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Worldwide population prevalence and impact of sub-diagnostic gastrointestinal symptoms

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Summary

Background: The Rome Foundation Global Epidemiology Study (RFGES) found that 40.3% of adults in 26 internet-surveyed countries met Rome IV criteria for disorders of gut–brain interaction (DGBI). However, additional people not meeting DGBI criteria may also be burdened by frequent gastrointestinal symptoms.

Aims: To explore the prevalence and demographic distribution of sub-diagnostic gastrointestinal symptoms, and the hypothesised associated effects on quality of life (QoL), life functioning and healthcare needs.

Methods: We analysed data from the RFGES survey, which included the Rome IV diagnostic questionnaire and QoL, psychological, work productivity and healthcare questions.

Results: Of the 50,033 people without a history of organic gastrointestinal disorders, 25.3% classified in the sub-diagnostic group (no DGBI but one or more frequent gastrointestinal symptoms), 41.4% had DGBI and 33.4% had no frequent gastrointestinal symptoms (non-GI group). Sub-diagnostic prevalence in different world regions ranged from 22.2% (North America) to 30.5% (Middle East), was slightly higher among males than females and decreased with age. The sub-diagnostic group was intermediate between the non-GI and DGBI groups, and significantly different from both of them on QoL, anxiety, depression, somatisation, healthcare utilisation and life and work impairment.

Conclusions: One in four adults without organic gastrointestinal disorders or DGBI report frequent gastrointestinal symptoms. This sub-diagnostic group has reduced QoL, greater psychological and non-GI bodily symptoms, impaired work productivity and life activities and greater healthcare use compared to non-GI individuals. This suggests that many in this sub-diagnostic group might benefit from healthcare services or symptom self-management advice.

'[Correction added on 12 February 2024, after first online publication: The copyright line was changed.]'

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1 | INTRODUCTION

The disorders of gut–brain interaction (DGBI), formerly known as functional gastrointestinal (GI) disorders (FGID), are a large class of digestive health problems characterised by chronic or recurrent GI symptoms that are not fully explained by objective findings on standard investigations or tests.[1] Diagnostic symptom criteria define these disorders, the latest being the Rome IV criteria, based on the chronic presence of either a single GI symptom or a combination of GI symptoms that exceed pre-defined minimum frequency and duration thresholds[2] that have been partly determined based on data on their occurrence in the general population.[3] In addition to meeting the minimum symptom frequency thresholds, qualifying for a DGBI diagnosis requires the symptoms to both be currently present (i.e. during the last 3 months) and show signs of chronicity (i.e. first onset reported to be at least 6 months before diagnosis).

DGBI are very common in the general population. In the Rome Foundation Global Epidemiology Study (RFGES), 40.3% of Internet-surveyed adults in 26 national populations collectively fulfilled criteria for at least one DGBI.[4] Most DGBI are female predominant, and having a DGBI is frequently associated with substantial adverse impact for the individual, including the suffering directly related to the GI symptoms, associated psychological and non-GI body symptoms, reduced quality of life, impaired work functioning and increased healthcare utilisation.[5,6]

Past surveys that focused on symptoms in the general adult population rather than formal diagnosable GI disorders have found that up to 60% of people report troublesome GI symptoms.[7,8] Therefore, it seems likely that a substantial additional proportion of adults who do not meet the diagnostic criteria for a DGBI by current definitions have what can be called 'sub-diagnostic' GI symptoms. This is supported by a recent survey assessing what the investigators termed 'minor digestive symptoms'. In 1924 randomly selected French adults without a confirmed DGBI or any other GI disease, these symptoms occurred in 66.5% of women and 47.7% of men, and they had a marked impact on vitality and self-image as well as emotional, social and physical well-being.[9] However, apart from this single-country survey, little is known about the importance of having GI symptoms not meeting diagnostic criteria for DGBI or organic GI disorders. It is unknown whether these sub-diagnostic symptoms are more common in specific sociodemographic segments, countries or geographic regions or what characteristics distinguish people who have troublesome sub-diagnostic GI symptoms from those without such symptoms or set them apart from those who have formally diagnosable GI disorders.

The RFGES study, which collected gastrointestinal symptom data reported with the frequency scales of the Rome IV diagnostic questionnaire[3] from populations in countries around the world, constitutes a unique opportunity not only for assessing DGBI on a global population level but also for evaluating how common it is to have no DGBI but still have GI symptoms frequent enough for them to be considered as clinical significance by DGBI experts; that is, sub-diagnostic GI symptoms. Furthermore, additional information collected in the RFGES survey along with GI symptom reporting makes it possible to assess the relevance of the symptoms in terms of healthcare needs, impairment in quality of life and emotional well-being, as well as potential effects on work and life activities.

Hence, the present study aimed to use the data from the RFGES to:

1. Characterise the worldwide population prevalence and sociodemographic characteristics of people with sub-diagnostic GI symptoms.
2. Assess the impact of sub-diagnostic GI symptoms on quality of life, healthcare and medication use, work and life activities, psychological well-being and GI concerns.
3. Evaluate the association of sub-diagnostic GI symptoms with non-GI symptoms and self-reported family history of organic GI disorders.

2 | MATERIALS AND METHODS

2.1 | Dataset

The data analysed in this study were the combined RFGES survey responses from 54,127 adults in the general population of 26 countries on six continents, who were surveyed in a uniform manner using the Internet between March 2017 and January 2018. The study aimed to determine the global prevalence of the various DGBI and examine associated factors of potential importance.[4] The Rome IV diagnostic questionnaire[3] used in that study collects information on the presence and frequency of a wide range of GI symptoms that define the various DGBI. The symptoms are reported on frequency scales and have established frequency thresholds delineating what is considered abnormal by the Rome Foundation DGBI experts based on frequency data in a population survey.[3] The main findings regarding the global DGBI prevalence have been previously presented.[4] The survey participants were individuals who had already registered in large online panels to complete a variety of surveys. They were invited via e-mail and enrolled in the study with the help of Qualtrics, Inc. (Provo, Utah, USA), a large global market research company, solely based on their demographic characteristics. They completed an online consent and then completed the survey in a manner that was anonymous to the investigators. To avoid possible self-selection bias regarding gastrointestinal symptoms, the participants were unaware that the survey concerned gastrointestinal symptoms when they enrolled. It was described only as a 'health survey' in the consent form. The survey contained several quality assurance methods to help ensure a high quality of responses, including two attention check questions, two repeated GI symptom questions to detect excessively inconsistent responders and automated monitoring of unusually quick survey responding. Persons with poor-quality

responses detected by any of these methods were eliminated automatically from the dataset during surveying. The survey was quota controlled to ensure comparable distribution of participants in all countries in regard to sex (50% female, 50% male) and age groups (40% of ages 18–39 years, 40% ages 40–64 years and 20% ages 65 years and older). The survey data collection was managed at the University of North Carolina at Chapel Hill (UNC-CH), which served as the data coordination centre of the project. The study was reviewed by the biomedical institutional review board at UNC-CH as well as by human ethics boards in the various surveyed countries. It was deemed exempt from ethical oversight due to the anonymity of the online survey method.

