical variables are reported as frequencies and percentages.

For the primary analyses, prevalences with 95% CIs were calculated for both fatigue definitions (i.e., PROMIS global-10 and PHQ-12) across the three groups, at both the global and country-specific levels, using the Wilson-method [18]. The groups were defined as follows: (I) individuals without a DGBI, (II) individuals with one DGBI, and (III) individuals with two or more DGBI. Additionally, the prevalence of fatigue was assessed for each Rome DGBI classification group and subtype (e.g., FD, IBS) at both the global and country-specific levels, where appropriate.

Determinants of fatigue in DGBI were examined using a logistic regression model with country-level dummy variables to account for the hierarchical structure of the data, with individuals nested within countries. This fixed-effects approach reduces the risk of omitting country-level confounders and avoids making distributional assumptions about the country effects [19]. A full-model approach was employed, with fatigue, defined either by PROMIS Global-10 or PHQ-12, as the dependent variable, and a priori-selected predictors, including demographic characteristics, health-related variables and gastrointestinal symptoms, as independent variables [20]. No causal interpretations should be made based on the reported estimates. Model assumptions were assessed and addressed when violated. Continuous predictors were examined for non-linear associations and, when appropriate, were modelled using restricted cubic splines with three knots. Adjusted odds ratios (aORs) with 95% CIs were reported. For continuous variables, aORs comparing the 75th vs. the 25th percentile (interquartile range) were calculated to aid interpretation. *p*-values were derived from likelihood ratio tests (LRTs) comparing the full model with a reduced model excluding the corresponding variable. A $p < 0.05$ was considered statistically significant. Predicted probability plots were generated to illustrate the functional form of non-linear associations, holding other covariates at representative values. Nomograms were constructed to provide a graphical representation of the multivariable models. The discriminative ability of the models was assessed using ROC and AUROC analyses.

Fatigue prevalence was additionally examined, for exploratory purposes, in relation to IBS symptom severity, with prevalence assessed across IBS-SSS severity categories using the Wilson method for calculating 95% CIs. Fatigue prevalence was also calculated separately for patients with painful DGBI, non-painful DGBI, and those with both, based on a previously reported classification (Supporting Information, Methods) [21].

Missing data were minimal overall. Only BMI had missing values with approximately 10% of BMI values missing. Factors associated with BMI missingness were examined, using logistic regression and included in the model with fatigue as the outcome (Supporting Information, Methods). A complete-case analysis approach was followed, as BMI was included only in secondary analyses.

3 | Results

3.1 | Participants

A total of 54,127 participants completed the internet survey across 26 countries. Participants were 49.1% female, with a mean age of 44.34 ± 16.19 years. Among them, 32,412 (59.9%)

TABLE 1 | Baseline Characteristics of Participants by DGBI Status.

Characteristic	Total population (*N* = 54,127)	No DGBI (*N* = 32,412)	1 DGBI (*N* = 14,403)	≥2 DGBI (*N* = 7,312)
Age, years, mean (SD)	44.34 (16.19)	45.49 (16.47)	42.75 (15.82)	42.33 (15.12)
Female sex, *n* (%)	26,578 (49.1)	14,253 (44.0)	8069 (56.0)	4256 (58.2)
Region, *n* (%)				
Africa	4041 (7.5)	2165 (6.7)	1178 (8.2)	698 (9.6)
Asia	9487 (17.5)	6066 (18.7)	2475 (17.2)	946 (12.9)
Europe	22,420 (41.4)	13,378 (41.3)	5970 (41.5)	3072 (42.0)
Latin America	8069 (14.9)	4634 (14.3)	2173 (15.1)	1262 (17.3)
Middle East	4022 (7.4)	2490 (7.7)	1104 (7.7)	428 (5.9)
North America	4052 (7.5)	2408 (7.4)	987 (6.9)	657 (9.0)
Oceania	2036 (3.8)	1271 (3.9)	516 (3.6)	249 (3.4)
BMI, kg/m^2, mean (SD)	25.59 (5.41)	25.47 (5.16)	25.60 (5.58)	26.09 (6.10)
Education, years, mean (SD)	14.13 (4.55)	14.11 (4.52)	14.19 (4.55)	14.06 (4.68)
Healthcare access, *n* (%)				
No access	305 (0.6)	185 (0.6)	68 (0.5)	52 (0.7)
Limited access	4369 (8.1)	2120 (6.5)	1292 (9.0)	957 (13.1)
Full access	49,453 (91.4)	30,107 (92.9)	13,043 (90.6)	6303 (86.2)
PHQ-4 score, mean (SD)	2.75 (2.95)	2.02 (2.50)	3.34 (3.00)	4.79 (3.40)
PHQ-12 score, mean (SD)	4.25 (3.21)	3.42 (2.85)	4.82 (3.00)	6.79 (3.51)
PROMIS Global Mental Health score, mean (SD)	13.55 (3.32)	14.23 (3.13)	12.91 (3.25)	11.80 (3.37)
Trouble sleeping, *n* (%)	8422 (15.6)	3272 (10.1)	2763 (19.2)	2387 (32.6)
Pain medication prescribed, *n* (%)	9390 (17.4)	4437 (13.7)	2643 (18.4)	2310 (31.6)
Anxiety medication, *n* (%)	4827 (8.9)	1896 (5.9)	1470 (10.2)	1461 (20.0)
Antidepressant medication, *n* (%)	4677 (8.6)	1921 (5.9)	1439 (10.0)	1317 (18.0)
Sleeping medication, *n* (%)	5140 (9.5)	2244 (6.9)	1446 (10.0)	1450 (19.8)

Note: Values are presented as means (standard deviations) or frequencies (%), as appropriate. Regions were classified using predefined geographic groupings. Trouble sleeping was assessed using an individual item from the PHQ-12 questionnaire.

participants were classified as not having a DGBI, 14,403 (26.6%) had one DGBI, and 7312 (13.5%) had two or more DGBI (range 2–10). Anxiety and depression scores (PHQ-4), somatic symptom scores (PHQ-12), trouble sleeping, and use of prescribed medications for pain, anxiety, depression and sleep gradually increased across groups, whereas overall psychological well-being scores (PROMIS Global Mental Health) decreased. Detailed characteristics are presented in Table 1.

3.2 | Global Prevalence of Fatigue

The global prevalence of fatigue was 13.1% (95% CI: 12.80–13.36) based on the PROMIS Global-10 and 20.1% (95% CI: 19.73–20.41) based on the PHQ-12; see Table 2. A substantial increase in fatigue prevalence was observed across the three DGBI groups for both instruments. Using the PROMIS Global-10, prevalence was 7.7% (95% CI: 7.46–8.04) in participants without a DGBI, 16.4% (95% CI: 15.79–17.00) in those with one DGBI, and 30.2% (95% CI: 29.16–31.26) in those with two or more DGBI. Using the PHQ-12, prevalence was 12.6% (95% CI: 12.24–12.96) in participants without a DGBI, 25.8% (95% CI: 25.06–26.49) in those with one DGBI, and 42.0% (95% CI: 40.83–43.09) in those with two or more DGBI. Moderate agreement was observed between fatigue defined by the PROMIS Global-10 and the PHQ-12 (Cohen's $\kappa = 0.43$, 95% CI: 0.42–0.44).

3.3 | Country-Specific Prevalence of Fatigue

Country-specific prevalence of fatigue varied considerably among the DGBI groups (Figures 1 and 2, Tables S7 and S8). Prevalence consistently increased across DGBI groups, with participants having no DGBI showing the lowest prevalence (PROMIS Global-10: 2.6%, 95% CI [1.94–3.37] in China; PHQ-12:

TABLE 2 | Global Prevalence of Fatigue Based on the PROMIS Global-10 and the PHQ-12.

Fatigue measure	Total *n* = (%)	95% CI	No DGBI *n* = (%)	95% CI	1 DGBI *n* = (%)	95% CI	≥ 2 DGBI *n* = (%)	95% CI
PROMIS Global-10	7078/54,127 (13.1%)	12.80–13.36	2510/32,412 (7.7%)	7.46–8.04	2360/14,403 (16.4%)	15.79–17.00	2208/7312 (30.2%)	29.16–31.26
PHQ-12	10,861/54,127 (20.1%)	19.73–20.41	4082/32,412 (12.6%)	12.24–12.96	3711/14,403 (25.8%)	25.06–26.49	3068/7312 (42.0%)	40.83–43.09

Note: 95% confidence intervals were calculated using the Wilson method.
Abbreviations: 95% CI, 95% confidence interval; DGBI, disorders of gut–brain interaction; PHQ-12, Patient Health Questionnaire-12; PROMIS Global-10, Patient-Reported Outcomes Measurement Information System Global-10.

7.3%, 95% CI [6.11–8.74] in Japan) and those with multiple DGBI showing the highest prevalence (PROMIS Global-10: up to 50.6%, 95% CI [44.54–56.59] in Korea; PHQ-12: up to 53.0%, 95% CI [47.63–58.09] in South Africa). This pattern was observed for both instruments and across all countries.

