

A questionnaire-based survey on the etiopathogenesis of chronic constipation during a medical check-up in Japan

Koji Otani,¹ Toshio Watanabe,^{2,*} Kanae Takahashi,³ Masaki Ominami,¹ Yuji Nadatani,² Shusei Fukunaga,¹ Shuhei Hosomi,¹ Noriko Kamata,¹ Fumio Tanaka,¹ Yasuaki Nagami,¹ Koichi Taira,¹ Tatsuo Kimura,² Shinya Fukumoto,² and Yasuhiro Fujiwara¹

¹Department of Gastroenterology and ²Department of Premier Preventive Medicine, Osaka City University Graduate School of Medicine, 12/F, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

³Department of Biostatistics, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8131, Japan

(Received 8 July, 2021; Accepted 20 August, 2021; Released online in J-STAGE as advance publication 19 January, 2022)

The study group of the Japanese Society of Gastroenterology released evidence-based clinical practice guidelines for chronic constipation (CC) in 2017, and irritable bowel syndrome (IBS) was treated as one of the causes of CC. We examined the differences in characteristics between IBS and non-IBS subjects with CC who underwent a medical check-up in Japan. A total of 10,658 subjects participated in this study, and we focused on 467 subjects who fulfilled the diagnostic criteria of CC using a questionnaire survey. The number of IBS subjects was 21, and they had sleep disorders, were more symptomatic (e.g., abdominal pain, abdominal bloating/distension, feeling stressed, annoyance, lack of motivation, fatigue upon waking, and feeling depressed), and had more episodes of sensation of incomplete evacuation and anorectal obstruction/blockage during defecation than non-IBS subjects. Furthermore, stool frequency of IBS subjects was significantly different from non-IBS subjects. Multivariate ordinal logistic regression analysis revealed that the factors associated with a higher stool frequency were IBS [odds ratio (OR), 2.46; 95% confidence interval (CI), 1.00–6.05; $p = 0.049$], male sex (OR, 1.97; 95% CI, 1.20–3.23; $p = 0.007$), and regular exercise (OR, 1.80; 95% CI, 1.05–3.07; $p = 0.033$). These findings suggest that IBS has unique characteristics in subjects with CC.

Key Words: chronic constipation, irritable bowel syndrome, Rome IV, stool frequency, medical check-up

Chronic constipation (CC) is one of the most common symptom-based bowel disorders. However, it cannot be ignored because it not only worsens daily quality of life (QOL) but may also increase the risk of poorer survival of affected individuals.^(1–3) Several new agents with various mechanisms have recently been introduced for the treatment of CC, and different approaches are necessary depending on the conditions of the patients with CC. Therefore, it is important to accurately understand and clarify the etiopathogenesis of CC.

The study group of the Japanese Society of Gastroenterology released evidence-based clinical practice guidelines for CC in 2017.⁽⁴⁾ In the guidelines, CC was defined based on the Rome IV criteria, and “loose stools rarely present without the use of laxatives” and “insufficient criteria for irritable bowel syndrome (IBS)”, both were included in the criteria for diagnosing functional constipation (FC), were excluded from the diagnostic criteria of CC. It means that CC includes FC and other etiologies, such as symptomatic constipation due to underlying diseases, medication-induced constipation, and IBS. Idiopathic constipa-

tion, symptomatic constipation, and medication-induced constipation were classified as slow transit constipation by the American Gastroenterological Association.⁽⁵⁾ Although IBS is generally considered to have normal transit, diarrhea-predominant IBS has a fast colonic transit and constipation-predominant IBS has a delayed colonic transit.^(5,6) In other words, these types of constipation cannot be distinguished by the colon transit time. Therefore, it is reasonable to consider that IBS is one of the causes of CC because IBS is typically accompanied by bowel disorders, including constipation and diarrhea, in clinical practice, and these conditions may not be discrete entities.⁽⁷⁾

Decreased stool frequency and hard stool form usually make patients aware that they are suffering from CC. The Bristol Stool Form Scale (BSFS) divides the stool form into seven categories ranging from lumpy stool (type 1) to watery stool (type 7); it represents a useful guide for the description of stool consistency and shape. In fact, “fewer than three spontaneous bowel movements per week” and “lumpy or hard stools (BSFS type 1 or 2) more than 25% of defecations” are included in the diagnostic criteria of CC, although these items alone are not sufficient to diagnose CC.