2.2 | Measures

The RFGES dataset contains survey responses to more than 160 questions, including several validated research questionnaires. The survey contents used in the present analyses were the following:

a. Demographics: age, sex, total years of education, community size and country of residence.
b. The Rome IV Diagnostic Questionnaire for Adults, consisting of 86 diagnostic questions about gastrointestinal symptoms, plus three additional red-flag symptom questions.[3]
c. The Patient-Reported Outcomes Measurement Information Systems (PROMIS) Global-10 general quality-of-life questionnaire.[10]
d. Anxiety and depression scores from the four-question Patient Health Questionnaire-4 (PHQ-4).[11]
e. The Patient Health Questionnaire-15 (PHQ-15) somatisation scale.[12] We used 11 of the 15 symptoms (3 GI symptoms and a menstruation-related symptom excluded) to assess amounts of general non-gastrointestinal bodily symptoms in the past 4 weeks.
f. A questionnaire about medications used regularly by the respondents, that is, at least once a week, assessed with yes/no checklist responses for 10 different medication categories.
g. Two healthcare use questions asked about typical frequency of doctor visits per year for any health problem and whether the respondents had ever visited a doctor for a bowel problem.
h. The Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH), a validated six-question measure that assesses the degree of impairment in work and life activities from ill health in the past 7 days.[13] The WPAI-GH data were collected in only eight countries in the survey: Germany, Israel, Italy, Japan, Netherlands, Poland, Spain and Sweden.
i. Three questions about concern, embarrassment and stress associated with bowel functioning were created specifically for the RFGES survey.
j. History of selected GI-relevant medical diagnoses and surgeries for identifying individuals with potential organic contributing factors to their gastrointestinal symptoms.
k. Height and weight questions were used to calculate body mass index (BMI).

2.3 | Defining sub-diagnostic symptoms

For the analyses in this paper, we were specifically interested in non-organic GI symptoms that might occur frequently enough to be troublesome to the person and potentially of clinical concern but which nonetheless do not meet the criteria for any DGBI diagnosis. The Rome IV Diagnostic Questionnaire administered in the RFGES provided an opportunity to evaluate this, as it identifies 22 different DGBI while at the same time providing information about the frequency of 24 key gastrointestinal symptoms throughout the entire digestive tract.

Our analyses required consistent and reliable rules for determining the minimum amount of symptoms that are of potential clinical concern among people with no GI diagnosis and may therefore be viewed as sub-diagnostic rather than normal. For this purpose, we decided to use the diagnostic frequency thresholds established by the Rome Foundation working teams of experts for the symptoms of the various DGBI. These published cut-offs are incorporated in the Rome IV diagnostic criteria for DGBI and used in the Rome IV Diagnostic Questionnaire scoring.[3] The 24 key GI symptoms in the Rome IV questionnaire and their minimum frequency threshold for diagnosing one or more DGBI are presented in Table 1. In our analyses, we defined individuals in the survey sample as having sub-diagnostic GI symptoms if they reported any of those 24 symptoms with a frequency at or above the threshold listed in the table. They also must not have a history of organic GI diagnosis by self-report (inflammatory bowel disease, coeliac disease, GI cancer, peptic ulcer disease, diverticulitis or a history of bowel resection) or meet diagnostic criteria for any DGBI. After 4094 individuals with self-reported organic conditions were removed from the total survey sample of 54,127 people, 50,033 participants remained for analysis.

2.4 | Group classification of the study sample

The 50,033 subjects retained for analysis were divided into three mutually exclusive study groups based on their level of self-reported GI symptoms in the survey:

a. **Sub-diagnostic GI group.** People with one or more of the 24 key diagnostic DGBI symptoms on the Rome IV Diagnostic Questionnaire (see Table 1) at or above the frequency threshold used for DGBI diagnosis in the past 3 months, but not meeting criteria for any of the 22 DGBI assessed by the Rome IV Diagnostic Questionnaire. Six-month duration of the symptoms (which is required for DGBI diagnoses to ensure chronicity) was not required for this sub-diagnostic GI group.
b. **DGBI group.** People who fulfilled Rome IV diagnostic criteria for one or more of the 22 DGBI as assessed with the Rome IV diagnostic questionnaire.
c. **Non-GI group.** Individuals who (a) did not report any of the 24 key GI diagnostic symptoms in the past 3 months at or above

TABLE 1 The 24 key diagnostic symptoms of the Rome IV diagnostic criteria that were used in defining the sub-diagnostic GI group.

Symptom	Minimum frequency for sub-diagnostic GI group status (equals DGBI diagnostic frequency threshold)
Lump in throat	Once a week
Pain in middle of chest (non-cardiac)	Once a week
Heartburn	2–3 days/week
Dysphagia – food sticking	Once a week
Uncomfortable fullness after meals	2–3 days/week
Early satiety	2–3 days/week
Epigastric pain/burning	Once a week
Nausea	Once a week
Vomiting	Once a week
Regurgitation	2–3 days/month
Belching	Most days
Abdominal pain	Once a week
Hard/lumpy stools	30%+ of BMs
<3 Bowel movements (BMs)/week	>50% of weeks
Straining with BMs	30%+ of BMs
Feeling of incomplete emptying after BM	30%+ of BMs
Sensation of blocked passage of stool	30%+ of BMs
Digital facilitation of BM	30%+ of BMs
Mushy/watery stools	30%+ of BMs
Urgency – rushing to toilet	30%+ of BMs
Bloating/distention	Once a week
Biliary (upper middle or right abdominal) pain	2–3 days/month
Accidental leakage of stool	2–3 days/month
Aching pain or pressure in rectum	1 day/month

Note: To be included in the sub-diagnostic GI group, a survey participant must meet the minimum frequency listed in the right column for one or more symptoms while not qualifying for any DGBI diagnosis.

