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Increased risk of irritable bowel syndrome in university students due to gastrointestinal symptom-specific anxiety

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Background: Gastrointestinal symptom-specific anxiety (GSA) has been reported to impact symptom severity in irritable bowel syndrome (IBS), suggesting that GSA may be an important treatment outcome. The present study explored whether higher levels of GSA were associated with increased risk of having IBS, and whether individuals with IBS were at greater risk for severe gastrointestinal (GI) symptoms.

Methods: Participants comprised 1156 university students. The Rome III modular questionnaire was used to assess for IBS. GSA was measured using the Japanese version of the Visceral Sensitivity Index (VSI). IBS-SI was used to assess severity of GI symptoms. Data were analyzed using univariate and multivariate logistic regression analysis.

Results: The prevalence rate of IBS (provisional diagnosis, based on Rome III questionnaire responses) was 21%. Logistic regression analysis was performed using the VSI cutoff point as the independent variable, and the presence or absence of IBS as the dependent variable. Results indicate that for individuals above the VSI cutoff point, the adjusted odds ratio for having IBS was 2.64 (95% CI: 1.87-3.71). Furthermore, results indicate that in participants with high GSA, adjusted odds ratios for severity of IBS symptoms were 0.44 (95% CI: 0.33-0.58) for subclinical, 1.15 (95% CI: 0.90–1.46) for mild symptoms, 2.19 (95% CI: 1.57–3.07) for moderate symptoms, and 5.63 (95% CI: 2.24–14.15) for severe symptoms.

Conclusion: Higher VSI scores were associated with having risk factors for IBS and greater severity of IBS symptoms.

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Key words: Irritable bowel syndrome, visceral sensitivity index, gastrointestinal symptom-specific anxiety

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Introduction

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract, primarily characterized by abdominal pain and constipation in the absence of an organic disease.[1] Prevalence is reportedly 5–11% in most developed countries.[2] Epidemiological research on IBS in Japan has found the disease to be most common in men and women in their 20s (14% and 22%, respectively).[3] Notably, its incidence dramatically increases in Japanese youths in their late teenage years; it has been reported to affect 21–26% of university students. [4-5]

IBS negatively affects an individual's quality of life (QOL), and it has a substantial impact on healthcare costs. [6-7] Its pathology can be divided into three major categories: gastrointestinal dysmotility,[8-9] hypersensitivity to visceral sensations,[10-11] and abnormal psychology.[12-14] The third category refers specifically to anxiety-related symptoms due to

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psychosocial stress experienced by IBS patients, which cause gastrointestinal symptoms to worsen.[15-16] This exacerbation of gastrointestinal symptoms can be attributed to elevated gastrointestinal-specific anxiety (GSA), which can be measured using the visceral sensitivity index (VSI).[17-18] GSA is defined as "the cognitive, affective, and behavioral response to fear of gastrointestinal sensations, symptoms, and the context in which these visceral sensations and symptoms occur."[17] GSA is associated with hyperactivity of the amygdala.[19-20] This brain region is activated via the insular cortex, the prefrontal cortex, and the anterior cingulate gyrus, leading to exacerbated gastrointestinal symptoms.[20] When individuals with IBS perform avoidance behaviors in response to situations that elicit GSA, they exhibit hypervigilance and attentional bias toward visceral sensations, and become sensitive to even low-level stimuli. [21]

Research to date suggests that GSA contributes to both the onset and symptomatic exacerbation of IBS, but this relationship has never been sufficiently investigated in university students, a population whose age puts members at particular risk for developing IBS. One instrument for measuring GSA is the VSI. This scale can measure psychological dysfunction in IBS patients, and can also provide an endpoint for assessing the efficacy of IBS treatment. The present study investigates whether GSA is a risk factor for developing IBS, and whether it is associated with IBS symptom severity in university students. This study explored the following two hypotheses:

Hypothesis 1. GSA is a risk factor for IBS.

Hypothesis 2. GSA is associated with more severe IBS symptoms.

Our findings suggest the importance of GSA as both an intervention target and an endpoint when evaluating IBS-related therapies, making it relevant in terms of both IBS symptoms and QOL.

Materials and Methods

Procedure

Questionnaire surveys were administered to university students during lecture classes from May 15, 2012, to Nov. 22, 2013. Participation was voluntary, and participants were not randomly selected. Consent was obtained after the purpose of the study and ethical considerations were explained verbally. Students were also verbally informed that non-participation would not result in any academic or other disadvantage. Only responses from students who provided consent were included in analysis.