Based on these findings, we consider that it is necessary to investigate lifestyle habits, underlying diseases including IBS, and medications that are associated with stool frequency and stool form to develop an appropriate therapeutic regimen for patients with CC in consideration of its etiopathogenesis. This study aimed to examine the differences in characteristics between IBS and non-IBS subjects with CC and the factors associated with stool frequency and stool form among subjects with CC who underwent a medical check-up in Japan.

Methods

Study design. This was a single-center, cross-sectional survey of prospective subjects.

Study population. A total of 13,729 subjects underwent a medical check-up at our clinic, MedCity21, that provides medical examination and health screening from the view of preventive medicine between April 2018 and March 2019. All subjects were given a questionnaire inquiring that covered the diagnostic criteria of CC and IBS, and all questionnaires were collected on the day of the medical check-up. A total of 10,658 participants

*To whom correspondence should be addressed.
E-mail: watanabet@med.osaka-cu.ac.jp

completed the questionnaires with written informed consent (response rate: 77.6%). This study focused on 467 participants who fulfilled the diagnostic criteria for CC. The exclusion criteria were subjects who refused to participate in this study and those judged as inappropriate by the principal investigator. The clinical data of the subjects were obtained from their medical records and general questionnaires during a medical check-up.

Questionnaire. The questionnaire inquired about seven levels of stool frequency (less than once in 3 days, once in 3 days, once in 2 days, once a day, twice a day, three times a day, or more than 4 times a day), seven types of stool form based on BSFS [separate hard lumps (type 1), sausage-shaped but lumpy (type 2), like a sausage with cracks on the surface (type 3), like a sausage or snake, smooth and soft (type 4), soft blobs with clear-cut edges (type 5), fluffy pieces with ragged edges, a mushy stool (type 6), or watery, no solid pieces, entirely liquid (type 7)], defecation situation [straining during more than one-fourth of defecation episodes, lumpy or hard stools (BSFS type 1 or 2) during more than one-fourth of defecation episodes, sensation of incomplete evacuation during more than one-fourth of defecation episodes, sensation of anorectal obstruction/blockage during more than one-fourth of defecation episodes, manual maneuvers to facilitate defecation during more than one-fourth of defecation episodes, fewer than three spontaneous bowel movements per week, and above symptoms present for the last 3 months with symptom onset at least 6 months prior], and abdominal pain occurring, on average, at least 1 day per week for the last 3 months [abdominal pain related to defecation, abdominal pain associated with a change in stool frequency, abdominal pain associated with a change in stool form (appearance), and above symptoms present for the last 3 months with symptom onset at least 6 months prior].

Diagnosis of CC and IBS. CC was diagnosed according to the Japanese evidence-based clinical practice guidelines for chronic constipation in 2017 based on the Rome IV criteria as follows: 1) presence of more than two of the following: straining during more than one-fourth of defecation episodes, lumpy or hard stools (BSFS type 1 or 2) during more than one-fourth of defecation episodes, sensation of incomplete evacuation during more than one-fourth of defecation episodes, sensation of anorectal obstruction/blockage during more than one-fourth of defecation episodes, manual maneuvers to facilitate defecation during more than one-fourth of defecation episodes, and fewer than three spontaneous bowel movements per week, and 2) fulfillment of the criteria for the last 3 months with symptom onset at least 6 months prior.