3.4 | Prevalence of Fatigue in DGBI Rome Classification Groups and Subtypes

Among participants with oesophageal disorders, fatigue prevalence was 31.4% (95% CI: 29.81–33.01) using the PROMIS Global-10 and 43.5% (95% CI: 41.75–45.17) using the PHQ-12. Corresponding prevalences were 29.7% (95% CI: 28.55–30.91) and 42.7% (95% CI: 41.43–43.98) for gastroduodenal disorders, 27.3% (95% CI: 26.00–28.70) and 37.4% (95% CI: 35.94–38.87) for anorectal disorders and 21.1% (95% CI: 20.51–21.70) and 30.8% (95% CI: 30.09–31.43) for bowel disorders, respectively (Table 3). Prevalence estimates for functional biliary pain and CAPS were based on small sample sizes, resulting in confidence intervals that were too broad. Detailed country-specific prevalence of fatigue among the DGBI classification groups is shown in the Tables S9 and S10.

Across specific DGBI, the lowest prevalence estimates were observed for functional bowel disorder, unspecified (PROMIS Global-10: 15.4%, 95% CI: 14.38–16.44; PHQ-12: 24.3%, 95% CI 23.12–25.57), whereas the highest estimates were observed for reflux hypersensitivity (PROMIS Global-10: 45.7%, 95% CI: 41.19–50.31; PHQ-12: 58.2%, 95% CI: 53.66–62.69) and IBS (PROMIS Global-10: 39.0%, 95% CI: 36.98–41.05; PHQ-12: 53.1%, 95% CI: 50.98–55.16) (Table 3). Estimates for rare DGBI, such as cannabinoid hyperemesis syndrome, functional biliary pain and CAPS, should be interpreted with caution.

3.5 | Factors Associated With Fatigue in DGBI

A full-model approach was applied to assess determinants potentially associated with fatigue in DGBI. Two separate models were created: one for fatigue defined by the PROMIS Global-10 and one for fatigue defined by the PHQ-12. Linearity assumption was violated for some continuous predictors and addressed by using restricted cubic splines (see Tables S36 and S61). No other model violations were identified (i.e., collinearity, influential outliers). Both models demonstrated good discrimination, with AUCs of 0.84 (95% CI: 0.83–0.85) for the PROMIS-defined fatigue model and 0.83 (95% CI: 0.82–0.83) for the PHQ-12-defined fatigue model.

In the PROMIS Global-10 fatigue model, female sex was associated with increased odds of fatigue in DGBI (OR = 1.24, 95% CI [1.14–1.36]) (Table 4). Additional factors associated with higher odds included having multiple DGBI (OR = 1.19, 95% CI [1.08–1.30]), trouble sleeping (OR = 1.56, 95% CI [1.42–1.72]), use of pain medication (OR = 1.15, 95% CI [1.04–1.28]), or antidepressant medication (OR = 1.25, 95% CI [1.09–1.45]), and GI symptoms, including satiety (OR = 1.13, 95% CI [1.02–1.25]), nausea (OR = 1.24, 95% CI [1.07–1.45]), abdominal pain (OR = 1.19, 95% CI [1.07–1.33]) and bloating (OR = 1.27, 95% CI [1.17–1.39]). Use of anxiety medication was associated with

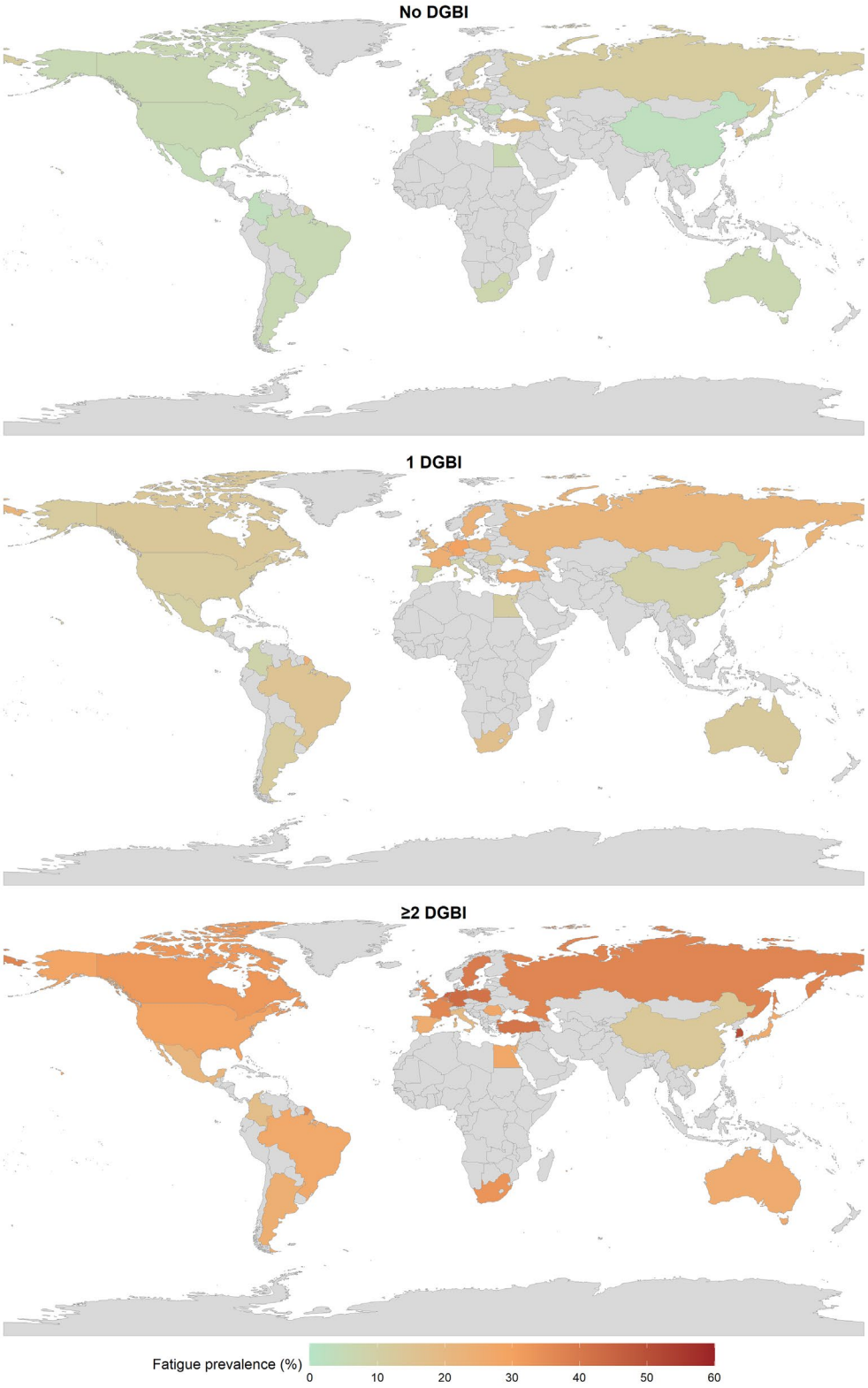

FIGURE 1 | Prevalence of Fatigue (based on the PROMIS Global-10) by Country and DGBI Group. Country-specific fatigue prevalence is shown by DGBI group: No DGBI, one DGBI, and >2 DGBI. Fatigue prevalence is colour-coded, with green indicating the lowest prevalence and red the highest.

lower odds (OR = 0.86, 95% CI [0.75–0.99]). Age, BMI, PHQ-4 score, PHQ-12-score and the PROMIS Global Mental Health score showed non-linear associations with the odds of fatigue (Table S36). Corresponding aORs comparing differences in the predictors across the interquartile range (IQR) are presented in Table 4. Predicted probability plots illustrated distinct non-linear patterns, including increasing fatigue probability with higher PHQ-4 scores and lower PROMIS Global Mental Health scores, as well as non-monotonic associations with age, BMI and PHQ-12 score (Figure 3).

