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ORIGINAL ARTICLE

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A comparative study of disorders of gut–brain interaction in Western Europe and Asia based on the Rome foundation global epidemiology study

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Abstract

Objective: Many studies have been published on disorders of the gut–brain interaction (DGBI) in Asia and Western Europe, but no previous study has directly assessed the difference between the two regions. The aim was to compare the prevalence of DGBI in Asia and Western Europe.

Methods: We used data collected in a population-based Internet survey, the Rome Foundation Global Epidemiology Study, from countries in Western Europe (Belgium,

France, Germany, Netherlands, Italy, Spain, Sweden, and the United Kingdom) and Asia (China, Japan, South Korea, and Singapore). We assessed DGBI diagnoses (Rome IV Adult Diagnostic Questionnaire), anxiety/depression (Patient Health Questionnaire-4, PHQ-4), non-GI somatic symptoms (PHQ-12), and access to and personal costs of doctor visits.

Results: The study included 9487 subjects in Asia and 16,314 in Western Europe. Overall, 38.0% had at least one DGBI; younger age, female sex, and higher scores on PHQ4 and PHQ12 were all associated with DGBI. The prevalence of having at least one DGBI was higher in Western Europe than in Asia (39.1% vs 36.1%, OR 1.14 [95% CI 1.08–1.20]). This difference was also observed for DGBI by anatomical regions, most prominently esophageal DGBI (OR 1.67 [1.48–1.88]). After adjustment, the difference in DGBI prevalence diminished and psychological (PHQ-4) and non-GI somatic symptoms (PHQ-12) had the greatest effect on the odds ratio estimates.

Conclusion: The prevalence of DGBI is generally higher in Western Europe compared to Asia. A considerable portion of the observed difference in prevalence rates seems to be explained by more severe psychological and non-GI somatic symptoms in Western Europe.

KEYWORDS
cross-sectional studies, functional constipation, functional dyspepsia, functional gastrointestinal disorders, irritable bowel syndrome

1 | INTRODUCTION

Disorders of the gut–brain interaction (DGBI) are prevalent disorders that affect the global population. DGBI diagnoses are based on the Rome criteria, which define the frequency and duration of symptoms or symptom combinations that are required for diagnosis of each disorder, as well as the necessary exclusion of organic diseases that might explain the symptoms.[1] DGBI in the Rome criteria are divided into anatomical regions based on the presumed origin of the symptoms, that is, esophageal, gastroduodenal, gallbladder and sphincter of Oddi, bowel and anorectal, and an additional category with centrally mediated disorders of gastrointestinal pain.

There are a wide range of studies available on individual DGBI in Western Europe and Asia, especially on the more common DGBI such as irritable bowel syndrome (IBS) and functional constipation. These studies have been summarized in meta-analyses[2–6] where the prevalence of DGBI has been found to be higher in Europe, although with some exceptions.[3] However, these meta-analyses have been severely limited by study heterogeneity. Furthermore, studies on the less common DGBI are scarce, and there is a lack of studies that collect data on both subjects from Western Europe and Asia with the same methodology, limiting the possibility to perform direct comparisons. Similarly, data on the differences and similarities regarding characteristics of subjects with DGBI in the two geographical regions are lacking. In addition, studies using factor analyses have identified different symptom clusters in Asia compared with Western countries, potentially indicating differences in gastrointestinal symptom patterns in Europe and Asia.[7,8]

Key Points

- The prevalence and overlap of disorders of gut–brain interaction (DGBI) is greater in Western Europe compared to Asia. This applies to all categories of DGBI by anatomical region and most individual DGBI.
- The observed difference in DGBI prevalence is largely explained by greater psychological and non-GI somatic symptoms in Western Europe compared to Asia.

The prevalence of IBS has been found to be lower when defined by the Rome IV compared to the Rome III,[2,9] but it is unclear whether this is true in both Western Europe and Asia, and more specifically, if the change in IBS prevalence between Rome III and IV criteria is similar in the two geographical regions. In addition, infectious diarrhea has been associated with the onset of IBS and the frequency of post-infection IBS has been shown to be similar in studies performed in Asia and Europe.[10] However, the proportion of IBS with onset after infectious diarrhea has not been directly compared in the two geographical regions using uniform methodology.

Hence, the primary aims of the study were to compare the prevalence and overlap of DGBI in Western Europe and Asia, and to compare the characteristics of individuals with DGBI in the two geographical regions. Secondary aims were to compare the occurrence

of post-infection IBS and to evaluate whether the change in IBS prevalence when using Rome IV criteria relative to the Rome III criteria was different in Western Europe and Asia.

2 | METHODS

2.1 | Study setting and participants

Data from the Rome Foundation Global Epidemiology Study (RFGES) were used in the current study, the methodology of which has been described in detail elsewhere.[9] Briefly, it was a cross-sectional survey study that included 33 countries, and the sample of the current study included subjects from Belgium, France, Germany, Netherlands, Italy, Spain, Sweden, United Kingdom, defined as *Western Europe*, and China, Japan, Korea, and Singapore, defined as *Asia*. Data in all countries included in the current analyses were collected via the Internet, from participants recruited on a nationwide basis by a large market research company (Qualtrics, LLC). The online surveys had built-in quality-assurance measures that ensured high-quality response sets without missing data, including attention-check questions, a speed-check, and response inconsistency assessment. Demographic parameters were predefined and controlled with quotas, including equal sex proportion, and age group proportions of 40% for 18–39 years, 40% for 40–64 years, and 20% for ≥65 years.

