

☐ ORIGINAL ARTICLE ☐

Depressive Symptoms and Coping Behaviors among Individuals with Irritable Bowel Syndrome in Japan

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Abstract

Objective Irritable bowel syndrome (IBS) is associated with a high prevalence of psychological disorders. Coping, which is used to manage stressful events, can have adaptive or maladaptive effects on a patient's health status. However, these coping behaviors have not been well studied in individuals with IBS. The association between the use of coping behaviors and the reported levels of depressive symptoms was examined in individuals with IBS.

Methods Among 993 volunteers (382 men and 611 women) who participated in the Iwaki Health Promotion Project in 2013, we included 58 subjects who fulfilled the Rome III criteria for IBS in our analysis. Coping behaviors were assessed using the Brief Scale for Coping Profile (BSCP). The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess the four dimensions of depressive symptoms (depressed affect, somatic symptoms, interpersonal problems, and lack of positive affect) and the prevalence of probable depression using a cut-off score of 16.

Results Among the 58 subjects with IBS, 22 (36.1%) exhibited probable depression. After adjustment for confounders, "active solution" was found to be significantly associated with somatic symptoms. Under the same conditions, "avoidance and suppression" was significantly associated with the CES-D total score, depressed affect, somatic symptoms, and (lack of) positive affect. There were no other significant relationships between depressive symptoms and the BSCP sub-scale scores.

Conclusion These findings indicate that coping behaviors may influence the experience of depressive symptoms among individuals with IBS. Psychological therapy may reduce depressive symptoms as well as the severity of IBS symptoms. Additional studies are needed to examine the relationships between coping behaviors and depressive symptoms using a longitudinal study design.

Key words: cross-sectional studies, coping behaviors, Japanese, irritable bowel syndrome, depressive symptoms

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder with a prevalence 3-20% based on the Rome III criteria (1-4). This functional bowel disease involves recurrent abdominal discomfort or pain associated with alterations in the bowel (5, 6). Although the etiology of IBS re-

mains elusive, there is support for the notion that a dysfunction of the brain-gut pathways contributes to the presentation of this disease (7). According to recent studies, up to 60% of IBS patients have psychiatric disorders such as depression, anxiety, and somatization (8, 9).

Although IBS is a non-life threatening disorder, chronic discomfort and pain place a heavy burden on patients with IBS. Stressful events have been shown to be significant pre-

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dictors of depressive symptoms, and coping behaviors can play an important role in individual well-being (10, 11). Coping has been described as a process in which cognitive or behavioral strategies are developed to manage specific internal and / or external sources of psychological stress (12, 13). To date, several studies have reported an association between coping behaviors and psychological symptoms among patients with IBS (14-16). Failure to cope with or adjust to stressful events may cause depression among patients with IBS. However, no studies have examined the potential link between coping behaviors and depressive symptoms among individuals with IBS in Japan.

In the present study, we aimed to investigate the prevalence of depressive symptoms and to assess the relationship between coping behaviors and depressive symptoms among individuals who were diagnosed with IBS according to the Rome III criteria. We hypothesized that passive coping behaviors, such as emotional expression, avoidance and suppression, would be associated with depressive symptoms.

Materials and Methods

Participants

This study included 58 individuals with IBS who were recruited from the local community. A total of 993 volunteers (382 men and 611 women) participated in the Iwaki Health Promotion Project in 2013. We included the subjects who fulfilled the Rome III criteria for IBS in our analysis (17). The characteristics of the study population have been reported previously (18). IBS was diagnosed based on the Japanese version of the Rome III Questionnaire, when a participant reported that they had experienced recurrent abdominal pain or discomfort for at least three days per month in the last three months together with two or more of the following conditions: 1) the alleviation of symptoms with defecation, 2) the onset of symptoms occurred in association with a change in the stool frequency and 3) the onset was associated with a change in the form (appearance) of the stool. The collection of data for the present study was approved by the ethics committee at the Hirosaki University School of Medicine, and all subjects provided their written informed consent before participating in this project. The patients' demographic data (age, sex, amount of education, and marital status) and medical history were obtained from self-reported questionnaires and interviews.