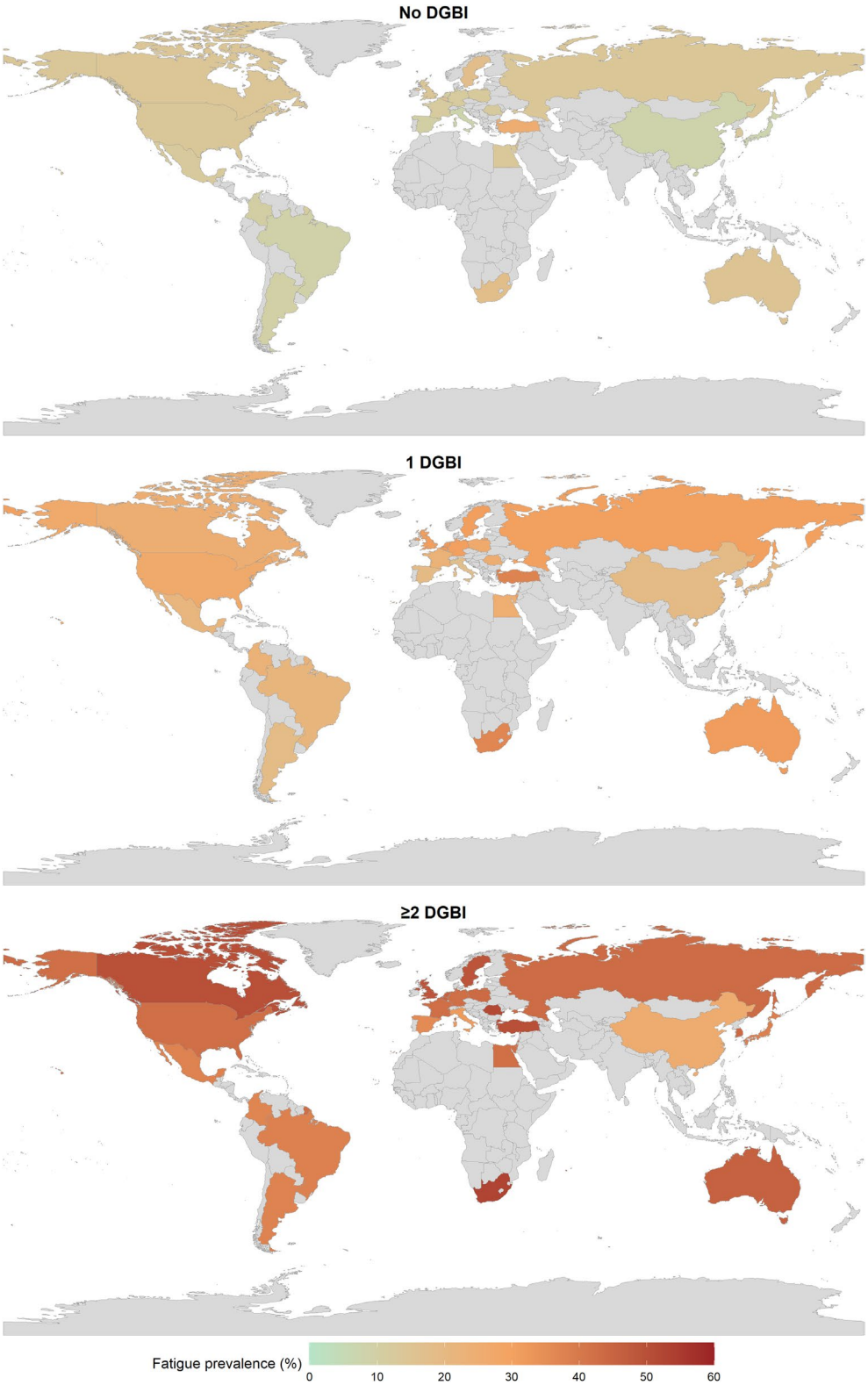

FIGURE 2 | Prevalence of Fatigue (based on the PHQ-12) by Country and DGBI Group. Country-specific fatigue prevalence is shown by DGBI group: No DGBI, one DGBI, and > 2 DGBI. Fatigue prevalence is colour-coded, with green indicating the lowest prevalence and red the highest.

In the PHQ-12 fatigue model, factors associated with higher odds of fatigue in DGBI included female sex (OR = 1.43, 95% CI [1.32–1.54]), trouble sleeping (OR = 2.64, 95% CI [2.42–2.88]), use of antidepressant medication (OR = 1.21, 95% CI [1.05–1.38]), satiety (OR = 1.24, 95% CI [1.13–1.35]), abdominal pain (OR = 1.26, 95% CI [1.14–1.40]) and bloating (OR = 1.13, 95% CI [1.04–1.22]). Age (30 vs. 54 years: OR = 0.67, 95% CI [0.63–0.71]) and use of sleeping medication (OR = 0.78, 95% CI [0.69–0.87]) were associated with lower odds of fatigue (Table 5). BMI, PHQ-4 score, PHQ-12 score, and the PROMIS Global Mental Health score demonstrated non-linear

TABLE 3 | Global Prevalence of Fatigue Among DGBI Subtypes.

DGBI	Fatigue, PROMIS Global-10	95% CI	Fatigue, PHQ-12	95% CI
Oesophageal disorders	1012/3224 (31.4%)	29.81–33.01	1401/3224 (43.5%)	41.75–45.17
Functional Heartburn	215/613 (35.1%)	31.40–38.93	297/613 (48.5%)	44.52–52.40
Functional Chest Pain	236/741 (31.9%)	28.60–35.29	315/741 (42.5%)	39.00–46.10
Reflux Hypersensitivity	208/455 (45.7%)	41.19–50.31	265/455 (58.2%)	53.66–62.69
Globus	108/408 (26.5%)	22.42–30.96	159/408 (39.0%)	34.36–43.78
Dysphagia	539/1712 (31.5%)	29.33–33.72	764/1712 (44.6%)	42.29–46.99
Gastroduodenal disorders	1708/5747 (29.7%)	28.55–30.91	2454/5747 (42.7%)	41.43–43.98
Functional Dyspepsia	1296/3910 (33.2%)	31.69–34.64	1819/3910 (46.5%)	44.96–48.09
PDS	1098/3313 (33.1%)	31.56–34.76	1577/3313 (47.6%)	45.90–49.30
EPS	508/1306 (38.9%)	36.29–41.57	665/1306 (50.9%)	48.21–53.62
Belching	179/525 (34.1%)	30.17–38.25	263/525 (50.1%)	45.83–54.36
Rumination	363/1511 (24.0%)	21.94–26.24	560/1511 (37.1%)	34.66–39.53
CNVS	193/503 (38.4%)	34.22–42.69	265/503 (52.7%)	48.32–57.01
Cyclic Vomiting	202/649 (31.1%)	27.68–34.79	269/649 (41.5%)	37.72–45.28
Cannabinoid Hyperemesis Syndrome	14/28 (50.0%)	32.63–67.37	12/28 (42.9%)	26.51–60.93
Bowel disorders	3794/17,980 (21.1%)	20.51–21.70	5530/17,980 (30.8%)	30.09–31.43
IBS	856/2195 (39.0%)	36.98–41.06	1165/2195 (53.1%)	50.98–55.16
Functional Constipation	1230/6333 (19.4%)	18.47–20.41	1859/6333 (29.4%)	28.25–30.49
Opioid Induced Constipation	222/846 (26.2%)	23.39–29.31	316/846 (37.4%)	34.16–40.66
Functional Diarrhoea	514/2547 (20.2%)	18.67–21.78	681/2547 (26.7%)	25.05–28.49
Functional Bloating	348/1658 (21.0%)	19.10–23.02	503/1658 (30.3%)	28.17–32.59
Functional Bowel Disorder, Unspecified	728/4732 (15.4%)	14.38–16.44	1151/4732 (24.3%)	23.12–25.57
Anorectal disorders	1143/4183 (27.3%)	26.00–28.70	1564/4183 (37.4%)	35.94–38.87
Faecal incontinence	239/851 (28.1%)	25.17–31.20	320/851 (37.6%)	34.41–40.91
Levator Ani	239/622 (38.4%)	34.68–42.31	291/622 (46.8%)	42.90–50.71
Proctalgia Fugax	784/3013 (26.0%)	24.49–27.62	1092/3013 (36.2%)	34.55–37.98
Functional Biliary Pain	16/44 (36.4%)	23.78–51.13	24/44 (54.6%)	40.07–68.29
CAPS	2/11 (18.2%)	5.14–47.70	6/11 (54.6%)	28.01–78.73

Abbreviations: 95% CI, 95% confidence interval; CAPS, centrally mediated abdominal pain syndrome; CNVS, chronic nausea and vomiting syndrome; DGBI, disorder of gut–brain interaction; EPS, epigastric pain syndrome; IBS, irritable bowel syndrome; PDS, postprandial distress syndrome; PHQ-12, Patient Health Questionnaire-12; PROMIS Global-10, Patient-Reported Outcomes Measurement Information System Global-10.

associations with the odds of fatigue (Table S61). Predicted probability plots illustrated increasing fatigue probability at higher BMI, PHQ-4 scores and PHQ-12 scores and lower PROMIS Global Mental Health scores (Figure 4). Nomograms summarizing the multivariable models are shown in, Figures S2 and S3.

3.6 | Fatigue in Relation to IBS Symptom Severity

Among 2195 participants meeting Rome IV criteria for IBS, 2183 had complete IBS-SSS data and were included in the analysis. Fatigue prevalence increased with IBS symptom severity. Using the PROMIS fatigue definition, fatigue was reported by 35.8% (95% CI: 27.41–45.12; $n = 109$) of participants with none/minimal symptoms, 29.7% (95% CI: 25.67–34.14; $n = 444$) with mild symptoms, 35.0% (95% CI: 31.99–38.18; $n = 908$) with moderate symptoms, and 50.4% (95% CI: 46.78–54.05; $n = 722$) with severe symptoms. Using the PHQ-12 fatigue definition, corresponding prevalences were 43.1% (95% CI: 34.21–52.49), 41.9% (95% CI: 37.39–46.53), 52.3% (95% CI: 49.06–55.54) and 62.6% (95% CI: 59.02–66.06), respectively (Table S63).