DGBI diagnostic frequency thresholds and (b) did not meet criteria for any DGBI.

2.5 | Definition of geographic regions

For the main descriptive prevalence findings, data were analysed on 3 different population levels: the entire global dataset, 6 distinct geographical world regions and each of the 26 individual countries. Division of the global sample into geographical region subsets followed a convention in analyses of data from the RFGES dataset that has been used in prior published articles,[14,15] and is as follows:

- *North America*: Canada and the United States
- *Latin America*: Argentina, Brazil, Mexico and Colombia
- *Western Europe*: Belgium, France, Germany, the Netherlands, Italy, Spain, Sweden and United Kingdom
- *Eastern Europe*: Poland, Romania and Russia
- *Middle East*: Israel, Egypt and Turkey
- *Asia*: China, Japan, South Korea and Singapore

Although South Africa and Australia were also surveyed and included in the dataset analysed, these two countries were included only in the global and country-by-country analyses but not in region comparisons because they do not logically fit into any of the geographical region groupings.

2.6 | Data analysis

Data were analysed with SAS version 9.2 and SPSS version 28.0. Data for groups of participants were summarised as means and standard deviations for continuous variables and as percent and 95% confidence intervals (CI) for ordinal and categorical variables. To assess differences between subgroups on key parameters of interest (i.e. quality-of-life scores, anxiety and depression scores, healthcare and medication utilisation, non-GI bodily symptoms and psychological aspects of bowel functioning), ANOVAs or unpaired t-tests were used

for continuous variables, and Chi-squared tests for comparison of proportions in subgroups. Wherever this involved multiple comparisons, Bonferroni-adjusted pairwise two-sided post hoc tests were used to determine the significance of difference between individual subgroups if the overall multigroup test yielded a significant p-value. To assess the practical or meaningful magnitude of differences between the three main study groups on quality-of-life and psychological symptom scores, Cohen's *d* effect sizes for subgroup differences were calculated for those outcomes. The recommended benchmarks by Cohen[16] to consider 0.2 to be small, 0.5 medium and 0.8 and above large effect sizes, respectively, were followed in interpretation of the results.

3 | RESULTS

3.1 | Sample characteristics

The general demographic characteristics of the analysis sample are presented in Table S1. It consisted of approximately equal proportions of males and females and included participants ranging in age from 18 to 94 years, with a mean age of 43.8 years. The mean education level was 14.1 years of formal schooling, and two-thirds of the sample were people living in cities.

3.2 | Prevalence of sub-diagnostic GI symptoms in the global sample and demographic subgroups

One in four people (25.3%; $n = 12{,}660$) in the global analysis sample were classified in the sub-diagnostic GI group, whereas 33.4% ($n = 16{,}705$) were in the non-GI group and 41.3% ($n = 20{,}668$) met the diagnostic criteria for a DGBI (Figure 1). The relative size of the sub-diagnostic group varied between geographic world regions (Figure 2 and Table S2), from 22.2% in North America to 30.5% in the Middle East. For the individual countries, the range was from 19.7% in the United Kingdom to 36.6% in Turkey (Table S3). The 95% confidence intervals for all prevalence estimates for the sub-diagnostic group and the other two comparison groups in the overall global sample, different world regions and individual countries are presented in Tables S2 and S3.

Males had a slightly higher prevalence of being in the sub-diagnostic group than females in the global sample, or 26.1% vs. 24.5%, and had numerically higher prevalence of sub-diagnostic individuals than females in 18 of the 26 countries (see sub-diagnostic group prevalence by sex for each country in Table S4). However, having a DGBI was more common among females than males (47.9% vs. 34.9%), and being in the non-GI group was conversely more common among males than females (39.0% vs. 27.6%); see Table 2. The sub-diagnostic group decreased in prevalence across the adult age spectrum, from 30.9% of ages 18–34 years to 19.8% of those 65 years or older (Table 2), and the prevalence of having any DGBI declined similarly with increasing age.

There was little difference between the three study groups on other demographic parameters than age and sex, even though the large sample size led to statistically significant differences. The mean number of formal years of education of people in the non-GI, sub-diagnostic and DGBI groups was similar: 14.3 (SD = 4.4), 14.0 (SD = 4.7) and 14.2 (SD = 4.6) respectively. The community size distribution was also similar in the three study groups, with 65.1% (64.4–65.8), 66.7% (65.9–67.5) and 67.4% (66.7–68.0) living in a city.

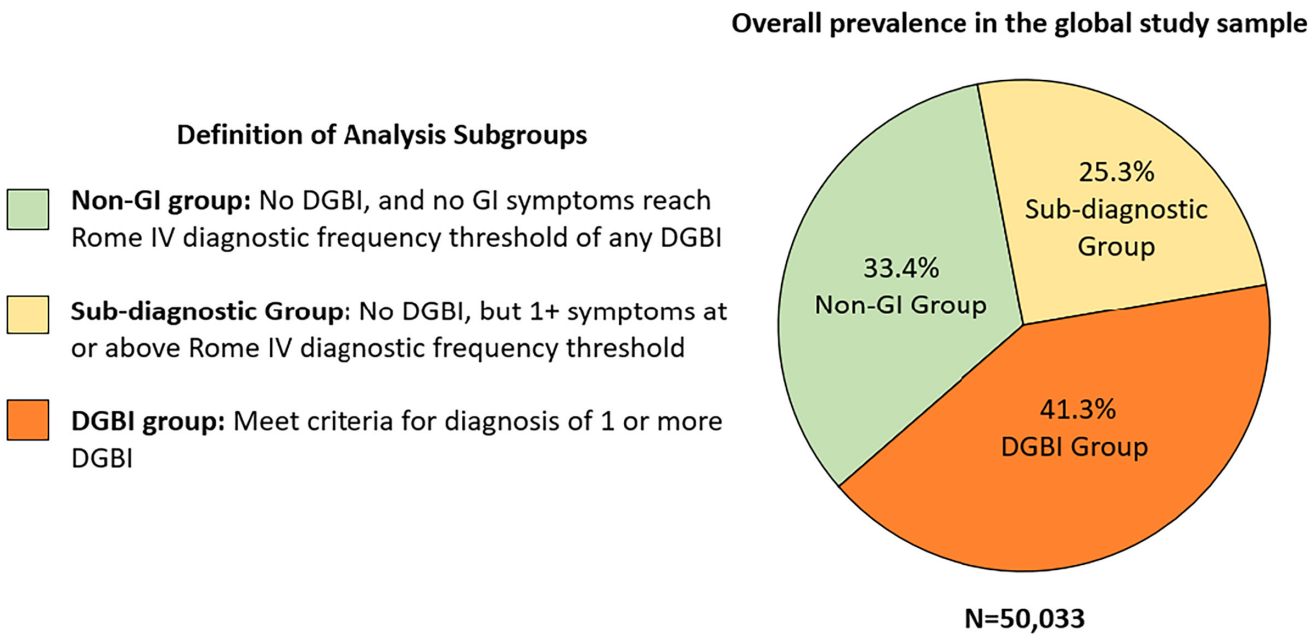

FIGURE 1 Summary of the definition of the three GI symptom analysis subgroups and their prevalence in the total global analysis sample.