The assessment of depressive symptoms

The Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D) as administered to all of the participants to measure their depressive symptoms (19). The CES-D is a 20-item self-reported measure that focuses on the depressive symptoms that the patient experienced during the week prior to completing the questionnaire. The maximum score is 60, with higher scores indicating more severe depressive symptoms. Probable depression (CES-D

16 depression) was considered to be present when a subject reported a CES-D score of \geq 16.

Studies in which factor analyses were performed have found the 20-item CES-D to be a multidimensional instrument that measures as many as four correlated but distinct factors (19, 20). The four underlying factors were labeled by Radloff as follows: depressed affect, somatic symptoms, interpersonal problems, and (lack of) positive affect.

The assessment of coping behaviors

We employed the Brief Scale for Coping Profile (BSCP) to assess coping behaviors. The BSCP consists of 18 items rated on a 4-point scale (21, 22). The participants were asked to indicate the frequency at which they used the strategy described by a particular item, ranging from 1 (almost never) to 4 (very often) in stressful situations. The scale assesses an individual's ability to cope in response to daily stressful circumstances using six sub-scales, "active solution (AC)", "seeking help for a solution (S)", "changing mood (CM)", "emotional expression involving others (EE)", "avoidance and suppression (AV)", and "changing one's point of view (CV)". These six sub-scales reflected three different coping dimensions: problem-focused (AC and S), adaptive emotion-focused (CM and EE), and maladaptive emotion-focused (AV and CV) coping strategies. A high score on a certain sub-scale indicates that the respondent frequently selected that coping method.

Statistical analysis

The data are presented as the mean ± standard deviation. p values of <0.05 were considered to indicate statistical significance. Pearson's correlation was used to explore the relationships between the psychological variables. All variables with a p value of <0.10 on a Pearson's correlation analysis were subsequently analyzed via a multivariate regression analysis, which was performed to assess the relationship between depressive symptoms and coping behaviors. Regression analyses were adjusted for confounding factors (age, gender, level of education, and marital status). The data were analyzed using the PASW Statistics software program for Windows, version 23.0.

Results

The characteristics of the participants

The characteristics of the study subjects with IBS are shown in Table 1. Thirteen of the 58 (22.4%) cases were categorized as IBS with constipation (IBS-C) subtype, 9 (15.5%) were categorized as IBS with diarrhea (IBS-D) subtype, and 15 (25.9%) were categorized as mixed IBS (IBS-M) subtype. Among the 58 subjects with IBS, 19 (32.8%) exhibited CES-D 16 depression.

Table 1. Characteristics of the Subjects with Irritable Bowel Syndrome.

		n	%
Gender	Male	19	32.8
	Female	39	67.2
Married	Yes	37	63.8
	No	21	36.2
		Mean	±SD
Age(years)		49.9	17.5
Amount of education (years)		12.0	2.0
Depressive symptoms (CES-D score)		12.1	9.0
Depressed affect		3.3	3.4
Somatic symptoms		4.2	3.7
Interpersonal problems		0.5	1.0
(Lack of) Positive affect		4.1	2.9
Coping profile (BSCP score)		9.1	2.7
Active solution		8.1	2.9
Seeking help for solution		8.0	2.2
Changing mood		4.4	1.9
Emotional expression involving others		6.2	2.3
Avoidance and suppression		8.3	2.5
Changing a point of view		49.9	17.5

CES-D: Center for Epidemilogic Studies Depression Scale,

BSCP: Brief Scales for Coping Profile

Pearson's correlations between the psychological variables

Table 2 shows the correlations between depressive symptoms and the BSCP sub-scale scores. "Active solution" showed tended to be associated with somatic symptoms but did not reach statistical significance (p=0.096). "Seeking help for solution" almost showed a statistically significant association (p=0.052) with (lack of) positive affect." Avoidance and suppression" were significantly associated with the CES-D total score, depressed affect, somatic symptoms, and (lack of) positive affect.