TABLE 4 | Multivariable Logistic Regression Model for Fatigue Defined by the PROMIS Global-10.

	aOR	95% CI	Global LRT *p* of association
Country			**< 0.001**
Argentina	0.96	0.68–1.35	
Australia	0.74	0.52–1.06	
Belgium	2.48	1.77–3.49	
Brazil	0.88	0.63–1.24	
Canada	0.87	0.60–1.27	
China	0.77	0.54–1.11	
Colombia	0.67	0.46–0.97	
Egypt	0.50	0.35–0.70	
France	2.31	1.68–3.20	
Germany	2.78	1.99–3.89	
Netherlands	2.64	1.86–3.75	
Israel	1.55	1.08–2.21	
Italy	0.58	0.41–0.83	
Japan	0.73	0.51–1.04	
Korea	3.45	2.48–4.82	
Mexico	0.80	0.56–1.14	
Poland	2.42	1.76–3.36	
Romania	0.97	0.69–1.38	
Russia	1.52	1.10–2.11	
Singapore	1.02	0.70–1.48	
South Africa	0.98	0.70–1.38	
Spain	0.77	0.55–1.10	
Sweden	1.93	1.38–2.72	
Turkey	1.51	1.09–2.11	
USA	0.82	0.57–1.17	
Age (30 vs. 54 years)	0.78	0.72–0.84	**< 0.001**
Sex			
Female	1.24	1.14–1.36	**< 0.001**
BMI (21.67 vs 28.65 kg/m^2)	1.20	1.12–1.29	**< 0.001**
Healthcare access			
Limited access	1.08	0.95–1.22	0.486
No access	1.06	0.60–1.84	
DGBI group			
≥ 2 DGBI	1.19	1.08–1.30	**0.001**
PHQ-4 score (1 vs. 6)	2.59	2.27–2.96	**< 0.001**
PHQ-12 score (3 vs. 7)	1.70	1.55–1.87	**< 0.001**
PROMIS Global Mental Health score (10 vs. 15)	0.51	0.47–0.56	**< 0.001**
Trouble Sleeping	1.56	1.42–1.72	**< 0.001**
Pain medication	1.15	1.04–1.28	**0.004**
Anxiety medication	0.86	0.75–0.99	**0.03**
Antidepressant medication	1.25	1.09–1.45	**0.002**
Sleeping medication	0.96	0.85–1.09	0.509
Satiety	1.13	1.02–1.25	**0.014**
Nausea	1.24	1.07–1.45	**0.006**
Epigastric Pain	0.96	0.83–1.12	0.548
Vomiting	0.99	0.80–1.23	0.878
Regurgitation	1.05	0.90–1.22	0.514
Belching	0.88	0.76–1.02	0.075
Abdominal Pain	1.19	1.07–1.33	**0.002**
Constipation	1.06	0.97–1.15	0.182
Diarrhoea	1.08	0.99–1.17	0.073
Bloating	1.27	1.17–1.39	**< 0.001**

Note: This table presents the multivariable model examining factors associated with the presence of fatigue in DGBI. Country was included as a fixed effect. Odds ratios (ORs) with 95% confidence intervals are shown. For continuous variables, ORs correspond to an increase from the 25th to the 75th percentile (interquartile range). *p*-values are derived from likelihood ratio tests (LRT) comparing the full model with a reduced model excluding the corresponding variable. The "Global LRT *p*-value of association" represents the overall association between the variable and the outcome and is also illustrated in the predicted probability curves. For variables modelled using restricted cubic splines, this overall test includes both linear and non-linear effects and may therefore differ from the odds ratio and confidence interval shown for a specific contrast. Bold values indicate statistical significance at $p < 0.05$. Model fit: AIC = 14850.23. BIC = 15362.65. AUROC = 0.84 (95% CI: 0.84–0.85). References: country (UK), sex (male), healthcare access (full healthcare access), DGBI group (having one DGBI), trouble sleeping (having no trouble sleeping), pain medication (not taking prescribed pain medication), anxiety medication (not taking prescribed anxiety medication), depression medication (not taking depression medication), sleeping medication (not taking sleeping medication), satiety (not having satiety), nausea (not having satiety), epigastric pain (not having epigastric pain), vomiting (not having to vomit), regurgitation (not having regurgitation), belching (not having belching), abdominal pain (not having abdominal pain), constipation (not having constipation), diarrhoea (not having diarrhoea), bloating (not having bloating). Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted Odds Ratio; BMI, body mass index; DGBI, disorder of gut–brain interaction; PHQ, patient health questionnaire.

3.7 | Fatigue Prevalence Across Painful and Non-Painful DGBI Categories

Based on the PROMIS Global-10, fatigue prevalence was 18.6% (95% CI: 17.92–19.32) among participants with non-painful DGBI, 23.5% (95% CI: 21.68–25.36) in painful DGBI, and 33.3% (95% CI: 31.90–34.70) in overlapping painful and non-painful DGBI. Corresponding prevalences using the PHQ-12 were 28.5% (95% CI: 27.64%–29.27%), 35.8% (95% CI: 33.73–37.89) and 44.7% (95% CI: 43.25–46.20), respectively (Table S64).

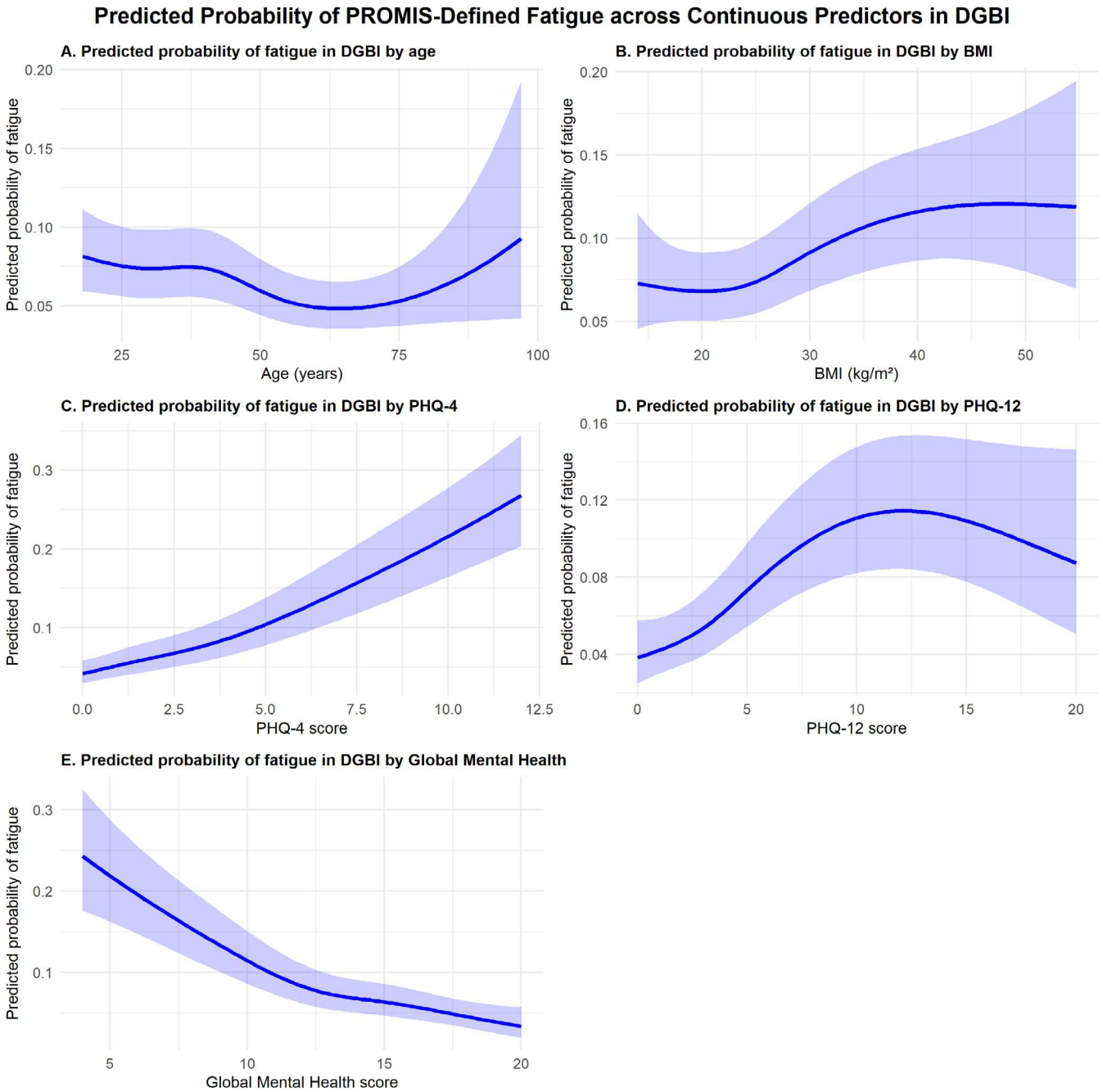

FIGURE 3 | Predicted Probability of PROMIS-Defined Fatigue across Continuous Predictors in DGBI. Plots show the estimated probability of fatigue for age, BMI, PHQ-4 score, PHQ-12 score and PROMIS Global Mental Health score, derived from the multivariable model. Shaded areas represent 95% confidence intervals. References: Country (UK), sex (female), healthcare access (full healthcare access), DGBI group (having one DGBI), trouble sleeping (having no trouble sleeping), pain medication (not taking prescribed pain medication), anxiety medication (not taking prescribed anxiety medication), depression medication (not taking depression medication), sleeping medication (not taking sleeping medication), satiety (not having satiety), nausea (not having satiety), epigastric pain (not having epigastric pain), vomiting (not having to vomit), regurgitation (not having regurgitation), belching (not having belching), abdominal pain (not having abdominal pain), constipation (not having constipation), diarrhoea (not having diarrhoea), bloating (not having bloating).