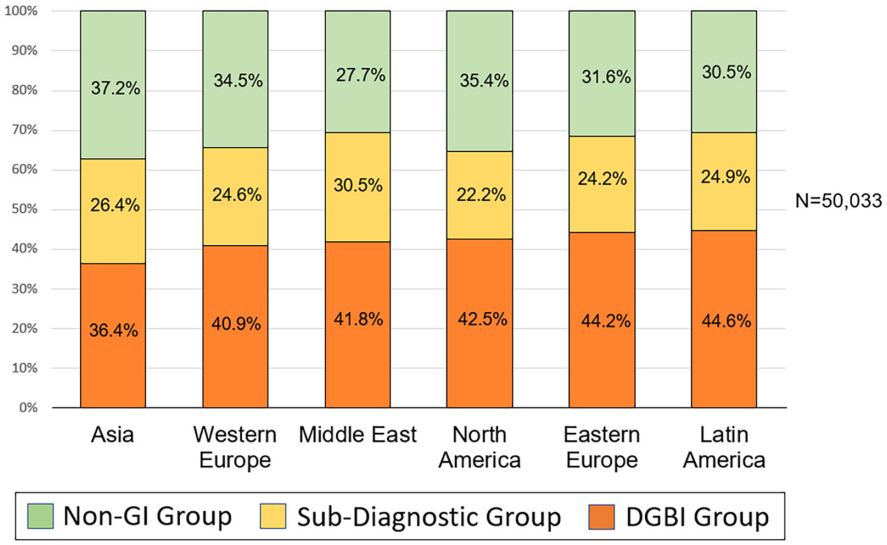

FIGURE 2 Prevalence of non-GI, sub-diagnostic GI and DGBI individuals in the population of different world regions.

TABLE 2 Distribution of prevalence of the three GI symptom comparison groups within different sex and age groups in the global dataset.

		% (95% CI)		
	N	Non-GI group	Sub-diagnostic group	DGBI group
Sex				
Male	25,378	39.0 (38.4–39.6)	26.1 (25.6–26.6)	34.9 (34.4–35.5)
Female	24,655	27.6 (27.1–28.2)	24.5 (24.0–25.0)	47.9 (47.3–48.6)
Age group				
18–34 years	16,830	23.7 (23.1–24.4)	30.9 (30.2–31.6)	45.4 (44.6–46.1)
35–49 years	15,339	32.4 (31.6–33.1)	25.0 (24.3–25.6)	42.7 (41.9–43.4)
50–64 years	10,194	40.7 (39.8.1–41.6)	20.7 (19.9–21.4)	38.6 (37.7–39.5)
≥65 years	7670	46.8 (45.6–47.8)	19.8 (18.9–20.8)	33.4 (32.2–34.5)

Note: Chi-square difference between the sexes overall (2×3 test) and within each of the three study groups: $p < 0.0001$. The prevalence distribution within every age group was significantly different between all three study groups at $p < 0.0001$ on pairwise Chi-square tests with Bonferroni adjustments for multiple comparisons.

The mean body mass index of people in the three study groups only differed slightly between the groups. It was 25.5 (25.4–25.6) in the non-GI group, 25.2 (25.1–25.3) in the sub-diagnostic group and 25.7 (25.6–25.8) in the DGBI group.

3.3 | Number and nature of sub-diagnostic symptoms in the sub-diagnostic group

The majority of people in the sub-diagnostic group reported more than 1 of the 24 GI symptoms at or above DGBI diagnostic frequency thresholds listed in Table 1: 43.1% of the sub-diagnostic group had only one symptom meeting that threshold, whereas 37.3% had two or three, and 25.4% had four or more at or above the DGBI diagnostic threshold. As seen in Table 3, the most common symptoms that people in the sub-diagnostic group experienced at DGBI diagnostic frequency levels were symptoms of constipation (hard/lumpy stools, straining with bowel movements and sensations of incomplete or blocked bowel movements) and diarrhoea (having to rush to the toilet or mushy/watery stools).

Relatively few individuals in the sub-diagnostic group, or 22.5% of that group (2845/12,660), equalling 5.7% of the total population sample (2845/50,033), had chronic sub-diagnostic symptoms, that is, symptoms with first onset at least 6 months ago. As seen in the last column in Table 3, the sub-diagnostic symptoms that were most commonly chronic were biliary-type pain (which by definition was classified as chronic if reported at a sub-diagnostic frequency, as it is only assessed in the Rome IV Diagnostic Questionnaire over a 6-month retrospective timeframe), lump in throat, heartburn and urgency to rush to the toilet.

3.4 | Quality of life and psychological symptoms

People in the sub-diagnostic group had significantly lower (i.e. poorer) physical and mental summary scores of the PROMIS Global-10 quality-of-life questionnaire (14.7, SD = 2.4 and 13.7, SD = 3.2, respectively), than those in the non-GI group (15.8, SD = 2.3 and 14.8, SD = 3.0). Conversely, they scored higher on both those QoL

TABLE 3 The percentage of the sub-diagnostic group that met or exceeded the DGBI minimum diagnostic frequency for each of the 24 key DGBI diagnostic GI symptoms assessed by the Rome IV Diagnostic Questionnaire, in descending order of prevalence.