Participants

There were 1300 respondents in total. We focused on students begning first year at young university student between 2012-2013. Study exclusion criteria were as follows: aged 26 years or older (N =17), (2) not having Japanese as their first language (N = 51), (3) incomplete or not responses at questionnaires (N = 76). This resulted in data from 1156 students (mean age 18.9 ± 0.9 years) being analyzed; of these, 237 (21%) met Rome III criteria for a diagnosis of IBS (male: N = 79, female: N = 158).

Measures

(Note: This study used the Japanese versions of all measures listed below.)

Rome III Modular Questionnaire

The Rome III modular questionnaire is a self-report assessment tool developed to screen patients for IBS according to Rome III criteria.[22] For a diagnosis of IBS, the Rome III criteria stipulate that a person must have (a) recurrent abdominal pain or discomfort for at least three days per month in the last three months, along with at least two of the following: (b) improvement of pain or discomfort with defecation, (c) symptom onset associated with change in defecation frequency, or (d) onset associated with change in stool form or appearance. The reliability and validity of this instrument has been verified. In the present study, participants whose questionnaire responses indicated they met Rome III criteria were treated as having IBS ("IBS-positive").

Visceral Sensitivity Index (VSI)

The VSI is a 15-item scale used to measure GSA.[18] Respondents rate the applicability of each item on a six-point scale, from 1 (strongly agree) to 6 (strongly disagree). All items are then reverse-scored (0–5 points) and summed: scores range from 0 points (no GI-specific anxiety) to 75 points (severe GI-specific anxiety).

IBS Severity Index (IBS-SI)

The IBS-SI is a self-report scale for assessing the severity of gastrointestinal symptoms associated with IBS. [23] It is a 5-item scale, and overall scores can range from 0 to 500 points. Symptom severity is classified as subclinical (0 to 74 points), mild (75 to 174), moderate (175 to 299), or severe (300 to 500).

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item self-report scale developed to assess anxiety and depression severity in patients with physical symptoms.[24] It consists of an anxiety and a depression subscale (HADS-A and HADS-D, respectively), containing seven items each. Respondents answer each item on a four-point scale ranging from 0 to 3. HADS-A and HADS-D subscale scores range from 0 to 21 points. The optimal cut-off points as 'caseness' was defined a score of 8 or greater on both HADS-A and HADS-D. [25]

Ethics

This study was conducted with the approval of the Ethics Committee of the Nagasaki University Graduate School of Biomedical Sciences, the research institution of the principal investigator (approval number: 12053008).

Data analysis

Statistical analysis was performed using SPSS 20.0 for Windows. Basic statistics are presented as mean ± standard deviation (SD), median, and interquartile range (IQR). The normally distributed of VSI was rejected by the Shapiro-Wilk normality test ($p < 0.05$). Therefore, Wilcoxon signed-rank test and chi-squared test were used to determine to significance for between IBS-positive and IBS-negative group differences. Wilcoxon signed-rank test and chi-squared test were applied for continuous and categorical variables, respectively. In addition, ROC analysis was performed to determine a cut-off score for the VSI, in order to ascertain the presence or absence of associations between GSA and IBS status. The optimal cut-off points of VSI determined that is calculated a maximum value of Youden index (sensitivity + (specifity-1)).[26] The Youden index, which maximizes the vertical distance from line of equality to the point on the receiver operating characteristic curve, was used to find the optimal threshold points. Next, several multiple logistic regression analyses were conducted using this cut-off value to examine whether students with VSI scores above the cut-off were at greater risk for having IBS or for having more severe IBS symptoms. Odds ratio (OR), 95% confidence intervals (CIs) and p value were calculated using logistic regression analysis. Statistical significance was defined as $p < 0.05$.

Results

Demographic data of participants are listed in Table 1. The mean age was not significance between IBS-positive and IBS-negative group ($z = -1.22$, $p = 0.219$). The prevalence of IBS as defined by the Rome III questionnaire was 21%. Chi-squared test showed that the portion of female was higher than male in the IBS-positive group, while the portion of female was lower than male in the IBS-negative group ($x^2 = 61.09$, $df = 1$, $p < 0.001$). Wilcoxon signed-rank test showed that IBS-positive individuals had significantly higher mean scores on the VSI ($z = 9.12$, $p < 0.001$), IBS-SI ($z = 12.69$, $p < 0.001$), and HADS-A ($z = 9.12$, $p = 0.014$) than IBS-negative participants. No significant difference was observed between the groups' mean HADS-D scores ($z = -0.86$, $p = 0.385$).