Some of the data in this paper have already been reported in previous Global Study papers. This is inevitable since the original paper[9] included a broad range of descriptive statistics for all countries (33) and all disorders (22). Other papers, including the present one, which use the same database, are reporting in-depth analyses for countries, disorders, and methods, and these include a brief overview of some specific data previously reported.

The Internet survey in the RFGES was reviewed by the Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill before data collection started and was deemed exempt from IRB oversight due to the anonymity of the participants.

2.2 | Variables and definitions

DGBI were defined according to the Rome IV criteria.[1] "Any" DGBI was defined as the presence of at least one DGBI. DGBI were categorized by anatomical regions as defined by the Rome IV criteria, as displayed in Table 1. 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 (less than 0.1% of the population surveyed). When estimating the prevalence of esophageal and gastroduodenal DGBI, subjects who reported celiac disease, GI cancer, inflammatory bowel disease, or peptic ulcer were excluded from being classified as DGBI but were retained as non-DGBI cases. For bowel and anorectal DGBI, subjects who reported celiac disease, GI cancer, inflammatory bowel disease, diverticulitis, or bowel resection were excluded from DGBI and retained as non-DGBI cases. Otherwise, no subjects were excluded. In the comparison of IBS prevalence by Rome III and Rome IV criteria, South Korea, Italy, Spain, Sweden, and the UK, where Rome III questions were not included in the survey, were excluded.

The presence of psychological co-morbidity was evaluated with the Patient Health Questionnaire-4 (PHQ-4). The PHQ-4 is a four-item questionnaire used to screen for anxiety and depression. Based on the PHQ-4, anxiety was defined as a total score of >2 on the first two questions of the questionnaire, and depression as a total score of >2 on the last two questions.[11]

The PHQ-12[12] is a 12 item questionnaire developed from the PHQ-15[13] questionnaire, where subjects are asked about somatic symptoms and asked to rate them on a three point Likert scale. The PHQ-12 does not include questions on somatic GI symptoms and is thus designed to measure severity of non-GI somatic symptoms.

To evaluate healthcare utilization, subjects answered questions about number of doctor visits per year, type of doctor visited, their ability to visit a doctor, and how much of the cost of doing so was covered by the individual or their family.

2.3 | Statistical analysis

Categorical variables are summarized as proportion in percentages and their 95% confidence intervals (95% CI). Continuous variables are summarized as means and 95% CIs. We planned to test differences in the proportion of subjects with at least one DGBI, esophageal, gastroduodenal, bowel, or anorectal DGBI in Western Europe and Asia, whereas other comparisons are descriptive. The magnitude of differences (effect sizes) is described with odds ratios

TABLE 1 All DGBI included in the study and their classification to anatomical regions.

Esophageal disorders	Gastroduodenal	Bowel disorders	Anorectal
Functional heartburn	Functional dyspepsia	Irritable bowel syndrome	Fecal incontinence
Functional chest pain	Belching disorders	Functional Constipation	Levator ani syndrome
Reflux hypersensitivity	Chronic nausea and vomiting syndrome	Opioid-induced constipation	Proctalgia fugax
Globus	Cyclic Vomiting Syndrome	Functional Diarrhea	
Functional dysphagia	Rumination syndrome	Functional abdominal bloating/distention	
	Cannabinoid Hyperemesis Syndrome	Unspecified functional bowel disorder	

between two binomial categorical variables, and with standardized mean difference (SMD) for differences between a binomial categorical dependent variable and a continuous independent variable. For SMD, values of 0.2–0.5 are considered small, values of 0.5–0.8 are considered medium, and values >0.8 are considered large.[14] Differences in proportions of subjects with DGBI categories in Western Europe and Asia were tested with the chi-squared test. Logistic regression was used to evaluate the difference in prevalence rates between the two geographical regions in any DGBI, by anatomical region, individual DGBI and overlap of DGBI categories. Individual DGBI prevalence was compared with simple logistic regression with geographical region as the dependent variable and individual DGBI as the independent variable. In the case of any DGBI and DGBI by anatomical regions, the OR estimates for difference in prevalence were reported both without adjustment and after adjusting for demographic and psychosocial factors that were judged as important based on clinical knowledge, previous literature, and univariable analysis. These included age, sex, BMI, PHQ-4 score (as a continuous variable), PHQ-12 score, ability to visit a doctor, and personal cost of doctor visit. To evaluate which of these factors contributed the most to the difference in the unadjusted and adjusted OR for any DGBI, separate logistic regression models were fitted for each of the demographic and psychosocial variables, with these factors and geographical regions as independent variables and any DGBI as the dependent variable. The unadjusted OR estimate for geographical region was then subtracted from the OR from each fitted model, resulting in a net change in OR when including each factor individually.

3 | RESULTS

3.1 | Subjects

The study included 25,801 subjects, 16,314 from Western Europe, mean age 46.4 (95% CI 46.1, 46.6), female sex 49.9% (49.1, 50.6) and 9487 from Asia, mean age 43.2 (42.9, 43.5), female sex 49.9% (48.9, 51.0).