Symptom	% of sub-diagnostic individuals at minimum DGBI diagnostic frequency threshold for the symptom (%)	% of sub-diagnostic individuals who have had this sub-diagnostic symptom for 6+ months (%)
Feeling of incomplete emptying after BM	35.0	0.0
Hard/lumpy stools	32.9	0.0
Straining with BMs	32.7	0.0
Urgency – having to rush to toilet	27.6	2.6
Sensation of blocked passage of stool	21.6	0.0
Mushy/watery stools	21.0	0.0
<3 BMs/week	12.4	0.0
Lump in throat	12.0	5.2
Biliary (upper middle or right abdominal) pain	11.3	11.3
Bloating/distention	8.6	0.0
Digital facilitation of BM	7.8	0.0
Aching pain or pressure in rectum	7.7	0.3
Heartburn	6.2	3.1
Uncomfortable fullness after meals	5.2	0.0
Regurgitation	4.9	0.8
Pain in middle of chest (non-cardiac)	4.1	0.9
Abdominal pain	4.1	0.0
Early satiety	3.8	0.0
Nausea	2.5	0.3
Dysphagia – food sticking	2.1	0.0
Epigastric pain/burning	1.4	0.0
Accidental leakage of stool	1.4	0.0
Vomiting	1.2	0.2
Belching	0.6	0.0

Abbreviation: BM, bowel movement.

dimensions than the DGBI group, which had corresponding scores of 13.5 (SD = 2.6) and 12.6 (SD = 3.3); see Figure 3A,B. Similarly, the sub-diagnostic group had higher mean anxiety and depression symptom scores (1.31, SD = 1.47 and 1.30, SD = 1.46) than non-GI individuals (0.70, SD = 1.10 and 0.69, SD = 1.11), but lower scores than the DGBI group (1.93, SD = 1.74 and 1.97, SD = 1.72); see Figure 3C,D. As seen from the Cohen's *d* values presented in the figure, the effect size of the difference between the non-GI and sub-diagnostic groups bordered on moderate size (which is 0.5 for Cohen's *d*) for physical quality-of-life scores and anxiety and depression symptoms, but it was smaller for mental quality-of-life scores.

To examine whether QoL impairment and emotional symptoms of people in the sub-diagnostic group were more pronounced if they had multiple or chronic GI symptoms at or above DGBI diagnostic frequency threshold, we repeated the analyses described above separately for sub-diagnostic individuals with and without those characteristics. Compared to people with only one sub-diagnostic symptom, those with multiple sub-diagnostic symptoms had significantly lower mean physical and mental QoL scores (14.3, SD = 2.4 and 13.4, SD = 3.1 vs. 15.2, SD = 2.3 and 14.2, SD = 3.1) and greater elevation in anxiety and depression scores (1.53, SD = 1.54 and 1.51, SD = 1.54 vs. 1.03, SD = 1.32 and 1.02, SD = 1.30), and the effect sizes of their difference from non-GI individuals on those parameters were of moderate size rather than small (Table S5). A similar pattern was seen in comparison of people with versus without chronic sub-diagnostic symptoms; the chronic sub-diagnostic subgroup had significantly lower physical and mental QoL scores (14.0, SD = 2.4 and 13.2, SD = 3.2 vs. 14.9, SD = 2.4 and 13.9, SD = 3.1) and greater anxiety and depression scores (1.59, SD = 1.56 and 1.54, SD = 1.54 vs. 1.23, SD = 1.43 and 1.22, SD = 1.43), and the effect sizes of their difference from non-GI individuals were within the moderate rather than small range (Table S6).

Due to the clear indications from the analyses described above that sub-diagnostic GI symptoms are associated with impaired quality of life, we followed up on those findings by exploring which symptoms in particular were associated with the poorest physical and mental QoL. To do this, we calculated the mean QoL scores of

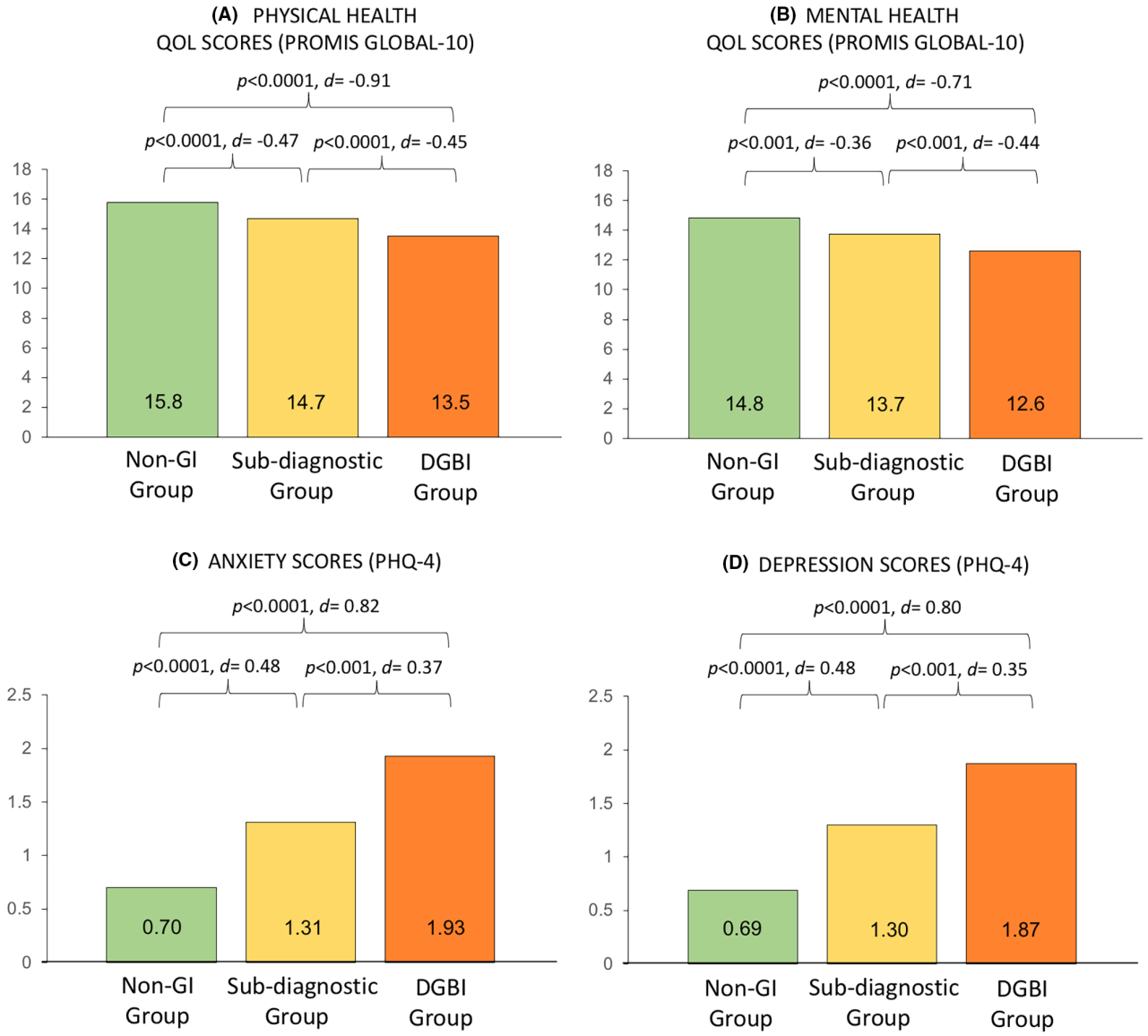

FIGURE 3 Comparison of physical and mental quality-of-life scores (A, B), and anxiety and depression scores (C, D), in individuals in the global survey sample in the three study groups. One-way ANOVAs with Bonferroni-adjusted post hoc tests; *d* = Cohen's effect size.