Figure 1 shows the results of ROC analysis. The probability of being classified as IBS-positive was associated with a score of 16 or greater on the VSI, with a corresponding sensitivity of 0.63, a false positive rate (i.e., 1 - specificity) of 0.33, and an AUC of 0.69. In addition, maximized Youden index (J = 0.296) showed that optimal cut-off was 16 on the VSI score.

Multiple logistic regression analysis was conducted with GSA severity (i.e., VSI score above ("high GSA") or below ("low GSA") the cutoff value) as the independent variable, and provisional IBS diagnosis (as described in the Methods section) as the dependent variable. Results are shown in Table 2. The crude OR for being IBS-positive among participants in the high GSA group was 3.40 (95% CI: 2.37–4.33) versus the low GSA group, which means that students with a VSI score above the cutoff value were at significantly greater risk for having IBS. The same analysis was then performed again, with age, sex, IBS-SI, HADS-A and HADS-D subscores as moderator variables. Results revealed that students with high GSA were at significantly greater risk of having IBS, with an adjusted OR of 2.64 (95% CI: 1.87–3.71).

Next, multiple logistic regression analysis was conducted with IBS symptom severity (i.e., subclinical, mild, moderate, or severe, based on IBS-SI score) as the independent variable, and GSA severity (i.e., high or low GSA, based on VSI score) as the dependent variable. Results are shown in Table 3.The crude OR for high GSA in the relation to each classification of the IBS symptoms were as follows: 0.32 (95% CI: 0.24-0.41) for subclinical, 1.06 (0.90–1.46) for mild, 3.09 (2.28–4.21) for moderate, and 7.33 (3.00–17.91). The same analysis was then run again, this time introducing age, sex, IBS status, HADS-A and HADS-D subscores as moderator variables. The corresponding adjusted odds ratios for classification of the IBS symptoms were 0.44 (95% CI: 0.33-0.58) for subclinical, 1.15 (0.90–1.46) for mild status, 2.19 (1.57–3.07) for moderate status, and 5.63 (2.24–14.15) for severe status, indicating that a high VSI score is associated with more severe pathology in IBS symptoms.

Table 1. Characteristics of the participants in this study

Variables	All participants (N = 1156)				IBS-positive (N = 237)				IBS-negative (N = 919)				P value
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	
Age	18.8 ± 0.9		19	18-19	18.7 ± 1.0		19	18-19	18.8 ± 0.9		19	18-19	0.219
Sex (% male)	55.8				33.3		-	-	66.7		-	-	< 0.001
IBS-positive (%)	21				-		-	-	-		-	-	-
VSI	14.7 ± 13.4		22	4-22	20.5 ± 12.5		20	11-28	13.2 ± 13.2		10	3-19	< 0.001
IBS-SI	107.3 ± 86.1		95	35-160	166.9 ± 73.5		170	110-212	91.9 ± 82.4		80	20-140	< 0.001
HADS-A	9.9 ± 4.3		9	6-13	10.4 ± 4.1		10	7-13	9.7 ± 4.3		9	6-13	0.014
HADS-D	10.1 ± 3.0		10	8-12	9.9 ± 2.9		10	8-12	10.1 ± 3.0		10	8-12	0.385

Note: Data are expressed as mean ± SD, median, IQR. Data were analyzed by Wilcoxon signed-rank test and x^2 test: IBS-positive vs. IBS-negative. Abbreviations: SD = standard deviation; IQR = interquartile range; IBS =irrtable bowel syndrome; VSI = visceral sensitivity index; IBS-SI = irritable bowel syndrome severity index; HADS-A and HADS-D = subscale of the hospital anxiety and depression scale.