The multiple regression analysis of the association between depressive symptoms and the BSCP subscale scores

Table 3 shows the results of the multiple regression analysis to determine the depressive symptoms that were associated with the BSCP sub-scale scores. After adjustment for confounders "active solution" was significantly associated with somatic symptoms. Under the same condition, "avoidance and suppression" was significantly associated with the CES-D total score, depressed affect, somatic symptoms, and (lack of) positive affect. There were no other significant relationships between depressive symptoms and the BSCP sub-scale scores.

Discussion

The present study investigated the prevalence of probable depression, as measured by the CES-D, and assessed the relationship between coping behaviors and depressive symptoms among individuals with IBS using a cross-sectional

study design. In this study, the prevalence of CES-D 16 depression among individuals with IBS was 32.8%. The prevalence of CES-D 16 depression in our study was within the range of previous results (16-39%) (2, 9, 23, 24). After adjustment for confounders, "active solution" coping behaviors were significantly associated with somatic symptoms. This association might indicate that the somatic symptoms of IBS evoke problem-focused coping strategies. Under adjusted conditions, "avoidance and suppression" coping behaviors were also significantly associated with the CES-D total score, depressed affect, somatic symptoms, and (lack of) positive affect. "Avoidance and suppression" coping behaviors are characterized by a tendency to escape or consciously push down any undesirable thoughts. This coping behavior has been reported to be associated with increased self-blame and to potentially lead to poor psychological adjustment (25).

To date, psychological distress has been thought to play a major role in IBS, although it remains to be determined how this distress is related to IBS and which of the two conditions (psychological distress or IBS) appears first. Recently, a bidirectional communication network between the central nervous system and the gastrointestinal tract has been suggested as a conceptual model of IBS. In the bottom-up model, brain functions are secondarily influenced by visceral symptoms from the gastrointestinal tract. Conversely, in the top-down model, psychological factors influence physiological factors, such as the motor, sensory, secretory, and immune functions of the gastrointestinal tract (7). Early life stressors such as maternal separation and sexual abuse have been reported to be associated with the development of IBS (26-28). Understanding the psychological problems of IBS patients could contribute to the development of effective treatments.

Previous studies have documented associations between coping behaviors and depressive symptoms among individuals with IBS. Pinto et al. first reported that IBS patients with depression tend to use predominantly negative coping styles, such as passivity, fatalism and escape-avoidance (29). Another study showed that higher levels of passive behavioral coping are associated with more severe depression among individuals with IBS (30). Stanculete et al. showed that IBS patients use problem-focused and avoidance-oriented coping strategies more frequently than healthy subjects (16). These researchers also clarified that the impact of IBS symptoms on health-related quality of life is mediated by irrational beliefs and avoidance-oriented coping. Furthermore, Grodzinsky et al. reported that IBS patients reported lower scores for positive self-esteem and coping ability assessed by sense of coherence than control (15).

Recently, a relationship between cognitive appraisal and depression has been reported in patients with IBS (31, 32). In cognitive behavioral therapy (CBT), a patient with depression whose coping behaviors are likely to promote depression is taught new coping skills in a structured manner (33). The present results indicating that "avoidance and

Table 2. Correlation between Depressive Symptoms and Coping Profile among Subjects with Irritable Bowel Syndrome.

	CES-D total score		Depressed affect		Somatic symptoms		Interpersonal problems		(Lack of) Positive affect		
Active solution	0.094		0.043		0.221	†	0.072		-0.058		
Seeking help for solution	-0.168		-0.184		-0.016		-0.108		-0.257	†	
Changing mood	0.140		0.108		0.174		0.037		0.079		
Emotional expression involving others	0.057		0.150		0.029		0.138		-0.078		
Avoidance and suppression	0.490	**	0.441	**	0.474	**	0.247	†	0.341	**	
Changing a point of view	0.193		0.141		0.215		0.130		0.125		

CES-D: Center for Epidemilogic Studies Depression Scale

Table 3. Multiple Regression Analysis with Predictive Variables.