4 | Discussion

In this multinational population-based study, fatigue prevalence increased with DGBI burden (i.e., none, one or multiple DGBI), a pattern that was consistent across all 26 countries. Among the more prevalent Rome IV DGBI diagnoses, oesophageal disorders, particularly reflux hypersensitivity, and IBS showed a high prevalence of fatigue. Within IBS, fatigue prevalence increased progressively with greater symptom severity. Fatigue prevalence also differed by DGBI pain classification, increasing progressively from non-painful to painful DGBI and being highest among participants with overlapping painful and non-painful DGBI. Factors consistently associated with fatigue across both definitions included age, female sex, BMI, sleep disturbance,

TABLE 5 | Multivariable Logistic Regression Model for Fatigue Defined by the PHQ-12.

	aOR	95% CI	Global LRT *p* of association
Country			**< 0.001**
Argentina	0.63	0.47–0.85	
Australia	1.01	0.75–1.36	
Belgium	0.99	0.73–1.33	
Brazil	0.57	0.42–0.76	
Canada	0.94	0.68–1.29	
China	0.63	0.47–0.84	
Colombia	0.73	0.54–0.97	
Egypt	0.47	0.35–0.63	
France	0.72	0.54–0.96	
Germany	0.87	0.64–1.17	
Netherlands	1.10	0.81–1.49	
Israel	1.31	0.97–1.76	
Italy	0.45	0.33–0.60	
Japan	0.64	0.47–0.87	
Korea	0.83	0.62–1.13	
Mexico	0.62	0.46–0.84	
Poland	0.85	0.64–1.12	
Romania	0.87	0.65–1.17	
Russia	0.75	0.57–1.00	
Singapore	0.66	0.49–0.91	
South Africa	1.00	0.75–1.33	
Spain	0.56	0.42–0.75	
Sweden	1.24	0.93–1.67	
Turkey	0.88	0.66–1.18	
USA	0.89	0.66–1.20	
Age (30 vs. 54 years)	0.67	0.63–0.71	**< 0.001**
Sex			
Female	1.43	1.32–1.54	**< 0.001**
BMI (21.67 vs. 28.65 kg/m^2)	1.01	0.95–1.07	**< 0.001**
Healthcare access			0.328
Limited access	0.98	0.87–1.11	
No access	0.65	0.38–1.12	
DGBI group			
≥ 2 DGBI	1.06	0.98–1.15	0.135
PHQ-4 score (1 vs. 6)	1.80	1.62–2.01	**< 0.001**
PHQ-12 score (3 vs. 7)	3.01	2.76–3.27	**< 0.001**
PROMIS Global Mental Health score (10 vs. 15)	0.81	0.75–0.88	**< 0.001**
Trouble Sleeping	2.64	2.42–2.88	**< 0.001**
Pain medication	1.06	0.97–1.16	0.182
Anxiety medication	1.05	0.93–1.20	0.396
Antidepressant medication	1.21	1.05–1.38	**0.006**
Sleeping medication	0.78	0.69–0.87	**< 0.001**
Satiety	1.24	1.13–1.35	**< 0.001**
Nausea	1.01	0.88–1.17	0.821
Epigastric Pain	0.97	0.84–1.11	0.596
Vomiting	1.00	0.81–1.22	0.889
Regurgitation	1.03	0.89–1.19	0.695
Belching	0.96	0.84–1.10	0.581
Abdominal Pain	1.26	1.14– 1.40	**< 0.001**
Constipation	0.99	0.92–1.07	0.792
Diarrhoea	1.00	0.92–1.07	0.897
Bloating	1.13	1.04–1.22	**0.003**

Note: This table presents the multivariable model examining factors associated with the presence of fatigue in DGBI. Country was included as a fixed effect. Odds ratios (ORs) with 95% confidence intervals are shown. For continuous variables, ORs correspond to an increase from the 25th to the 75th percentile (interquartile range). *p*-values are derived from likelihood ratio tests (LRT) comparing the full model with a reduced model excluding the corresponding variable. The "Global LRT *p*-value of association" represents the overall association between the variable and the outcome and is also illustrated in the predicted probability curves. For variables modelled using restricted cubic splines, this overall test includes both linear and non-linear effects and may therefore differ from the odds ratio and confidence interval shown for a specific contrast. Bold values indicate statistical significance at $p < 0.05$. Model fit: AIC = 18209.88. BIC = 18698.65. AUROC = 0.83 (95% CI: 0.82–0.83). References: country (UK), sex (male), healthcare access (full healthcare access), DGBI group (having one DGBI), trouble sleeping (having no trouble sleeping), pain medication (not taking prescribed pain medication), anxiety medication (not taking prescribed anxiety medication), depression medication (not taking depression medication), sleeping medication (not taking sleeping medication), satiety (not having satiety), nausea (not having satiety), epigastric pain (not having epigastric pain), vomiting (not having to vomit), regurgitation (not having regurgitation), belching (not having belching), abdominal pain (not having abdominal pain), constipation (not having constipation), diarrhoea (not having diarrhoea), bloating (not having bloating).
Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted Odds Ratio; BMI, body mass index; DGBI, disorder of gut–brain interaction; PHQ, patient health questionnaire.

higher anxiety and depression scores (PHQ-4), higher PHQ-12 somatic symptom scale scores, lower psychological well-being (PROMIS Global Mental Health), antidepressant use, and the presence of satiety, abdominal pain, and bloating.

Fatigue prevalence increased progressively with DGBI overlap, supporting our hypothesis that greater diagnostic overlap reflects a higher disease burden. Previous research has

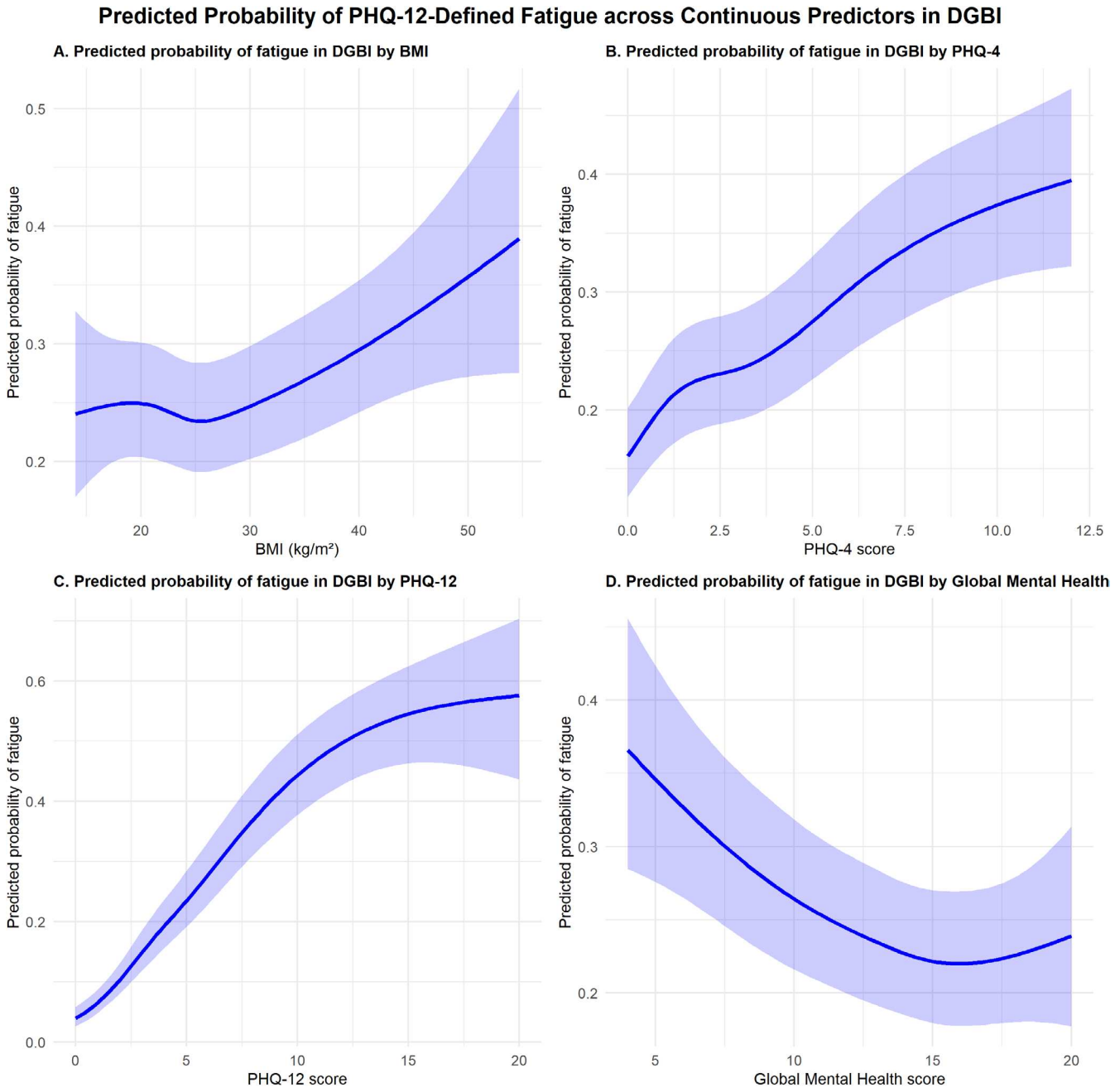

FIGURE 4 | Predicted Probability of PHQ-12-Defined Fatigue across Continuous Predictors in DGBI. Plots show the estimated probability of fatigue for BMI, PHQ-4 score, PHQ-12 score and PROMIS Global Mental Health score, derived from the multivariable model. Shaded areas represent 95% confidence intervals. References: Country (UK), sex (female), healthcare access (full healthcare access), DGBI group (having one DGBI), trouble sleeping (having no trouble sleeping), pain medication (not taking prescribed pain medication), anxiety medication (not taking prescribed anxiety medication), depression medication (not taking depression medication), sleeping medication (not taking sleeping medication), satiety (not having satiety), nausea (not having satiety), epigastric pain (not having epigastric pain), vomiting (not having to vomit), regurgitation (not having regurgitation), belching (not having belching), abdominal pain (not having abdominal pain), constipation (not having constipation), diarrhoea (not having diarrhoea), bloating (not having bloating).