people with versus without each of the 24 key GI symptoms within the sub-diagnostic group. As seen in Table S7, the lowest average physical health QoL scores (i.e. the poorest QoL) on the PROMIS Global-10 questionnaire were seen among people with sub-diagnostic symptoms of epigastric pain/burning, nausea, accidental stool leakage and abdominal pain. The lowest mental health QoL scores were similarly seen among people with sub-diagnostic epigastric pain/burning, nausea and abdominal pain (Table S8).

3.5 | Impairment in life activities and work productivity

To further examine the impact of sub-diagnostic symptoms on people's lives and well-being, we compared scores for the three study groups on the Work Productivity and Activity Impairment – General Health scale[13] that was administered in 8 of the 26 countries surveyed, providing 16,820 responses. ANOVA tests showed all three groups to be significantly different ($p < 0.0001$) from each other, with the sub-diagnostic group in the middle between the others, both in regard to per cent impairment of non-work life activities (non-GI group 7.1% (95% CI: 6.7–7.5)), sub-diagnostic group (13.7% (13.0–14.4)), DGBI group (22.9% (22.2–23.6)) and per cent impairment of work productivity (4.1% (3.7–4.5) vs. 9.4% (8.7–10.2) vs. 14.6% (13.9–15.3)).

3.6 | Psychological aspects related to bowel functioning

The RFGES included three custom-created questions for the survey that were designed to succinctly assess concerns, embarrassment

and stress impact relating to bowel functioning. The sub-diagnostic group was significantly different ($p < 0.0001$) from the other two groups, and in the middle between them, on responses to all these three questions. Moderate or great concern about their bowel functioning was reported by 39.8% (38.9–40.6) of people in the sub-diagnostic group compared to 22.3% (21.7–22.9) of those in the non-GI group and 65.1% (64.5–65.8) of DGBI individuals. Embarrassment about discussing bowel functioning with others was reported by 36.5% (35.7–37.4) of the sub-diagnostic group compared to 25.7% (25.0–26.3) of the non-GI group and 47.9% (47.3–48.6) of the DGBI Group. Of the sub-diagnostic group, 54.3% stated that stress affected their bowel functioning moderately or a lot compared to 34.7% (34.0–35.5) of the non-GI group and 73.2% (72.6–73.8) of DGBI individuals.

3.7 | Healthcare and medication utilisation

Compared to the non-GI group, the sub-diagnostic group had a significantly higher prevalence of frequent doctor visits for any health problem, which we defined as visiting doctors at least once a month, but lower prevalence of such high utilisation compared to the DGBI group (Table 4). Similarly, individuals in the sub-diagnostic group were more likely to have ever consulted a doctor for a bowel problem than those in the non-GI group but less likely to have done so than people with DGBI.

The three study groups differed significantly in their prevalence of regularly (defined for the respondents as 'at least once a week') using each of the 10 major types of medications asked about in the survey, with the sub-diagnostic group at an intermediate level of use for all medication types compared to the other two groups (Table 4).

To explore whether the observed increased healthcare utilisation among sub-diagnostic individuals compared to the non-GI group was related to particular types of symptoms, we calculated the mean percentage of sub-diagnostic individuals with each of the 24 key GI symptoms at DGBI diagnostic frequency level who reported visiting doctors frequently (at least once a month) and who reported having ever consulted a doctor about a bowel problem respectively. As seen in Table S9, people with sub-diagnostic symptoms of accidental stool leakage, epigastric pain/burning, nausea or belching were the most likely to report visiting doctors at least once a month. Those with sub-diagnostic symptoms of epigastric pain/burning, rectal pain or pressure or abdominal pain were most likely to have ever visited a doctor for a bowel problem (Table S10).

3.8 | Family history of organic GI disorders

The Rome IV Diagnostic Questionnaire contains red-flag symptom questions about a history of GI cancer (cancer of the oesophagus,

TABLE 4 Percentage of survey respondents in the three study groups reporting frequent doctor visits, history of consulting a doctor for a bowel problem and using different classes of medications regularly.

	% (95% CI)		
	Non-GI group	Sub-diagnostic group	DGBI group
Visits to doctors			
Frequent visits to doctors (at least once a month)	7.2 (7.2–7.2)	10.4 (10.3–10.4)	15.0 (15.0–15.0)
History of having ever consulted a doctor for a bowel problem	18.7 (18.1–19.3)	27.8 (27.0–28.6)	45.1 (44.0–45.8)
Types of medications used regularly (at least weekly)			
For constipation	1.7 (1.5–1.9)	4.3 (4.0–4.6)	13.1 (12.71–13.6)
For diarrhoea	1.4 (1.2–1.6)	4.2 (3.9–4.6)	7.8 (7.5–8.2)
For nausea	1.0 (0.8–1.1)	3.1 (2.8–3.4)	6.7 (6.4–7.0)
For heartburn or acid reduction	8.8 (8.3–9.2)	16.0 (15.4–16.7)	27.8 (27.2–28.4)
Prescription pain medication	9.3 (8.8–9.7)	14.6 (14.0–15.2)	21.9 (21.3–22.4)
Pain medication not prescribed by a doctor	12.0 (11.5–12.5)	19.2 (18.5–19.8)	28.8 (28.2–29.4)
Medication for gas or bloating	2.9 (2.7–3.2)	6.9 (6.5–7.4)	14.7 (14.2–15.2)
Medication for anxiety	3.9 (3.6–4.2)	6.5 (6.1–6.9)	13.1 (12.7–13.6)
Medication for depression	4.0 (3.7–4.3)	6.6 (6.2–7.0)	12.3 (11.9–12.8)
Medication for sleep	4.7 (4.4–5.1)	7.0 (6.6–7.5)	12.9 (12.4–13.3)