IBS was diagnosed based on the Rome IV criteria as follows: 1) recurrent abdominal pain occurring, on average, at least 1 day per week for the last 3 months and associated with more than two of the following: abdominal pain related to defecation, abdominal pain associated with a change in stool frequency, abdominal pain associated with a change in stool form (appearance), and 2) fulfillment of the criteria for the last 3 months with symptom onset at least 6 months prior. IBS with predominant constipation or mixed bowel habits (IBS-C/M) was defined as IBS with lumpy or hard stools (BSFS type 1 or 2) during more than one-fourth of defecation episodes.

Outcome measurement. The primary aim of this study was to examine the clinical characteristics of subjects with CC and the factors associated with stool frequency and stool form among subjects with CC based on the data from a medical check-up.

Ethical approval. The study protocol was approved by the ethics committee of the Osaka City University Graduate School of Medicine (No. 3928) on December 27, 2017. Written informed consent was obtained from each subject included in the study. We disclosed information about this study on the webpage of the institution, and the subjects had the opportunity to opt out. The study was conducted in accordance with the Declaration of

Helsinki ethical principles for medical research involving human subjects.

Statistical analysis. Data are expressed as median and interquartile range for continuous variables and as numbers and percentage for categorical variables. Continuous variables were compared using the Mann–Whitney *U* test, and categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Clinical factors associated with stool frequency and stool form were analyzed using proportional odds ordinal logistic regression analysis, and the odds ratio (OR) and 95% confidence interval (CI) were estimated for each factor. Statistical calculations and analyses were performed using IBM SPSS Statistics ver. 26 (IBM Corporation, Armonk, NY) or R software, ver. 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics of subjects with CC. The median age of a total of 10,658 subjects was 51.0 (range, 43.0–60.0), 5,047 subjects (47.4%) were men, and their median body mass index (BMI) was 22.3 (range, 20.2–24.7). The median age of the 467 subjects who fulfilled the diagnostic criteria of CC was 49.0 (range, 42.0–57.0) years, 92 (19.7%) subjects were men, and their median BMI was 21.2 (range, 19.4–23.8) kg/m².

Among the 467 subjects with CC, the number of subjects who fulfilled the diagnostic criteria of IBS was 21 (4.5%). Among these 21 IBS subjects, 16 (76.2%) met the diagnostic criteria for IBS-C/M. IBS subjects had less time of sleep ($p = 0.013$), insufficient rest by sleep ($p = 0.012$), and more complaints of abdominal bloating/distension, feeling stressed, annoyance, lack of motivation, fatigue upon waking, and feeling depressed, compared with non-IBS subjects (52.4% vs 22.0%; $p = 0.003$; 57.1% vs 29.1%; $p = 0.005$; 38.1% vs 17.5%; $p = 0.038$; 33.3% vs 10.5%; $p = 0.007$; 47.6% vs 23.8%; $p = 0.014$; 28.6% vs 10.3%; $p = 0.024$, respectively). Furthermore, IBS subjects had a higher *Helicobacter pylori* (*H. pylori*) eradication history than non-IBS subjects (33.3% vs 13.9%; $p = 0.024$) (Table 1).

Stool frequency and stool form, defecation situation, and abdominal pain based on questionnaire responses. The most common average stool frequency and stool form among all subjects were once a day (51.3%) and type 4 (like a sausage or snake, smooth and soft) (62.9%), respectively. The most common average stool frequency and stool form among all subjects with CC were once in 3 days (35.1%) and type 2 (sausage-shaped but lumpy) (27.0%), respectively.

There was a significant deviation in stool frequency between IBS subjects and non-IBS subjects ($p = 0.009$). However, the stool form based on the BSFS was not significantly different between the two groups ($p = 0.170$). In defecation situations, IBS subjects had more episodes of sensation of incomplete evacuation and sensation of anorectal obstruction/blockage during defecation (90.5% vs 64.1%; $p = 0.017$ and 57.1% vs 30.7%; $p = 0.016$, respectively) (Table 2).