demonstrated that overlap across GI anatomical regions is common in DGBI and may reflect shared clinical features and underlying pathophysiological mechanisms [3, 11]. Of note is that our primary research question was whether fatigue prevalence increases with DGBI diagnostic load, rather than with GI anatomical spread per se. For this reason, we defined overlap at the level of individual DGBI diagnoses. The number of coexisting DGBI diagnoses directly reflects cumulative symptom-burden complexity, which is more likely to relate to fatigue than the number of anatomical regions involved. Consistent with this, the presence of multiple DGBI has been associated with greater symptom severity, increased psychosocial comorbidities, higher healthcare utilization, and reduced quality of life [2, 11, 22]. This burden poses clinical challenges, as current Rome-based

diagnostic and therapeutic frameworks largely focus on single disease entities, underscoring the importance of comprehensive history taking that accounts for symptom timing, overlap, and coherence [23].

The co-existence of non-GI symptoms such as fatigue warrants explicit consideration in DGBI care [2]. Our findings confirm that fatigue is a globally relevant and distressing symptom in this population, with particularly high prevalence in reflux hypersensitivity and IBS. Reflux hypersensitivity is, unlike most symptom-defined DGBI, characterized by a positive symptom association on objective reflux testing despite normal oesophageal acid exposure [24]. Amplification of oesophageal sensory signalling may promote central sensitization, potentially influenced by heightened autonomic arousal, psychological comorbidity and poor sleep, thereby potentially contributing to fatigue [25, 26]. Physiological nocturnal reflux events or reflux-related sleep disruption may further contribute to daytime fatigue [25]. Within IBS, fatigue prevalence increased with symptom severity, suggesting an association between fatigue and GI symptom burden. Fatigue was also more prevalent in patients with painful DGBI than in those with non-painful DGBI, and highest among individuals with overlapping painful and non-painful DGBI, further supporting a specific association between chronic pain and fatigue [27]. Notably, however, substantial fatigue prevalence was also observed among individuals in IBS remission, indicating that fatigue cannot be fully explained by current GI symptoms. Meta-analytic data similarly identified fatigue as a major somatic complaint in IBS, with a pooled prevalence of 54.2%, and demonstrated associations with greater symptom severity and psychological distress [6, 8]. Despite this burden, fatigue is often overlooked due to its subjective and non-specific nature and its frequent attribution to comorbid organic (e.g., IBD) or mental disorders (e.g., depression) [8]. Shared complex mechanisms, including alterations in the hypothalamic–pituitary–adrenal axis, serotonin neurotransmission, and immune activation with low-grade inflammation, are implicated in overlapping symptom expression and may obscure the clinical relevance of fatigue [7, 10, 11]. This reinforces the need for greater awareness, systematic screening and integration of fatigue into DGBI care pathways [5].

Importantly, the way fatigue is measured influences the observed burden. In our study, prevalence patterns were consistent across PROMIS and PHQ-12 definitions, but absolute prevalence estimates differed, with only moderate agreement between measures (Cohen's $\kappa = 0.43$). While both instruments capture subjective fatigue burden, they differ in measurement intent and severity thresholds. The PROMIS fatigue item, anchored in quality-of-life assessment, captures only severe or very severe fatigue and reflects the degree to which fatigue impairs the participant [28]. In contrast, the PHQ-12 item screens for somatic symptom burden, defining fatigue as being 'bothered a lot' by feeling tired or having low energy [29]. This broader response category may include individuals with moderate fatigue as captured by the PROMIS, explaining the differing prevalence estimates despite similar associations with DGBI burden.

Recognizing these measurement nuances highlights that fatigue is a complex, multidimensional symptom encompassing physical, cognitive, emotional, motivational and mental components, which are not fully captured by single-item measures [30]. Ideally, a validated multidimensional fatigue assessment would be used to capture the full spectrum of fatigue. However, since the survey had already been constructed, such instruments could not be added. Additionally, the individual items from the PROMIS Global-10 and the PHQ-12 have not been formally validated as standalone measures of fatigue. Nevertheless, single-item measures are commonly used in large population-based studies, and our sensitivity analysis using both fatigue items confirmed the robustness of our findings [31].

Building on these robust measures, we examined participant characteristics associated with fatigue in DGBI. Although causality cannot be inferred, several factors emerged. Fatigue was more common in females, consistent with prior findings demonstrating sex differences in DGBI, with a higher overall burden and greater comorbidity reported in women [1, 2, 32–34]. Sleep disturbances were also associated with increased fatigue. Poor sleep quality, reflected in patients feeling unrefreshed after sleep, has been strongly linked to greater fatigue severity and reduced daily functioning in IBS [35]. Notably, Borren et al. reported that disturbed sleep in non-fatigued IBD patients, both with active disease and in remission, was the strongest predictor of fatigue 6 months later [12, 36]. In this context, circadian rhythm disruption may represent a biologically plausible contributing factor, given its established influence on gastrointestinal barrier function, motility and immune regulation, and may offer a useful direction for further research and targeted symptom management [37]. A higher symptomatic symptom burden, as captured by the PHQ-12, was strongly associated with fatigue, suggesting that fatigue is not solely related to GI symptom severity but is also linked to broader somatic symptom distress [38]. Although directionality cannot be determined, this finding aligns with chronic pain literature, where pain and fatigue frequently co-occur and may share underlying mechanisms [27]. Higher anxiety and depression scores and lower psychological well-being (as measured by the PROMIS Global Mental Health score) were similarly associated with fatigue, consistent with prior studies highlighting psychosocial comorbidities as key determinants of symptom severity and overlap in DGBI [2, 8, 11, 23, 39–41]. In IBS specifically, fatigue has likewise been linked to greater anxiety, depression, and reduced quality of life compared to non-fatigued patients [6, 8, 12]. Antidepressant use was also associated, potentially reflecting side effects or residual fatigue following partial recovery from depression [42]. Among GI symptoms, bloating and abdominal pain were particularly associated with fatigue, consistent with prior IBS findings, with similar patterns observed for satiety [6, 8].

The predicted probability plots and nomograms were developed solely for illustrative purposes and hypothesis generation, facilitating interpretation of a complex multivariable model with many predictors, some exhibiting non-linear effects [43]. Nevertheless, these findings can inform targeted fatigue management strategies in DGBI, suggesting that addressing fatigue as a potentially modifiable factor may help alleviate overall symptom burden and improve patient functioning. Effective management begins with patient and clinician awareness and systematic screening. Fatigue diaries, for example, can provide valuable insight into symptom patterns and triggers [8, 44]. Once identified, general strategies may be

integrated, including structured daily planning, activity prioritization, energy distribution and scheduled rest periods [44]. Discouraging maladaptive coping, such as excessive daytime napping, all-or-nothing behaviour, and catastrophizing, may further support patient well-being [45]. Psychological interventions, including cognitive behavioural therapy, should be considered early, particularly in patients linking psychological factors to their symptoms [39, 44]. Given the frequent overlap between DGBI and non-GI symptoms, these approaches are best delivered within a comprehensive, multidisciplinary care model [2].

Despite providing valuable insights into the burden of fatigue in DGBI, several methodological limitations warrant consideration. First, diagnostic misclassification may have occurred. A small proportion of participants with > 2 DGBI (8.6%) met criteria for multiple DGBI diagnoses that may not fully co-exist under strict Rome IV diagnostic definitions (e.g., chronic nausea and vomiting syndrome and cyclic vomiting syndrome) (Table S6). Because the survey design did not allow assessment of temporal relationships or causal attribution, such co-occurrence may have modestly overestimated the number of participants with multiple DGBI and associated fatigue. Additionally, outcomes were based on self-reported symptoms rather than clinically confirmed diagnoses, so organic diseases presenting with similar GI symptoms could not be fully excluded. To partially address this, participants reporting major organic conditions (e.g., inflammatory bowel disease, celiac disease, GI cancer and abdominal or pelvic surgery) were excluded from relevant DGBI diagnoses. These diagnostic issues affected only a small proportion of participants and are unlikely to have materially affected the overall results. Second, online participant recruitment may introduce selection bias, which was partly mitigated using prespecified demographic criteria intended to improve representativeness. Third, despite careful translation, linguistic validation, and cultural adaptation, the questionnaire may not have been fully comprehensible to all participants. Finally, missing data were limited, with 10.6% missing for BMI. As BMI was included only in secondary analyses, the primary aim was unaffected. To make the missing at random (MAR) assumption more plausible, predictors of missingness were included in the logistic regression models for fatigue (Table S2).