3.2 | Prevalence of DGBI and the impact of associated factors

In unadjusted comparison, the proportion of patients with any DGBI was higher in Western Europe when compared to Asia (OR 1.14; 95% CI 1.08–1.20), and the same was true when comparing DGBI prevalence by anatomical regions (esophageal, gastroduodenal, bowel, and anorectal), OR 1.08–1.45, $p < 0.05$ (Figure 1). When assessing factors to be adjusted for when comparing prevalence rates between regions, the following variables were all associated with DGBI; younger age, female sex, and higher scores on PHQ-4, PHQ-12, access to a doctor and personal costs of a doctor visit (Table 2). In an adjusted comparison, correcting for the abovementioned variables, the differences noted in the unadjusted analysis were diminished. For any DGBI, gastroduodenal, and bowel DGBI, the adjusted ORs were 1.02–1.11 and their 95% CIs included the possibility of no difference, $p > 0.05$ (Figure 1). The adjusted ORs when comparing proportions with esophageal and anorectal DGBI in Western Europe and Asia were higher, 1.20–1.45, and statistically significant, $p < 0.05$ (Figure 1). When analyzing separately which of the adjusted variables made the greatest difference in OR for any DGBI, psychological (PHQ-4) and non-GI somatic symptoms (PHQ-12) had the greatest effect, lowering the OR by 0.094–0.138, and personal costs of doctor visits increased the OR by 0.056, but other variables had negligible effect (change in OR ≤0.05, Table 3).

Subjects with DGBI in Western Europe were less likely to have DGBI in only one anatomical region when compared to Asia, OR 0.70 (95% CI 0.64, 0.77) (Figure 2). The overlap of DGBI by anatomical regions involved was greater in Western Europe compared to Asia, with a greater proportion of DGBI subjects having DGBI in two, three, or four anatomical regions, ORs 1.30–1.58 (Figure 2).

Individual DGBI diagnoses were generally more common in Western Europe, with the greatest differences in the prevalence of functional heartburn, reflux hypersensitivity, and functional bloating, ORs 2.09–3.73, Figure 3. In Asia, functional constipation, functional diarrhea, cyclic vomiting syndrome, and excessive belching were more common when compared to Western Europe, ORs

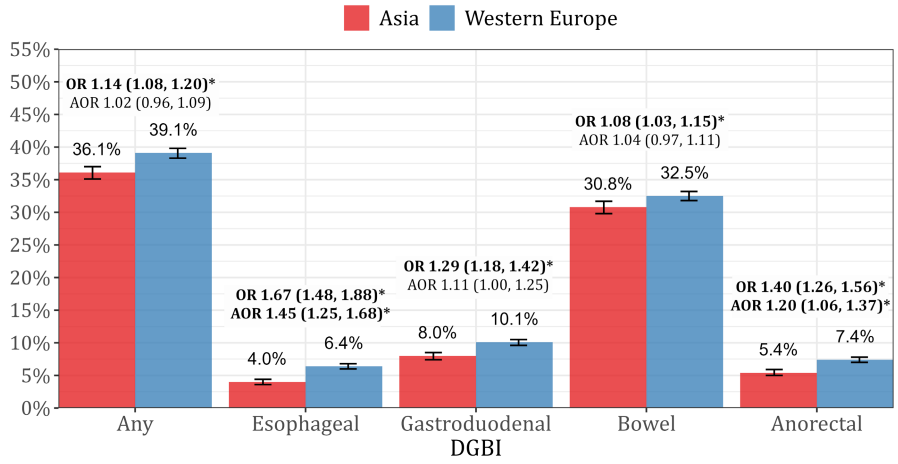

FIGURE 1 Prevalence of any DGBI and DGBI by anatomical region in Western Europe (blue) and Asia (red). Odds ratios (OR) were estimated by logistic regression. Adjusted odds ratios (AOR) were estimated while correcting for age, sex, BMI, psychological factors, non-GI somatic symptoms, ability to visit a doctor, and personal cost of doctor visit. Error bars and numbers in parentheses are 95% confidence intervals. *$p < 0.05$.

TABLE 2 Demographic variables of subjects with and without DGBI in the total sample.