Note: All three comparison groups were significantly different for frequency of doctor visits, history of consulting doctors for bowel problems and for every type of medication in the table at $p < 0.0001$ on overall Chi-square tests and on pairwise post hoc tests with Bonferroni adjustment for multiple comparisons.

stomach or colon), inflammatory bowel disease (Crohn's disease or ulcerative colitis) and coeliac disease in the immediate family (parents, brothers or sisters). We compared the three study groups on their responses to these questions to explore potential differences in the family history of GI disorders in a limited way. The prevalence of self-reported family history of GI cancers was not significantly different between the non-GI and sub-diagnostic groups: 7.7% (7.3–8.1%) vs. 8.1% (7.6–8.6). However, individuals in the DGBI group reported a GI cancer history at an elevated compared to the other groups, or 11.2% (10.8–11.6); $p < 0.0001$. People in the sub-diagnostic group reported inflammatory bowel disease family history more often than the non-GI group: 3.9% (3.6–4.2) vs. 2.8% (2.6–3.0). The DGBI group had even more prevalent history of inflammatory bowel disease in the family, or 6.7% (6.3–7.0); all three groups different at $p < 0.001$ level. Coeliac disease family history was reported by 3.0% (2.7–3.3) of sub-diagnostic individuals and this was similar, or 3.2% (2.9–3.3), among DGBI individuals. However, at 1.7% (1.5–1.9), the prevalence was significantly lower ($p < 0.0001$) in the non-GI group compared to each of the other groups.

3.9 | Prevalence of diabetes diagnosis

As diabetes can have various physiological effects that disturb GI functions and can cause GI symptoms, and the study survey collected data on self-reported history of diabetes diagnosis by a physician, we assessed differences in diabetes prevalence between the three comparison groups. The diabetes prevalence was not different between the non-GI and sub-diagnostic groups, or 6.6% (6.2–7.0) versus 6.0% (5.6–6.4), but was significantly higher ($p < 0.01$) in the DGBI group compared to the other groups, or 7.4% (7.0–7.8).

3.10 | Non-gastrointestinal bodily symptoms

All three study groups were significantly ($p < 0.0001$) different from each other in their mean number of non-GI symptoms on the PHQ-15 questionnaire that had bothered them at all in the past 4 weeks: non-GI group 2.78 (SD = 2.12), sub-diagnostic group 3.97 (SD = 2.31) and the DGBI group 5.57 (SD = 2.39). The three groups were also significantly different in the percentage of people bothered at all by each of the 11 individual symptoms in the past 4 weeks (see Table S11).

4 | DISCUSSION

The findings presented in this paper demonstrate that a substantial proportion of the global adult population, or about one in every four people, has frequent gastrointestinal symptoms despite not meeting Rome IV criteria for any DGBI and having no history of organic GI diagnoses. This sub-diagnostic group has relatively similar prevalence (22%–30%) across different regions of the world. It is about equally common among males and females, but it becomes steadily less prevalent with increasing age across the adult age spectrum, along with a similar decline in DGBI prevalence.

Sub-diagnostic GI symptoms are associated with significantly poorer general quality of life, measurable impairment in work productivity and life activities and increased anxiety and depression symptoms. In all these respects, the sub-diagnostic group is less adversely affected on average than people with DGBI. Nonetheless, the size of the negative effect on life and well-being borders on moderate size for the sub-diagnostic group as a whole, and is firmly in the moderate effect size range for the majority of sub-diagnostic individuals with multiple frequent GI symptoms, as well as for those who have at least one chronic sub-diagnostic symptom. Our findings also indicate that the different sub-diagnostic GI symptoms vary substantially in the extent of their adverse impact. Epigastric pain/burning, abdominal pain, faecal incontinence and nausea seem to be the symptoms most strongly associated with impaired quality of life, and our data indicate that they likely drive healthcare seeking among people in the sub-diagnostic group more than other symptoms (see Tables S5–S8).

Although a single time-point population assessment with a survey cannot establish causation, we believe that it is probable that the level of GI symptoms in the sub-diagnostic group is a direct contributor to the observed association with impaired well-being. This is suggested compellingly by the stepwise increase in QoL impairment and psychological symptoms seen in our comparisons of population sub-groups with no frequent GI symptoms (the non-GI group) versus those with one sub-diagnostic symptom, multiple sub-diagnostic symptoms and DGBI. Our effect size data show that the effect size of reduced well-being compared to people without any frequent GI symptoms is small, medium and large, respectively, for the latter three groups.

A noteworthy finding in our study was that only a minority (22.5%) of people in the sub-diagnostic GI group had sub-diagnostic symptoms that had become chronic; that is, that had started more than 6 months ago. Since the 24 different GI symptoms assessed in our study were those that characterise DGBI, and DGBI diagnosis requires 6 months duration since the onset of symptoms, we believe that this is an indication that the Rome IV diagnostic criteria generally capture individuals with frequent digestive tract symptoms very effectively once their symptoms become chronic. The common chronic and frequent GI symptoms of the sub-diagnostic group, which were biliary-type pain, lump in throat, heartburn and urgency to rush to the toilet (Table 3), may highlight a few areas where the Rome IV diagnostic criteria need improvement in order to comprehensively classify persistent troublesome GI symptoms in the population.

The primary importance of our study lies in the fact that we have identified a sizeable segment of the population in societies around the world with a high frequency of current gastrointestinal symptoms that affect their lives, which has been largely overlooked in GI research and clinical care. The symptoms of this group probably should not be viewed as representing disease entities,

but nevertheless, these persons have symptoms that need to be identified and possibly treated. Unlike DGBI, the symptoms that land people in this category are not necessarily chronic since we did not require a 6-month duration of the symptoms for inclusion in the sub-diagnostic group. However, this segment of the population shares a broad set of characteristics with people who have DGBI. Like those with DGBI, individuals with sub-diagnostic GI symptoms have increased anxiety and depression symptoms, an excess of non-GI bodily symptoms, elevated concerns about their GI functioning and commonly report that stress impacts their bowel functioning. These similarities are perhaps not surprising, considering that the symptom questions that defined this group in our analyses are designed to identify DGBI. However, they also suggest that some of the intervention and management approaches that are effective for helping the less severe cases of DGBI may be useful for the sub-diagnostic group as well. For many of them, self-management approaches such as diet adjustment, probiotics or fibre supplementation might be the most appropriate ways to reduce these troublesome symptoms. This is supported by the fact that we found constipation and diarrhoea symptoms, which often can be addressed effectively with such methods in the less severe cases, to be the most common types of sub-diagnostic symptoms. For many sub-diagnostic individuals, lifestyle changes to reduce stress or increase physical activity would likely also reduce their symptoms. It seems clear from our data on the broad adverse impact associated with having sub-diagnostic symptoms that many people in this group in society, especially those with multiple frequent symptoms, would benefit from such intervention approaches. Further research is needed to examine which interventions are most suitable for reducing the symptoms of this sub-diagnostic group, as therapies may have different degrees of effectiveness for this group than in DGBI individuals with corresponding symptoms. This should include studies examining whether specific psychological or social factors are associated with having sub-diagnostic GI symptoms, which might point to utility for particular brain–gut behavioural interventions or self-help methods for such individuals.