In conclusion, this study underscores the substantial burden associated with overlapping DGBI and identifies fatigue as a clinically relevant non-GI symptom that warrants greater recognition and tailored management. Several factors associated with fatigue were identified, providing potential targets to inform such interventions. Recognizing fatigue as a multidimensional construct, future research should account for this complexity to fully capture its impact and support personalized care.

Author Contributions

Francesco Innocenti: conceptualization, writing – review and editing, formal analysis, methodology, data curation. **Ami D. Sperber:** conceptualization, writing – review and editing, methodology, data curation, investigation, project administration. **Shrikant I. Bangdiwala:** investigation, methodology, writing – review and editing, conceptualization, project administration, data curation. **Asma Fikree:** conceptualization, writing – review and editing, methodology. **Olafur Palsson:** conceptualization, writing – review and editing, methodology, data curation, investigation, project administration. **Imran Aziz:** conceptualization, writing – review and editing, methodology. **Fleur Veldman:** conceptualization, writing – original draft, formal analysis, visualization, methodology, data curation. **Daniel Keszthelyi:** conceptualization, writing – review and editing, supervision, methodology, funding acquisition.

Acknowledgements

This study was conducted under the auspices of the Rome Foundation Research Institute. We extend our gratitude to all participants for their commitment and invaluable involvement in this international research effort. Artificial Intelligence-based tools (ChatGPT) were used to assist with language editing and to support R programming tasks, including code formatting and error troubleshooting. All statistical analyses and code were reviewed and verified by a qualified statistician. The authors take full responsibility for the content of the manuscript.

Funding

This work was supported by the Horizon Europe Grant ERC-2022-STG RESILIENCE (Grant Agreement No. 101075884), funded by the European Research Council (ERC).

Ethics Statement

Institutional Review Boards (IRBs) and ethics committees in each participating country reviewed the study and deemed it exempt from ethics oversight due to anonymous data collection.

Consent

Electronic informed consent was obtained from all participants.

Conflicts of Interest

F.V.: None to declare. F.I.: None to declare. I.A.: Received research funding and speaker fees from the Rome Foundation and Precisionbiotics (paid to host institute). A.F: None to declare. S.I.B.: None to declare. O.P: None to declare. A.D.S.: None to declare. D.K.: has received research funding from Rome Foundation, United European Gastroenterology, Horizon 2020, Horizon Europe, ZonMw, Dutch Foundation for Gastroenterology and has received speaker's fee from Rome Foundation (paid to host institute).

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this manuscript.

References

1. A. D. Sperber, S. I. Bangdiwala, D. A. Drossman, et al., "Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study," *Gastroenterology* 160, no. 1 (2021): 99–114.e3.

2. G. Barbara, I. Aziz, S. Ballou, et al., "Rome Foundation Working Team Report on Overlap in Disorders of Gut-Brain Interaction," *Nature Reviews. Gastroenterology & Hepatology* 22, no. 4 (2025): 228–251.

3. I. Aziz, O. S. Palsson, H. Törnblom, A. D. Sperber, W. E. Whitehead, and M. Simrén, "The Prevalence and Impact of Overlapping Rome IV-Diagnosed Functional Gastrointestinal Disorders on Somatization, Quality of Life, and Healthcare Utilization: A Cross-Sectional General Population Study in Three Countries," *American Journal of Gastroenterology* 113, no. 1 (2018): 86–96.

4. Å. Frändemark, E. Jakobsson Ung, H. Törnblom, M. Simrén, and S. Jakobsson, "Fatigue: A Distressing Symptom for Patients With Irritable

Bowel Syndrome," *Neurogastroenterology and Motility* 29, no. 1 (2017): 12898, https://doi.org/10.1111/nmo.12898.

5. M. Truyens, H. Lernout, M. De Vos, D. Laukens, and T. Lobaton, "Unraveling the Fatigue Puzzle: Insights Into the Pathogenesis and Management of IBD-Related Fatigue Including the Role of the Gut-Brain Axis," *Frontiers in Medicine* 11 (2024): 1424926.

6. C. J. Han and G. S. Yang, "Fatigue in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Pooled Frequency and Severity of Fatigue," *Asian Nursing Research (Korean Society of Nursing Science)* 10, no. 1 (2016): 1–10.

7. T. Piche, P. M. Huet, E. Gelsi, et al., "Fatigue in Irritable Bowel Syndrome: Characterization and Putative Role of Leptin," *European Journal of Gastroenterology & Hepatology* 19, no. 3 (2007): 237–243.

8. J. M. Lackner, G. D. Gudleski, J. Dimuro, L. Keefer, and D. M. Brenner, "Psychosocial Predictors of Self-Reported Fatigue in Patients With Moderate to Severe Irritable Bowel Syndrome," *Behaviour Research and Therapy* 51, no. 6 (2013): 323–331.

9. Å. Frändemark, H. Törnblom, J. P. Hreinsson, et al., "Work Productivity and Activity Impairment in Disorders of Gut-Brain Interaction: Data From the Rome Foundation Global Epidemiology Study," *United European Gastroenterology Journal* 11, no. 6 (2023): 503–513.

10. T. Piche, M. C. Saint-Paul, R. Dainese, et al., "Mast Cells and Cellularity of the Colonic Mucosa Correlated With Fatigue and Depression in Irritable Bowel Syndrome," *Gut* 57, no. 4 (2008): 468–473.

11. A. D. Sperber, T. Freud, I. Aziz, et al., "Greater Overlap of Rome IV Disorders of Gut-Brain Interactions Leads to Increased Disease Severity and Poorer Quality of Life," *Clinical Gastroenterology and Hepatology* 20, no. 5 (2022): e945–e956.

12. M. Simrén, J. Svedlund, I. Posserud, E. S. Bjornsson, and H. Abrahamsson, "Predictors of Subjective Fatigue in Chronic Gastrointestinal Disease," *Alimentary Pharmacology & Therapeutics* 28, no. 5 (2008): 638–647.

13. A. D. Sperber, "The Rome Foundation Global Epidemiology Study: Conception, Implementation, Results, and Future Potential," *Neurogastroenterology and Motility* 35, no. 6 (2023): e14567.

14. C. Y. Francis, J. Morris, and P. J. Whorwell, "The Irritable Bowel Severity Scoring System: A Simple Method of Monitoring Irritable Bowel Syndrome and Its Progress," *Alimentary Pharmacology & Therapeutics* 11, no. 2 (1997): 395–402.

15. PROMIS Global-10. https://www.codetechnology.com/blog/promis-global-10/.

16. K. Kroenke, R. L. Spitzer, and J. B. Williams, "The PHQ-15: Validity of a New Measure for Evaluating the Severity of Somatic Symptoms," *Psychosomatic Medicine* 64, no. 2 (2002): 258–266.

17. R Core Team, "R: A Language and Environment for Statistical Computing Vienna, Austria," (2025), https://www.R-project.org/.

18. L. Brown, T. Cai, and A. DasGupta, "Interval Estimation for a Binomial Proportion," *Statistical Science* 16, no. 2 (2001): 101–117.

19. D. McNeish and K. Kelley, "Fixed Effects Models Versus Mixed Effects Models for Clustered Data: Reviewing the Approaches, Disentangling the Differences, and Making Recommendations," *Psychological Methods* 24, no. 1 (2019): 20–35.

20. F. E. Harrell, Jr., *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*, 2nd ed. (Springer, 2015).

21. R. Marx, A. B. Lopes, R. Picon, et al., "Painful Disorders of Gut-Brain Interaction Are More Associated With Worse Health-Related Quality of Life and Psychological Disorders Than Non-Painful Disorders in Latin American Countries," *Neurogastroenterology and Motility* 37, no. 12 (2025): e70194.

22. T. Fairlie, A. Shah, N. J. Talley, et al., "Overlap of Disorders of Gut-Brain Interaction: A Systematic Review and Meta-Analysis," *Lancet Gastroenterology & Hepatology* 8, no. 7 (2023): 646–659.

23. L. M. Balsiger, F. Carbone, K. Raymenants, E. Scarpellini, and J. Tack, "Understanding and Managing Patients With Overlapping Disorders of Gut-Brain Interaction," *Lancet Gastroenterology & Hepatology* 8, no. 4 (2023): 383–390.

24. M. J. Schmulson and D. A. Drossman, "What Is New in Rome IV," *Journal of Neurogastroenterology and Motility* 23, no. 2 (2017): 151–163.

25. A. Sawada, D. Sifrim, and Y. Fujiwara, "Esophageal Reflux Hypersensitivity: A Comprehensive Review," *Gut and Liver* 17, no. 6 (2023): 831–842.

26. T. Yamasaki and R. Fass, "Reflux Hypersensitivity: A New Functional Esophageal Disorder," *Journal of Neurogastroenterology and Motility* 23, no. 4 (2017): 495–503.