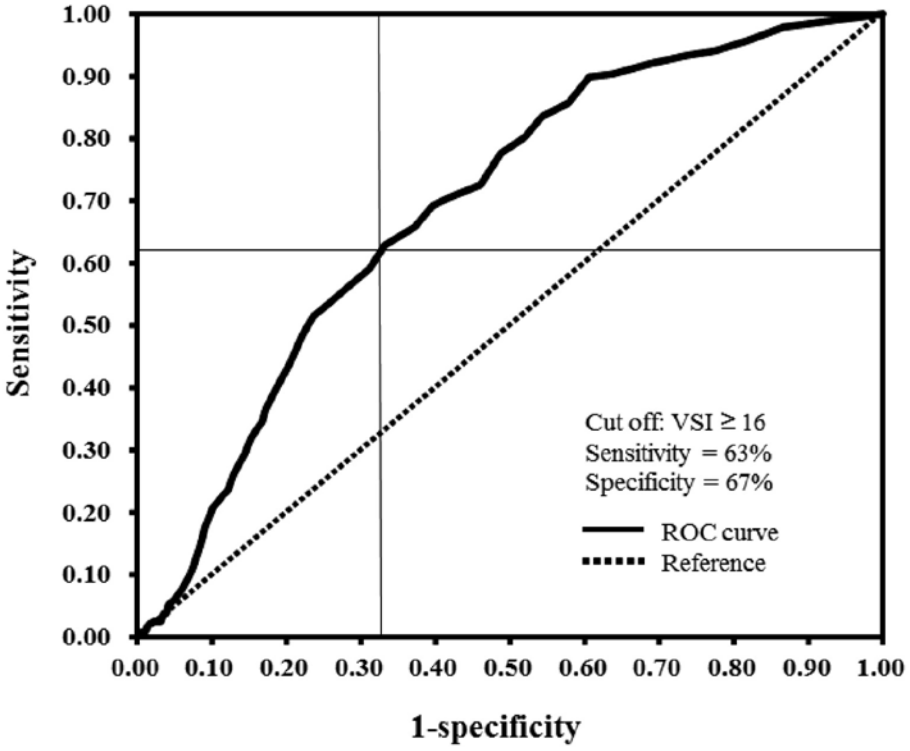

Figure 1. Receiver operating characteristics (ROC) curve for VSI scores obtained from all participants, area under the ROC curve (AUC) 0.69, P < 0.001, Youden index (J) = 0.296.

Table 2. Univariate and multivariate logistic analysis of the associations between IBS status and severity symptoms for high GSA

Variables		IBS-positive / IBS-negative	Univariate model			Multivariate model		
			Crude OR	95%CI	P value	Adjusted OR^a	95%CI	P value
Age (years old)								
	10s (18-19)	203/793	1.00	-	-	1.00	-	-
	20s (20-25)	34/126	1.08	(0.70-1.58)	0.800	1.13	(0.71-1.80)	0.580
Sex								
	Male	79/563	1.00	-	-	1.00	-	-
	Female	158/353	3.20	(2.37-4.33)	< 0.001	2.68	(1.93-3.74)	< 0.001
GSA								
	Low GSA	305 / 614	1.00	-	-	1.00	-	-
	High GSA	149 / 88	3.40	(2.53-4.59)	< 0.001	2.64	(1.87-3.71)	< 0.001
IBS-SI								
	subclinical	26/452	1.00	-	-	1.00	-	-
	mild	102/328	1.36	(1.01-1.82)	0.037	4.56	(2.86-7.26)	< 0.001
	moderate	98/117	4.88	(3.53-6.74)	< 0.001	9.89	(5.99-16.34)	< 0.001
	severe	11/22	1.98	(0.94-4.15)	0.068	5.46	(2.28-13.08)	< 0.001
HADS-A								
	noncaseness	71/317	1.00	-	-	1.00	-	-
	caseness	166/602	1.23	(0.90-1.67)		0.88	(0.60-1.29)	0.523
HADS-D								
	noncaseness	54/180	1.00	-	-	1.00	-	-
	caseness	183/739	0.82	(0.58-1.16)	0.275	0.68	(0.60-1.29)	0.077

Note: ^{a}OR adjusted for age, sex, IBS-SI, HADS-A and HADS-D. Abbreviations: CI = confidence intervals; OR = odds ratio; IBS = irritable bowel syndrome; GSA = gastrointestinal symptom-specific anxiety; High GSA (VSI score of ≥ 16 points); Low GSA (VSI score of ≤ 15 points); IBS-SI = irritable bowel syndrome severity index; Subclinical, Mild, Moderate, and Severe = classification of IBS severity; HADS-A and HADS-D = subscale of the hospital anxiety and depression scale.