	Multiple regression statistics					Multiple regression statistics					
	В	SE	β	t value	p value		В	SE	β	t value	p value
ACTIVE SOLUTION						SEEKING HELP FOR S	OLUTIO	ON			
Somatic symptoms						(Lack of) Positive affect					
Age	-0.02	0.03	-0.07	-0.49	0.630	Age	0.00	0.02	-0.01	-0.06	0.950
Gender	-1.85	1.13	-0.24	-1.63	0.109	Gender	-1.58	0.83	-0.26	-1.90	0.063
Amount of education	-0.15	0.26	-0.09	-0.60	0.552	Amount of education	-0.37	0.19	-0.26	-1.94	0.058
Married	-0.18	1.07	-0.02	-0.17	0.864	Married	0.80	0.78	0.14	1.02	0.311
Active solution	0.42	0.2	0.31	2.14	< 0.05	Seeking help for solution	-0.16	0.13	-0.16	-1.23	0.225
AVOIDANCE AND SUPI	PRESSIC	N									
CES-D total score						Depressed affect					
Age	0.01	0.07	0.02	0.16	0.870	Age	0.00	0.03	0.02	0.16	0.873
Gender	-2.60	2.43	-0.14	-1.07	0.289	Gender	-0.75	0.95	-0.11	-0.79	0.431
Amount of education	-0.90	0.56	-0.20	-1.62	0.112	Amount of education	-0.27	0.22	-0.16	-1.24	0.220
Married	1.49	2.27	0.08	0.66	0.515	Married	0.25	0.89	0.04	0.28	0.784
Avoidance and suppression	2.00	0.48	0.50	4.19	< 0.001	Avoidance and suppression	0.67	0.19	0.45	3.57	< 0.01
Somatic symptoms						Interpersonal problems					
Age	0.01	0.03	0.03	0.21	0.832	Age	-0.02	0.01	-0.28	-1.93	0.059
Gender	-0.69	1.03	-0.09	-0.67	0.505	Gender	0.21	0.27	0.11	0.78	0.440
Amount of education	-0.07	0.24	-0.04	-0.28	0.780	Amount of education	-0.17	0.06	-0.36	-2.68	0.010
Married	0.48	0.96	0.06	0.50	0.620	Married	0.01	0.26	0.00	0.02	0.981
Avoidance and suppression	0.77	0.20	0.48	3.82	< 0.001	Avoidance and suppression	0.10	0.05	0.23	1.83	0.073
(Lack of) Positive affect											
Age	0.02	0.02	0.10	0.72	0.476						
Gender	-1.37	0.78	-0.23	-1.77	0.083						
Amount of education	-0.39	0.18	-0.28	-2.22	0.031						
Married	0.76	0.73	0.13	1.05	0.300						
Avoidance and suppression	0.46	0.15	0.36	3.04	< 0.01						

CES-D: Center for Epidemilogic Studies Depression Scale

suppression" coping behaviors are associated with depressive symptoms may be utilized to design an evidence-based CBT approach to treat depressive patients with IBS. Current studies in clinical psychiatry have shown that CBT is as effective as antidepressant drug therapy in the treatment of patients with depression (34, 35). Furthermore, clinical evidence has indicated that CBT could improve IBS symptoms (36).