27. D. A. Fishbain, B. Cole, R. B. Cutler, J. Lewis, H. L. Rosomoff, and R. S. Fosomoff, "Is Pain Fatiguing? A Structured Evidence-Based Review," *Pain Medicine* 4, no. 1 (2003): 51–62.

28. D. Cella, J. S. Lai, S. E. Jensen, et al., "PROMIS Fatigue Item Bank Had Clinical Validity Across Diverse Chronic Conditions," *Journal of Clinical Epidemiology* 73 (2016): 128–134.

29. J. Hybelius, A. Kosic, S. Salomonsson, et al., "Measurement Properties of the Patient Health Questionnaire-15 and Somatic Symptom Scale-8: A Systematic Review and Meta-Analysis," *JAMA Network Open* 7, no. 11 (2024): e2446603.

30. R. Billones, J. K. Liwang, K. Butler, L. Graves, and L. N. Saligan, "Dissecting the Fatigue Experience: A Scoping Review of Fatigue Definitions, Dimensions, and Measures in Non-Oncologic Medical Conditions," *Brain Behavior & Immunity-Health* 15 (2021): 100266.

31. J. Song, E. Howe, J. R. Oltmanns, and A. J. Fisher, "Examining the Concurrent and Predictive Validity of Single Items in Ecological Momentary Assessments," *Assessment* 30, no. 5 (2023): 1662–1671.

32. J. Liu, K. Cheng, Y. Lu, H. Cabral, and H. C. Weber, "Effects of Sex and Race on Epidemiology and Comorbidities of Patients With Irritable Bowel Syndrome: A Rome III Era Retrospective Study," *Diseases (Basel, Switzerland)* 13, no. 5 (2025): 161.

33. R. P. Sarnoff, J. P. Hreinsson, J. Kim, et al., "Sex Differences, Menses-Related Symptoms and Menopause in Disorders of Gut-Brain Interaction," *Neurogastroenterology and Motility* 37, no. 2 (2025): e14977.

34. A. Mulak, T. Freud, M. Waluga, S. I. Bangdiwala, O. S. Palsson, and A. D. Sperber, "Sex- and Gender-Related Differences in the Prevalence and Burden of Disorders of Gut-Brain Interaction in Poland," *Neurogastroenterology and Motility* 35, no. 6 (2023): e14568.

35. S. Ballou, E. Alhassan, E. Hon, et al., "Sleep Disturbances Are Commonly Reported Among Patients Presenting to a Gastroenterology Clinic," *Digestive Diseases and Sciences* 63, no. 11 (2018): 2983–2991.

36. N. Z. Borren, M. D. Long, R. S. Sandler, and A. N. Ananthakrishnan, "Longitudinal Trajectory of Fatigue in Patients With Inflammatory Bowel Disease: A Prospective Study," *Inflammatory Bowel Diseases* 27, no. 11 (2021): 1740–1746.

37. S. Fowler, E. C. Hoedt, N. J. Talley, S. Keely, and G. L. Burns, "Circadian Rhythms and Melatonin Metabolism in Patients With Disorders of Gut-Brain Interactions," *Frontiers in Neuroscience* 16 (2022): 825246.

38. M. G. Shiha, Z. Asghar, M. Thoufeeq, et al., "Increased Psychological Distress and Somatization in Patients With Irritable Bowel Syndrome Compared With Functional Diarrhea or Functional Constipation, Based on Rome IV Criteria," *Neurogastroenterology and Motility* 33, no. 10 (2021): e14121.

39. M. G. Shiha and I. Aziz, "Review Article: Physical and Psychological Comorbidities Associated With Irritable Bowel Syndrome," *Alimentary Pharmacology & Therapeutics* 54, no. 1 (2021): S12–S23.

40. N. T. Tornkvist, M. Simrén, J. P. Hreinsson, et al., "Prevalence and Impact of Disorders of Gut-Brain Interaction in Sweden," *Neurogastroenterology and Motility* 35, no. 6 (2023): e14578.

41. I. Midenfjord, A. Polster, H. Sjövall, H. Törnblom, and M. Simrén, "Anxiety and Depression in Irritable Bowel Syndrome: Exploring the Interaction With Other Symptoms and Pathophysiology Using Multivariate Analyses," *Neurogastroenterology and Motility* 31, no. 8 (2019): e13619.

42. J. Shen, N. Hossain, D. L. Streiner, et al., "Excessive Daytime Sleepiness and Fatigue in Depressed Patients and Therapeutic Response of a Sedating Antidepressant," *Journal of Affective Disorders* 134, no. 1–3 (2011): 421–426.

43. E. W. Steyerberg and Y. Vergouwe, "Towards Better Clinical Prediction Models: Seven Steps for Development and an ABCD for Validation," *European Heart Journal* 35, no. 29 (2014): 1925–1931.

44. J. E. Kreijne, M. R. Lie, L. Vogelaar, and C. J. van der Woude, "Practical Guideline for Fatigue Management in Inflammatory Bowel Disease," *Journal of Crohn's and Colitis* 10, no. 1 (2016): 105–111.

45. C. D. Moulton, C. Jordan, B. Hayee, and T. Chalder, "All-Or-Nothing Behavior and Catastrophic Thinking Predict Fatigue in Inflammatory Bowel Disease: A Prospective Cohort Study," *Inflammatory Bowel Diseases* 30, no. 10 (2024): 1903–1906.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Missingness for variables with missing data. **Table S2:** Logistic regression for missingness of BMI. **Table S3:** Classification groups. **Table S4:** Participants excluded from a DGBI diagnosis. **Table S5:** DGBI count. **Table S6:** Rome-IV diagnoses that are clinically unlikely to co-exist together within the > 2 DGBI group. **Table S7:** Country-Specific Prevalence of Fatigue Based on the PROMIS Global-10. **Table S8:** Country-Specific Prevalence of Fatigue Based on the PHQ-12. **Table S9:** Country-specific prevalence of fatigue (PROMIS Global-10) among DGBI classification groups. **Table S10:** Country-specific prevalence of fatigue (PHQ-12) among DGBI classification groups. **Table S11:** Agreement between PROMIS Global-10 and PHQ-12. **Table S12:** A crude model to show the unadjusted association between country and fatigue in individuals with a DGBI. **Table S13:** Age. **Table S14:** Sex. **Table S15:** Healthcare access. **Table S16:** DGBI group. **Table S17:** BMI. **Table S18:** PHQ4. **Table S19:** PHQ12. **Table S20:** PROMIS Global Mental Health score. **Table S21:** Trouble Sleeping. **Table S22:** Pain medication. **Table S23:** Anxiety medication. **Table S24:** Depression medication. **Table S25:** Sleeping medication. **Table S26:** Satiety. **Table S27:** Nausea. **Table S28:** Epigastric Pain. **Table S29:** Vomiting. **Table S30:** Regurgitation. **Table S31:** Belching. **Table S32:** Abdominal Pain. **Table S33:** Constipation. **Table S34:** Diarrhoea. **Table S35:** Bloating. **Table S36:** Linearity of continuous predictors evaluated prior to model fitting. **Table S37:** A crude model to show the unadjusted association between country and fatigue in individuals with a DGBI. **Table S38:** Age. **Table S39:** Sex. **Table S40:** Healthcare access. **Table S41:** DGBI group. **Table S42:** BMI. **Table S43:** PHQ4. **Table S44:** PHQ12. **Table S45:** PROMIS global mental health score. **Table S46:** Trouble Sleeping. **Table S47:** Pain medication. **Table S48:** Anxiety medication. **Table S49:** Depression medication. **Table S50:** Sleeping medication. **Table S51:** Satiety. **Table S52:** Nausea. **Table S53:** Epigastric pain. **Table S54:** Vomiting. **Table S55:** Regurgitation. **Table S56:** Belching. **Table S57:** Abdominal pain. **Table S58:** Constipation. **Table S59:** Diarrhoea. **Table S60:** Bloating. **Table S61:** Linearity of continuous predictors evaluated prior to model fitting. **Table S62:** AUC. **Figure S1:** ROC curves. Receiver operating characteristic (ROC) curves showing model discrimination of multivariable logistic regression models for fatigue defined by PROMIS Global-10 and PHQ-12. Curves are based on predicted probabilities from fully adjusted models. AUC indicates the area under the curve. **Figure S2:** Multivariable Nomogram for PROMIS-Defined Fatigue in DGBI. Nomogram derived from the final multivariable logistic regression model. Higher total points correspond to a higher predicted probability of fatigue. **Figure S3:** Multivariable Nomogram for PHQ-12-Defined Fatigue in DGBI. Nomogram derived from the final multivariable logistic regression model. Higher total points correspond to a higher predicted probability of fatigue. Reference for country: 1 = Argentina; 2 = Australia; 3 = Belgium; 4 = Brazil; 5 = Canada; 6 = China; 7 = Colombia; 8 = Egypt; 9 = France; 10 = Germany; 11 = Netherlands; 12 = Israel; 13 = Italy; 14 = Japan; 15 = Korea; 16 = Mexico; 17 = Poland; 18 = Romania; 19 = Russia; 20 = Singapore; 21 = South Africa; 22 = Spain; 23 = Sweden; 24 = Turkey; 25 = USA. **Table S63:** Fatigue in Relation to IBS Symptom Severity (IBS-SSS). **Table S64:** Fatigue prevalence across painful and non-painful DGBI categories.