Variable	No DGBI (*N* = 16,003)	DGBI (*N* = 9798)	OR/SMD (95% CI)
Demographics			
Age	46.4 (46.2–46.7)	43.3 (43.0–43.6)	**−0.20 (−0.22, −0.17)†**
Female gender	44.9% (44.2–45.7)	58.0% (57.0–59.0)	**1.69 (1.61, 1.78)**
Education (Years)	13.7 (13.6–13.7)	13.6 (13.5–13.7)	−0.01 (−0.03, 0.02)†
BMI	24.6 (24.5–24.7)	24.7 (24.5–24.8)	0.01 (−0.02, 0.04)†
Relationship status			
Single	29.6% (28.9–30.3)	30.8% (29.9–31.7)	**1.06 (1.01, 1.12)**
Married/Co-habiting	61.9% (61.1–62.6)	60.7% (59.8–61.7)	**0.95 (0.91, 1)**
Divorced	6.0% (5.7–6.4)	6.5% (6.0–7.0)	1.08 (0.98, 1.2)
Widowed	2.5% (2.3–2.8)	1.9% (1.7–2.2)	**0.75 (0.63, 0.9)**
Psychological factors			
Anxiety	9.4% (8.9–9.8)	25.7% (24.8–26.6)	**3.34 (3.12, 3.58)**
Depression	8.6% (8.2–9.1)	23.8% (23.0–24.7)	**3.3 (3.08, 3.55)**
Non-GI somatic symptoms			
PHQ-12	3.8 (3.8–3.9)	6.3 (6.2–6.3)	**0.72 (0.63, 0.83)†**
Healthcare utilization			
Number of doctor visits			
Once a month	1471 (9.2%)	1535 (15.7%)	**1.84 (1.7, 1.98)**
A few times a year	7597 (47.5%)	5123 (52.3%)	**1.21 (1.15, 1.28)**
Once a year	2714 (17.0%)	1281 (13.1%)	**0.74 (0.69, 0.79)**
Less than once a year	3568 (22.3%)	1564 (16.0%)	**0.66 (0.62, 0.71)**
Never	653 (4.1%)	295 (3.0%)	**0.73 (0.63, 0.84)**
Doctor visit due to bowel problem	28.5% (27.8–29.2)	47.6% (46.6–48.6)	**2.28 (2.16, 2.4)**
General practitioner	20.3% (19.7–21.0)	36.3% (35.3–37.2)	**2.23 (2.11, 2.36)**
Gastroenterologist	13.5% (13.0–14.1)	22.9% (22.1–23.7)	**1.9 (1.78, 2.02)**
Surgeon	2.3% (2.1–2.6)	2.6% (2.3–2.9)	1.11 (0.94, 1.3)
Type of health care			
Western medicine	78.9% (78.3–79.6)	79.8% (79.0–80.6)	1.05 (0.99, 1.12)
Traditional/folk healer	1.9% (1.7–2.1)	2.2% (2.0–2.5)	**1.2 (1.01, 1.43)**
Both	13.2% (12.7–13.7)	12.5% (11.9–13.2)	0.94 (0.88, 1.02)
Neither	6.0% (5.7–6.4)	5.5% (5.0–5.9)	0.9 (0.81, 1.01)
Ability to visit doctor if needed?			
No	0.5% (0.4–0.7)	0.6% (0.4–0.7)	1.04 (0.74, 1.46)
Yes, easily	94.3% (93.9–94.6)	91.5% (91.0–92.1)	**0.66 (0.59, 0.72)**
Yes, but difficult	5.2% (4.8–5.5)	7.9% (7.4–8.4)	**1.57 (1.42, 1.74)**
Cost of medical care?			
No medical expenses	30.7% (29.9–31.4)	30.9% (29.9–31.8)	1.01 (0.96, 1.07)
Small fee	50.7% (49.9–51.4)	48.7% (47.7–49.7)	**0.92 (0.88, 0.97)**
Substantial	11.9% (11.4–12.4)	13.7% (13.1–14.4)	**1.18 (1.09, 1.27)**
All medical expenses	6.8% (6.4–7.2)	6.8% (6.3–7.3)	1 (0.9, 1.1)

Note: OR, Odds ratio (categorical variables); SMD, Standardized mean difference (continuous variables) where values of 0.2–0.5 are considered small, values of 0.5–0.8 are considered medium, and values >0.8 are considered large. SMD values are denoted with†.

Bold values signify 95% confidence intervals that do not cross zero (for SMD) or one (for OR).

0.78–0.94, but the 95% confidence intervals of the estimates did include the possibility of no difference for cyclic vomiting and excessive belching (Figure 3). Certain DGBI were so rare that reliable ORs and CIs could not be estimated and therefore not included Figure 2; these were functional biliary pain (prevalence 0.098% vs 0.021% in Western Europe and Asia, respectively), centrally mediated

abdominal pain syndrome (0.025% vs 0%), and cannabinoid hyperemesis syndrome (0.037% vs 0.021%). Further details on individual DGBI are provided in Tables S1 and S2.

When analyzing prevalence rates in individual countries within regions, in Western Europe the countries with the highest prevalence of at any DGBI were France, Spain, and Italy (47%, 44% and 43%, respectively), the Netherlands had the lowest (31%). In Asia, the prevalence of at any DGBI in Japan and South Korea was the highest (39% in both); it was lowest in Singapore (31%) (Figure 4).

3.3 | IBS

When comparing the difference in IBS prevalence estimated by Rome III and Rome IV criteria, IBS was more common in Western Europe compared to Asia according to both Rome III (10.8% vs 8.1%) and IV criteria (3.7% vs 2.0%). The difference in prevalence was slightly higher for IBS according to Rome IV compared to Rome III, OR 1.90 (1.56, 2.32) vs 1.38 (1.24, 1.54), respectively. (Table S20). Postinfectious onset of IBS was less common in Western Europe compared to Asia, 9.9% vs 18.0%, OR 0.46 (95% 0.40–0.52).

TABLE 3 Change in odds ratio (OR) when variables were individually added one at a time to a logistic regression model with any DGBI as the dependent variable and regions as independent variable.

Variable	Change in OR
Age	0.046
Sex	−0.003
BMI	0.017
Psychological symptoms (PHQ4)	−0.094
Non-GI somatic symptoms (PHQ12)	−0.138
Doctor access	−0.004
Cost of doctor visit	0.056

Note: This demonstrates the individual effect each variable had on the DGBI prevalence estimates.