This study is associated with several notable limitations. First, the assessment of depressive symptoms was based on the CES-D rather than clinician-administered structured diagnostic interviews according to established criteria such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The second limitation of this study was the recruitment strategy, which involved the recruitment of individuals with IBS from the community. These individuals may not be representative of clinical IBS

patients. The severity of IBS or depressive symptoms among our participants might be lower than that among clinical IBS patients. Third, the data on several potential confounding factors were not obtained because of strict ethical considerations and a reluctance to share medical information. This limitation is important, as interpersonal relationships between family members and the severity of IBS symptoms may have influenced the results of this study. Finally, this study is limited by its cross-sectional design; thus, we cannot determine a causal relationship between the coping behaviors and the onset of depressive symptoms among the patients in our study population. A follow-up survey is needed to investigate these associations. In conclusion, "avoidance and suppression" was significantly associated with depressive symptoms. These findings indicate that coping behaviors may affect depressive symptoms among individuals with IBS. Furthermore, IBS patients might benefit

^{**}p<0.01, *p<0.05, †p<0.10

from psycho-educational interventions such as CBT, which are designed to assist them in reducing their "avoidance and suppression" behaviors when coping with the symptoms of their illness. Additional studies using a longitudinal study design are needed to examine the relationships between coping behaviors and depressive symptoms among IBS patients.

The authors state that they have no Conflict of Interest (COI).

References

- Miwa H. Prevalence of irritable bowel syndrome in Japan: internet survey using Rome III criteria. Patient Prefer Adherence 2: 143-147, 2008.
- Mykletun A, Jacka F, Williams L, et al. Prevalence of mood and anxiety disorder in self reported irritable bowel syndrome (IBS). An epidemiological population based study of women. BMC Gastroenterol 10: 88, 2010.
- Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. J Gastroenterol Hepatol 25: 691-699, 2010.
- Guo Y, Niu K, Momma H, et al. Irritable bowel syndrome is positively related to metabolic syndrome: a population-based cross-sectional study. PLoS One 9: e112289, 2014.
- Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. J Manag Care Pharm 19: 755-764, 2013.
- Fukudo S, Kaneko H, Akiho H, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome. J Gastroenterol 50: 11-30, 2015.
- Stasi C, Rosselli M, Bellini M, Laffi G, Milani S. Altered neuroendocrine-immune pathways in the irritable bowel syndrome: the top-down and the bottom-up model. J Gastroenterol 47: 1177-1185, 2012.
- Levy RL, Olden KW, Naliboff BD, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology 130: 1447-1458, 2006.
- Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 264: 651-660, 2014.
- 10. Sokratous S, Merkouris A, Middleton N, Karanikola M. The association between stressful life events and depressive symptoms among Cypriot university students: a cross-sectional descriptive correlational study. BMC Public Health 13: 1121, 2013.
- Sugawara N, Yasui-Furukori N, Sasaki G, et al. Coping behaviors in relation to depressive symptoms and suicidal ideation among middle-aged workers in Japan. J Affect Disord 142: 264-268, 2012.
- Folkman S, Lazarus RS. An analysis of coping in a middle-aged community sample. J Health Soc Behav 21: 219-239, 1980.
- 13. Folkman S, Lazarus RS, Dunkel-Schetter C, DeLongis A, Gruen RJ. Dynamics of a stressful encounter: cognitive appraisal, coping, and encounter outcomes. J Pers Soc Psychol 50: 992-1003, 1986.
- 14. Seres G, Kovács Z, Kovács A, et al. Different associations of health related quality of life with pain, psychological distress and coping strategies in patients with irritable bowel syndrome and inflammatory bowel disorder. J Clin Psychol Med Settings 15: 287-295, 2008.
- 15. Grodzinsky E, Walter S, Viktorsson L, Carlsson AK, Jones MP, Faresjö Å. More negative self-esteem and inferior coping strategies among patients diagnosed with IBS compared with patients without IBS: a case-control study in primary care. BMC Fam Pract 16:

- 6, 2015.
- 16. Stanculete MF, Matu S, Pojoga C, Dumitrascu DL. Coping strategies and irrational beliefs as mediators of the health-related quality of life impairments in irritable bowel syndrome. J Gastrointestin Liver Dis 24: 159-164, 2015.
- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 130: 1480-1491, 2006.
- **18.** Satake R, Sugawara N, Sato K, et al. Prevalence and predictive factors of irritable bowel syndrome in a community-dwelling population in Japan. Intern Med **54**: 3105-3112, 2015.
- Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1: 385-401, 1977.
- 20. Sugawara N, Yasui-Furukori N, Takahashi I, Matsuzaka M, Nakaji S. Age and gender differences in the factor structure of the Center for Epidemiological Studies Depression Scale among Japanese working individuals. Compr Psychiatry 56: 272-278, 2015.
- 21. Kageyama T, Kobayashi T, Kawashima M, Kanamaru Y. Development of the Brief Scales for Coping Profile (BSCP) for workers: basic information about its reliability and validity. Sangyo Eiseigaku Zasshi 46: 103-114, 2004 (in Japanese, Abstract in English).
- **22.** Tomotsune Y, Sasahara S, Umeda T, et al. The association of sense of coherence and coping profile with stress among research park city workers in Japan. Ind Health **47**: 664-672, 2009.
- Thijssen AY, Jonkers DM, Leue C, et al. Dysfunctional cognitions, anxiety and depression in irritable bowel syndrome. J Clin Gastroenterol 44: e236-e241, 2010.
- 24. Cho HS, Park JM, Lim CH, et al. Anxiety, depression and quality of life in patients with irritable bowel syndrome. Gut Liver 5: 29-36, 2011.
- 25. Voth J, Sirois FM. The role of self-blame and responsibility in adjustment to inflammatory bowel disease. Rehabil Psychol 54: 99-108, 2009.
- 26. Chitkara DK, van Tilburg MA, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol 103: 765-774, 2008
- 27. Klooker TK, Braak B, Painter RC, et al. Exposure to severe wartime conditions in early life is associated with an increased risk of irritable bowel syndrome: a population-based cohort study. Am J Gastroenterol 104: 2250-2256, 2009.
- 28. van Tilburg MA, Runyan DK, Zolotor AJ, et al. Unexplained gastrointestinal symptoms after abuse in a prospective study of children at risk for abuse and neglect. Ann Fam Med 8: 134-140, 2010.
- **29.** Pinto C, Lele MV, Joglekar AS, Panwar VS, Dhavale HS. Stressful life-events, anxiety, depression and coping in patients of irritable bowel syndrome. J Assoc Physicians India **48**: 589-953, 2000.
- **30.** Crane C, Martin M. Social learning, affective state and passive coping in irritable bowel syndrome and inflammatory bowel disease. Gen Hosp Psychiatry **26**: 50-58, 2004.
- Jones MP, Wessinger S, Crowell MD. Coping strategies and interpersonal support in patients with irritable bowel syndrome and inflammatory bowel disease. Clin Gastroenterol Hepatol 4: 474-481, 2006.
- **32.** Ben-Ezra M, Hamama-Raz Y, Palgi S, Palgi Y. Cognitive appraisal and psychological distress among patients with irritable bowel syndrome. Isr J Psychiatry Relat Sci **52**: 54-59, 2015.
- **33.** Adler AD, Strunk DR, Fazio RH. What changes in cognitive therapy for depression? An examination of cognitive therapy skills and maladaptive beliefs. Behav Ther **46**: 96-109, 2015.
- 34. Hollon SD, Jarrett RB, Nierenberg AA, Thase ME, Trivedi M, Rush AJ. Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? J Clin Psychiatry 66: 455-468, 2005.

- **35.** Zu S, Xiang YT, Liu J, et al. A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate-severe major depressive disorders. J Affect Disord **152-154**: 262-267, 2014.
- **36.** Li L, Xiong L, Zhang S, Yu Q, Chen M. Cognitive-behavioral therapy for irritable bowel syndrome: a meta-analysis. J Psycho-

som Res 77: 1-12, 2014.

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