Table 3. Univariate and multivariate logistic analysis of the associations between GSA and IBS-SI

Variables		Classification of IBS severity	Univariate model			Multivariate model		
			Crude OR	95%CI	P value	Adjusted OR^a	95%CI	P value
IBS-SI								
Subclinical								
	Low GSA	362/340	1.00	-	-	1.00	-	-
	High GSA	116/338	0.32	(0.24-0.41)	< 0.001	0.44	(0.33-0.58)	< 0.001
Mild								
	Low GSA	252/450	1.00	-	-	1.00	-	-
	High GSA	178/276	1.06	(0.81-1.37)	0.659	1.15	(0.90-1.46)	0.255
Moderate								
	Low GSA	82/620	1.00	-		1.00	-	-
	High GSA	133/322	3.09	(2.28-4.21)	< 0.001	2.19	(1.57-3.07)	< 0.001
Severe								
	Low GSA	6/696	1.00	-	-	1.00	-	-
	High GSA	27/427	7.33	(3.00-17.91)	< 0.001	5.63	(2.24-14.15)	< 0.001

Note: ^{a}OR adjusted for age, sex, IBS status, HADS-A and HADS-D. Abbreviations: CI = confidence intervals; OR = odds ratio; IBS = irritable bowel syndrome; GSA = gastrointestinal symptom-specific anxiety; High GSA (VSI score of ≥ 16 points); Low GSA (VSI score of ≤ 15 points); IBS-SI = irritable bowel syndrome severity index; Subclinical, Mild, Moderate, and Severe = classification of IBS severity; HADS-A and HADS-D = subscale of the hospital anxiety and depression scale.

Discussion

We consider the hypotheses of the present study in turn. Hypothesis 1 was supported: students with a VSI score above the ROC cutoff value were more likely to have IBS than students with a score below it. Hypothesis 2 was also supported: students with a VSI score above the ROC cutoff value were at risk for symptomatic exacerbation of IBS symptoms. A discussion of the research findings supporting these two hypotheses follows.

Previous studies have shown that IBS patients can experience worsening gastrointestinal symptoms not only due to exogenous, psychosocial stress, but also due to endogenous stress triggered by GSA.[20] The present study demonstrated that GSA may act as a psychological stressor in university students, as well, resulting in exacerbation of gastrointestinal symptoms. This finding supports the hypothesis of a previous study, which focused on developing the VSI as an instrument capable of measuring GSA.[17] Moreover, our findings show that university students with VSI scores above the proposed cut-off value are more likely to have IBS than students with scores below this value. This trend was significant, and persisted even after controlling for anxiety and depression severity, as measured by the HADS. These findings indicate that the GSA may be a promising therapeutic marker when treating IBS in university students.

In one human study, IBS patients exhibited stronger activation of emotion-related brain regions associated with visceral sensations following colonic stimulation using a barostat than healthy adults.[11, 27-28] In addition, when IBS patients perform avoidance behaviors in response to situations that elicit GSA, they exhibit hypervigilance and attentional bias towards visceral sensations, and become sensitive to even low-level stimuli.[21] This creates a vicious cycle: the repeated appearance of gastrointestinal symptoms elicits anxiety, which in turn further exacerbates symptoms, and so on.

We hope that the results of the present study will lead to GSA being included as a treatment endpoint in more interventions, whether they involve pharmacological treatments or non-drug approaches, such as behavioral, psychological, and nutritional therapies. Notably, recent years have seen psychotherapy, specifically cognitive-behavioral therapy, conducted with the goal of reducing GSA. Reports on cognitive-behavioral therapy to date have confirmed the approach to be effective in reducing GSA and in improving gastrointestinal symptom severity and QOL.[30-31]

Three limitations of the present study should be noted. The first is that this study was conducted at a single institution, a university located in a medium-sized city in Kyushu, in western Japan. Generalizability of findings is thus limited. The second is that this was a questionnaire-based study. Because IBS diagnoses were not made or confirmed by physicians, it is possible that the disease was over-diagnosed. The third limitation is that as a cross-sectional survey, cause-effect relationships cannot be inferred from our results.

In conclusion, our findings indicate that people with elevated GSA—specifically, a score of 16 points or higher on the VSI—are more likely to have IBS, as well as more severe gastrointestinal symptoms.

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Disclosure Statement

All authors declare that they have no conflicts of interest.

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