3.4 | Comparison of subjects with DGBI in Western Europe and Asia

With regard to demographic factors, subjects with DGBI in Western Europe compared to Asia were older, more likely to be female, and had higher BMI but lower education level (Table 4). Furthermore, psychological factors were more prominent among DGBI subjects in Western Europe, and they were more likely to report no/small personal cost of medical care, but no difference was observed in the subjects' ability to visit a doctor if needed (Table 4). Additional details are provided in Table S3.

Subanalyses were performed in the same manner as above for subjects with IBS, functional dyspepsia, functional constipation, and functional bloating in Western Europe and Asia. The most notable differences when comparing these subanalyses to the overall analyses for the entire DGBI group were that subjects with IBS in the two geographical regions were similar with regard to mean age, psychological factors, and non-GI somatic symptoms in Western Europe and in Asia. The same was true for age and sex for subjects with functional constipation in the two regions. Apart from that, the same general pattern of differences and similarities was found when comparing these subanalyses to the main analysis on all DGBI (Tables S4–S19).

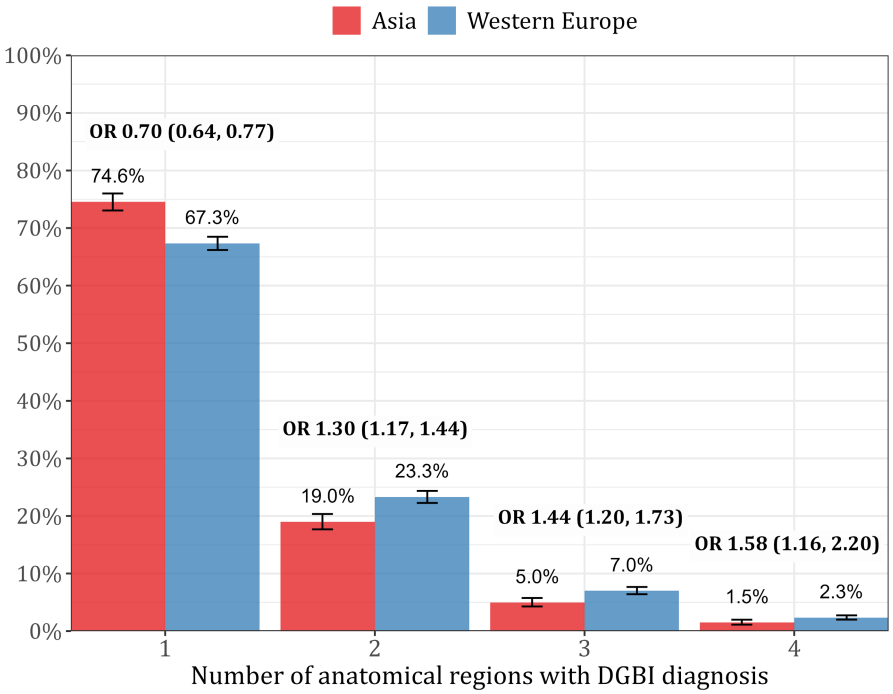

FIGURE 2 Proportion of subjects with DGBI by number of anatomical regions involved in Western Europe (blue) compared to Asia (red). Odds ratios (OR) were evaluated with logistic regression. Error bars and numbers in parentheses represent 95% confidence intervals.