However, this raises the question of how to identify or reach sub-diagnostic individuals to offer them guidance and support if they are not diagnosable as having a digestive disease. One way to address this might be public health education efforts to help the public better understand when GI symptoms are frequent enough to warrant addressing through self-management approaches, which methods work well for which symptoms and when seeking medical consultation is more appropriate. It may also be worth developing an efficient screening questionnaire for primary and secondary care settings to identify people with a sub-diagnostic level of GI symptoms routinely. This may be of value because one of the likely main reasons that GI symptoms, even when frequent, are not identified in healthcare is that there are so many to consider, so specific individual symptoms do not become a focus of medical concern. A quick and comprehensive symptom screening for frequent GI symptoms might facilitate more reliably providing people with the advice and support they need to reduce their frequent GI symptoms when visiting healthcare for general purposes. The Rome Foundation has in part tried to address this concern by establishing clinical criteria for Rome IV diagnosis[17] to be used in practice settings. The clinical criteria permit a diagnosis even when the symptoms do not meet the 6-month duration or the frequency criteria for a formal Rome IV diagnosis, as long as the patient considers the symptoms bothersome enough that they interfere with daily activity, or the patient desires treatment.

The analyses presented here have several notable strengths. One of these is the quality and scope of the RFGES survey sample used for this assessment. It was optimal for our purpose due to the very large sample size, broad participation by all age groups, equal sex proportions and nationwide samples from a large number of different countries on six continents, rendering it generally representative of gastrointestinal symptoms in the global adult population.[4] Another strength was the use of the entire Rome IV Diagnostic Questionnaire,[3] which allowed us to evaluate the frequency of 24 key GI symptoms encompassing nearly all common digestive tract symptoms. We also believe that our reliance on the Rome IV DGBI diagnostic frequency cut-offs for each symptom in our assessment added strength to our analyses, as these have been determined by leading experts in disorders in each anatomical region of the gastrointestinal tract, and therefore helped to ensure the clinical relevance of the specific symptom levels that we used to define the sub-diagnostic group.

The main limitations of this work apply to large epidemiologic population surveys in general. The people in the survey sample could not be medically investigated, and most of them had not visited doctors because of the gastrointestinal symptoms we assessed. Therefore, some of the symptoms in the sub-diagnostic group might be due to diagnosable organic disorders if they had been clinically evaluated. However, considering that organic GI disorders are much less prevalent than the DGBI, and our method assessed the presence of the latter comprehensively, the size of the sub-diagnostic group in our analyses was likely not substantially biased by this. Furthermore, all information collected was by self-report, which may have affected the accuracy of data such as history of medical diagnoses. Another limitation was that some groups of individuals in every society are hard to reach via Internet surveying and they are therefore under-represented in online surveys. This includes the poorest people, the homeless, the most rural and the oldest, all of whom typically have more limited Internet access than the rest of the population. Additionally, illiterate people, those with cognitive impairment and immigrants who are not fluent in the languages used in the surveys are also unable to participate in Internet surveys. However, as we have no reason to believe that these sub-groups have GI symptom levels different from their demographic peers in the same communities, it seems unlikely that this affected the overall results of our analyses in important ways.

Another limitation of this study is that data were not collected in the survey on some potential factors that could be modulators of

GI symptom amounts and therefore relevant to having, or not having, sub-diagnostic frequency levels of symptoms; for example, such factors might include race or ethnicity, smoking or alcohol use, income level or details of diet. Furthermore, the survey did not obtain some data relevant to the effects of symptoms on individuals that might have been valuable for better understanding of the sub-diagnostic group and its differences from the comparison groups, such as ratings of intensity or severity, bothersomeness and life interference for each of the 24 individual GI symptoms. Future studies of individuals with sub-diagnostic symptoms would do well to examine those variables in order to better characterise the personal significance and impact of sub-diagnostic GI symptoms.

In conclusion, we found that a substantial proportion of the adult population has sub-diagnostic GI symptoms associated with comorbidities and impairment in quality of life. Many of those individuals would likely benefit from treatment of their symptoms, but are currently unidentified. Therefore, we believe that further work should be devoted to understanding the nature of this group that we have delineated in this study. Much more needs to be understood about them, including what interventions or self-management methods are helpful for their troublesome symptoms, and what happens to those symptoms over time. We also need to know to what extent this group remains sub-diagnostic, and to what degree they transition into and out of diagnosable DGBI entities. This can only be addressed in prospective and longitudinal studies. This large group of people troubled by frequent GI symptoms has been mostly overlooked in GI research that traditionally focuses on specific disease entities. This is a blind spot that needs to be addressed in our field, to advance scientific understanding of GI functioning and to improve the overall health of the population.

AUTHOR CONTRIBUTIONS

Olafur S. Palsson: Data curation; writing – original draft; conceptualization; methodology; investigation; formal analysis; writing – review and editing; project administration. **Jan Tack:** Conceptualization; writing – review and editing; methodology. **Douglas Drossman:** Conceptualization; writing – review and editing; methodology. **Boris Le Nevé:** Conceptualization; writing – review and editing. **Laurent Quinquis:** Conceptualization; writing – review and editing. **Rim Hassouna:** Conceptualization; writing – review and editing. **Johannah Ruddy:** Conceptualization; writing – review and editing; project administration. **Carolyn B. Morris:** Conceptualization; writing – review and editing; formal analysis. **Ami D. Sperber:** Conceptualization; writing – review and editing. **Shrikant I. Bangdiwala:** Conceptualization; writing – review and editing; supervision; methodology. **Magnus Simrén:** Writing – review and editing; conceptualization; methodology.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare in regard to this manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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