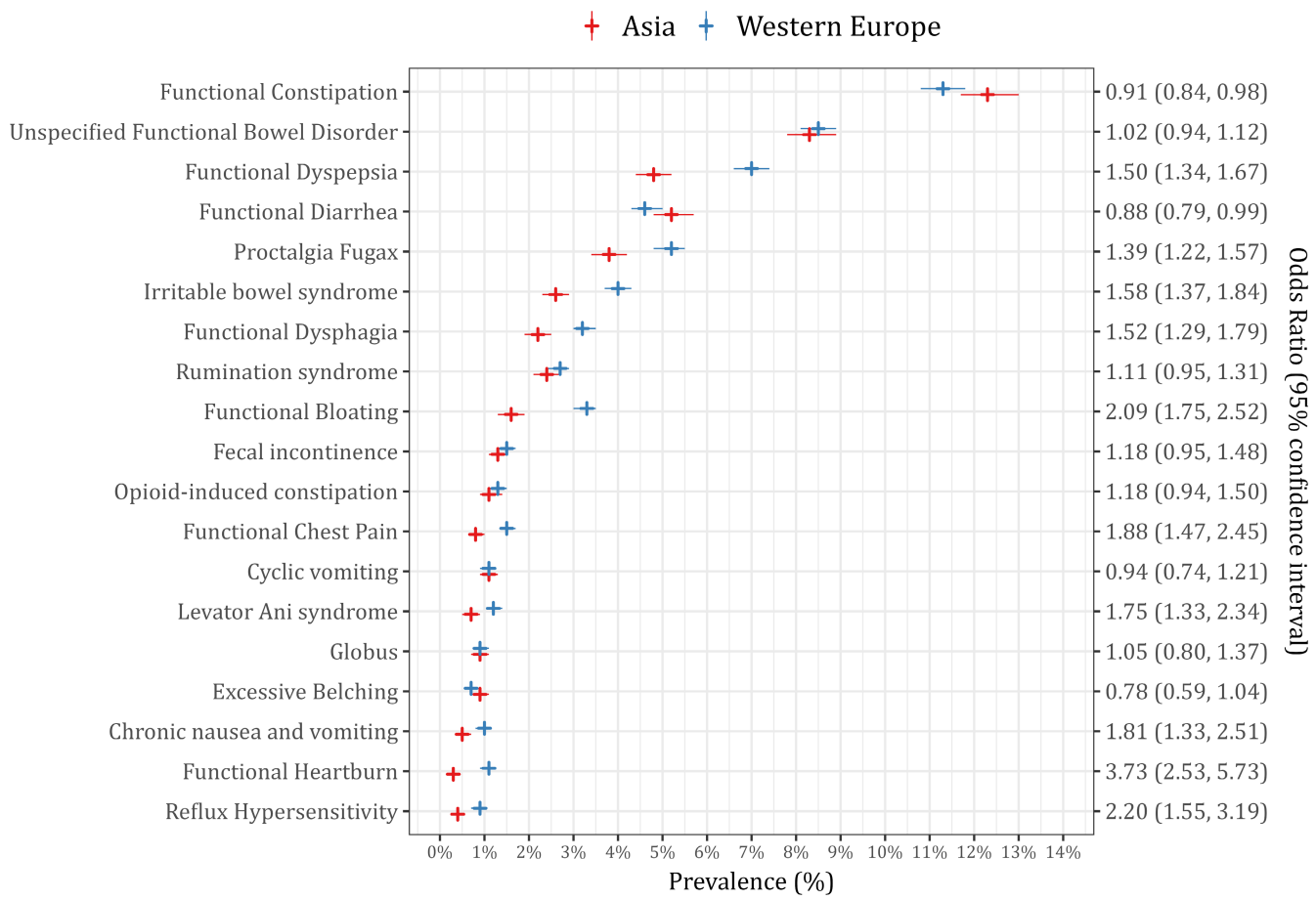

FIGURE 3 Prevalence of individual DGBI in Western Europe (blue) and Asia (red). Odds ratios derived from a simple logistic regression model with geographical region as dependent variable and each DGBI as an independent variable are displayed on the right side of the graph. Error bars and numbers in parentheses represent 95% confidence intervals.

4 | DISCUSSION

In this study, we found that the prevalence of DGBI was generally higher in Western Europe when compared to Asia. However, when taking psychological and non-GI somatic symptoms into account, the difference in DGBI prevalence between the two regions was significantly diminished. Overlap of DGBI across anatomical regions was greater in Western Europe, further substantiating its greater DGBI burden when compared to Asia. The characteristics of subjects with DGBI in the two geographical regions varied considerably, and how they varied was different for individual DGBI, for example, subjects with IBS were quite similar in the two geographical regions. Post-infection onset of IBS was more common in Asia, but IBS was more common in Western Europe, as was the case for several other DGBI. Lastly, the difference in IBS prevalence between these world regions seemed to be greater when using the Rome IV compared to Rome III criteria.

To our knowledge, this is the first time that prevalence rates of all DGBI in Western Europe and Asia are compared in a single study where all data were obtained and defined with the same methodology. Most previous studies have reported the prevalence of a single or few DGBI in only one of these geographical regions. There are systematic reviews and meta-analyses available that have gathered and compared prevalences of IBS,[2–4] functional constipation,[5] and uninvestigated dyspepsia.[6] These have generally shown that the prevalance of these DGBI are higher in Europe compared to Asia. In a meta-analysis from 2012, the prevalence of IBS according to Manning and Rome I-III criteria in Northern and Southern Europe was shown to be 12%–15%, higher than the 7% prevalence found in Southeast Asia.[3] In contrast, one meta-analysis showed higher prevalence of IBS in Asia, 9.6%, compared to Europe pooled with North America, Australia, and New Zealand, 8.1%.[4] In a meta-analysis on functional constipation, the prevalence was often higher in Western European countries compared to Asia, but the pooled prevalence across geographical regions was not reported and it is important to note that the study included data from the RFGES data set.[5] With regard to uninvestigated dyspepsia, a meta-analysis showed a prevalence of 14.6% in Southeast Asia and 21.7%–24.3% in North and South Europe.[6] All of these meta-analyses have been severely limited by study heterogeneity, and few studies exist that directly compare Asia and European countries using the same methodology.

In the current study, psychological factors and non-GI somatic symptoms were shown to have an important role in DGBI prevalence differences between Western Europe and Asia. The association

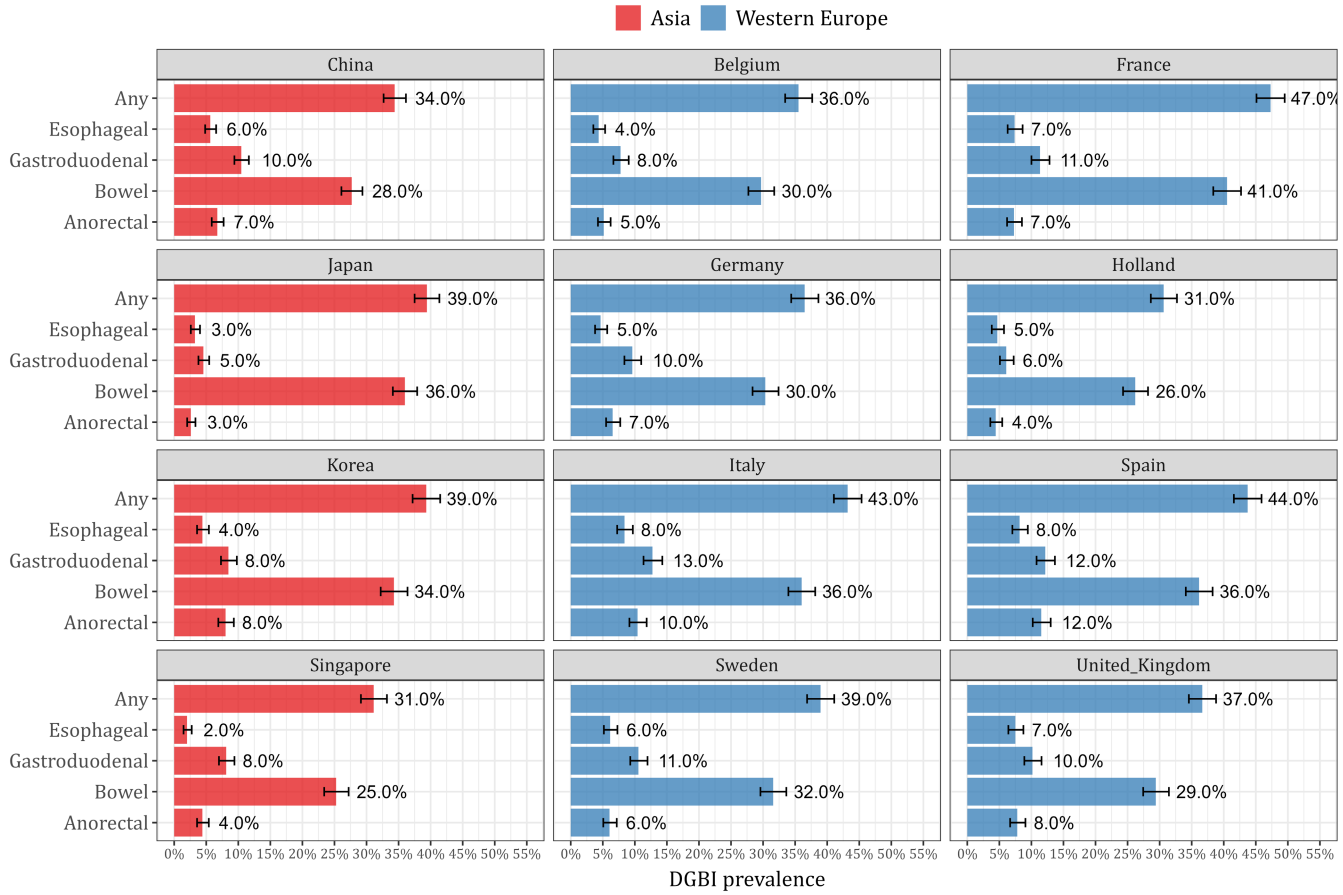

FIGURE 4 Prevalence of any DGBI and DGBI by anatomical region in all countries included in the study. Error bars represent 95% confidence intervals.

between these factors and DGBI is well known and is thought to be mediated through the brain–gut axis.[15] Importantly, the association has been shown to be bidirectional.[16] The current study was cross-sectional, so data on DGBI, psychological factors, and non-GI somatic symptoms were collected at a single time point; therefore, we cannot conclude on the direction of the association. Furthermore, it is likely that these factors only constitute a part of the explanation for different prevalence between the two geographical regions, as our analysis did not include all known risk factors for DGBI and it is likely that complex residual confounders exist between the two regions that we were not able to account for.

The general pattern was that most DGBI were more common in Western Europe than in Asia. However, there were four DGBI that were marginally more common in Asia, that is, functional constipation, functional diarrhea, cyclic vomiting syndrome, and excessive belching. The reason why only these DGBI were found more commonly in Asia is unclear and we have no unifying explanatory factor or theory for these findings. However, it should be noted that for three out of these four DGBI the differences in prevalence rates were small. The characteristics of DGBI subjects in Western Europe and Asia were quite different, which may be related to the fact that certain DGBI were more common in Western Europe and some were less common, which may lead to an imbalance in the characteristics of the two groups. Additionally, a part of the explanation may be underlying differences in certain characteristics that may be more prominent in either region without it being related to DGBI in any way.

It is well known that prevalence of IBS is lower when defined by the Rome IV compared to the Rome III[2,9,17] and the results of the current study showed that this applies to both Western Europe and Asia. Furthermore, when comparing IBS prevalence in the two geographical regions the OR was higher using the Rome IV criteria, meaning that IBS prevalence decreases proportionally more in Asia compared to Western Europe when Rome IV criteria are used instead of Rome III criteria. In Western analyses, the severity level and psychosocial co-morbidity are higher in those fulfilling Rome IV IBS criteria, compared to those only fulfilling Rome III criteria.[18,19] In an analysis on Chinese patients, there was no difference in psychological co-morbidity in those fulfilling Rome IV criteria, compared to those only fulfilling Rome III criteria.[20] These observations suggest that a larger proportion of subjects with impactful symptoms do not fulfill Rome IV IBS criteria in Asia compared to the West, which may also have contributed to the differences in Rome IV IBS prevalence observed in the current analysis.

Gastroenteritis is a known risk factor for the development of IBS[10] and in the current study a considerable proportion of subjects with IBS reported a post-infection onset, which was more commonly seen in Asia. This difference is not easily explained, but one possible explanation could be that infectious diarrhea is more common in Asia

TABLE 4 A comparison of subjects with DGBI in Western Europe and Asia.

Variable	Asia (*N* = 3421)	Western Europe (*N* = 6377)	OR/SMD (95% CI)
Demographics			
Age	42.1 (41.6–42.6)	43.9 (43.5–44.3)	**0.12 (0.07, 0.16)†**
Female gender	55.2% (53.6–56.9)	59.4% (58.2–60.6)	**1.19 (1.09, 1.29)**
Education (Years)	15.0 (14.9–15.1)	12.9 (12.8–13.1)	**−0.42 (−0.46, −0.37)†**
BMI	22.7 (22.6–22.9)	25.7 (25.6–25.9)	**0.57 (0.52, 0.61)†**
Psychological factors			
Anxiety	20.2% (18.9–21.6)	28.6% (27.5–29.8)	**1.58 (1.43, 1.75)**
Depression	21.5% (20.1–22.9)	25.1% (24.0–26.2)	**1.22 (1.11, 1.35)**
Non-GI somatic symptoms	5.8 (5.6–5.9)	6.5 (6.4–6.6)	**0.20 (0.16, 0.24)†**
Healthcare utilization			
Ability to visit doctor if needed?			
No	0.5% (0.3–0.8)	0.6% (0.4–0.8)	1.1 (0.64, 1.98)
Yes, easily	91.8% (90.8–92.7)	91.4% (90.7–92.1)	0.95 (0.82, 1.11)
Yes, but difficult	7.7% (6.8–8.6)	8.0% (7.3–8.7)	1.04 (0.89, 1.22)
Cost of medical care?			
No medical expenses	3.8% (3.2–4.5)	45.4% (44.1–46.6)	**21.02 (17.6, 25.33)**
Small fee	60.9% (59.2–62.5)	42.1% (40.9–43.3)	**0.47 (0.43, 0.51)**
Substantial	23.7% (22.3–25.1)	8.4% (7.7–9.1)	**0.3 (0.26, 0.33)**
All medical expenses	11.7% (10.6–12.8)	4.1% (3.6–4.6)	**0.33 (0.28, 0.38)**

Note: OR, Odds ratio (categorical variables); SMD, Standardized mean difference (continuous variables) where values of 0.2–0.5 are considered small, values of 0.5–0.8 are considered medium, and values >0.8 are considered large. SMD values are denoted with†. CI, Confidence intervals.
Bold values signify 95% confidence intervals that do not cross zero (for SMD) or one (for OR).

compared to Europe, but reliable estimates comparing the frequency of infectious diarrhea in these regions are scarce. Previously, the prevalence of IBS after infectious diarrhea has been shown to be similar in Asia and Europe,[10] so different susceptibility to post-infection IBS in the two geographical regions does not seem to be an explanation.

The strengths of the current study include its large sample size and electronic data gathering that ensured completeness of data. Furthermore, the data gathering was conducted in the same way in each country and efforts were made to translate questionnaires as accurately as possible. With regard to limitations, there are factors important for the context of DGBI about which data were not collected in the current study. These factors may differ between Western Europe and Asia, for example diet differences and *H.pylori* status. Furthermore, there are additional differences between the regions that are less definable, such as cultural, environmental, and language differences. However, our inability to correct for all of these factors does not change the fact that DGBI were found to be more common in Western Europe. There were some intra-regional variations observed in the study analyses. To account for this, we considered using mixed models with country as a nested random effect within region, but unfortunately the number of countries in Asia was too low to carry out this analysis. Of course, the results of the study have to be interpreted with these intra-regional variations in mind, but ultimately the primary aim of the study was to compare geographical regions and not countries.

To conclude, in this large, multinational survey using uniform methodology across countries, DGBI were found to be more common and have greater overlap in Western Europe compared to Asia. However, the difference was less apparent when correcting for differences in the severity of psychological and non-GI somatic symptoms, underlining the importance of these factors for DGBI. The characteristics of subjects with DGBI varied by geographical region, especially with regard to psychological symptoms and non-GI somatic symptoms. Postinfectious onset of IBS was more common in Asia, and the difference in IBS prevalence between these two regions tended to be greater when using the Rome IV rather than the Rome III criteria.

AUTHORS CONTRIBUTIONS

JPH conceptualized the study, analyzed and interpreted data, wrote the first and revised manuscripts and approved of the final paper. RKMW conceptualized the study, contributed to data aquisition and interpretation, provided critical review of all manuscript versions and approved of the final paper. JT, PW, MAB, VA, BB, SCC, ESC, JS, SF, MK, XF, SIB, ADS, and OSP contributed to the design of the study, aquisition and interpretation of data, contributed to the first draft and revised draft and approved of the final version of the paper. MS conceptualized the study, contributed to data aquisition and interpretation, provided critical review of all manuscript versions and approved of the final paper.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare regarding this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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