Multivariate ordinal logistic regression analysis of factors associated with a higher stool frequency or a looser stool form among subjects with CC. Multivariate ordinal logistic regression analysis revealed that the factors associated with a higher stool frequency among CC patients were male sex (OR, 1.97; 95% CI, 1.20–3.23; $p = 0.007$), exercise for more than 30 min at least twice a week for more than 1 year (OR, 1.80; 95% CI, 1.05–3.07; $p = 0.033$), and presence of IBS (OR, 2.46; 95% CI, 1.00–6.05; $p = 0.049$). On the other hand, factors associated with a looser stool form were male sex (OR, 2.47; 95% CI, 1.50–4.06; $p < 0.001$), current smoking (OR, 2.36; 95% CI, 1.38–4.03; $p = 0.002$), and exercise for more than 30 min at least twice a week for more than 1 year (OR, 1.83; 95% CI, 1.08–3.08; $p = 0.024$) (Table 3).

Table 1. Baseline characteristics of subjects with chronic constipation

Variables	All subjects	CC	CC		<i>p</i> value (IBS vs non-IBS)
			IBS	Non-IBS	
Number of cases	10,658	467	21	446	
Age (years, median [IQR])	51.0 [43.0–60.0]	49.0 [42.0–57.0]	49.0 [43.0–55.0]	49.0 [42.0–57.0]	0.584
Age group					0.538
<30	148 (1.4%)	6 (1.3%)	1 (4.8%)	5 (1.1%)	
30–39	1,343 (12.6%)	63 (13.5%)	4 (19.0%)	59 (13.2%)	
40–49	3,372 (31.6%)	172 (36.8%)	7 (33.3%)	165 (37.0%)	
50–59	3,116 (29.2%)	131 (28.1%)	6 (28.6%)	125 (28.0%)	
60–69	1,964 (18.4%)	71 (15.2%)	2 (9.5%)	69 (15.5%)	
≥70	715 (6.7%)	24 (5.1%)	1 (4.8%)	23 (5.2%)	
Sex					1
Male	5,047 (47.4%)	92 (19.7%)	4 (19.0%)	88 (19.7%)	
Female	5,611 (52.6%)	375 (80.3%)	17 (81.0%)	358 (80.3%)	
BMI (kg/m ² , median [IQR])	22.3 [20.2–24.7]	21.2 [19.4–23.8]	20.4 [18.4–22.9]	21.2 [19.5–23.8]	0.2
Alcohol intake (≥5 days a week)	2,726 (25.6%)	55 (11.8%)	3 (14.3%)	52 (11.7%)	0.726
Daily drinking quantity					0.245
<1 go (180 ml of Japanese sake)	6,706 (62.9%)	356 (76.2%)	15 (71.4%)	341 (76.5%)	
≥1 and <2 go	1,782 (16.7%)	61 (13.1%)	2 (9.5%)	59 (13.2%)	
≥2 and <3 go	1,525 (14.3%)	37 (7.9%)	2 (9.5%)	35 (7.8%)	
≥3 go	586 (5.5%)	13 (2.8%)	2 (9.5%)	11 (2.5%)	
Smoking habit (current smoker)	1,566 (14.7%)	57 (12.2%)	2 (9.5%)	55 (12.3%)	1
Exercise for ≥30 min at least twice a week for ≥1 year	2,638 (24.8%)	63 (13.5%)	5 (23.8%)	58 (13.0%)	0.183
Walking (or an equal amount of exercise) for ≥1 h a day	4,399 (41.3%)	160 (34.3%)	9 (42.9%)	151 (33.9%)	0.481
Walking faster than other people of the same age and sex	5,536 (51.9%)	217 (46.5%)	10 (47.6%)	207 (46.4%)	1
Sleep for ≥6 h a day	7,022 (65.9%)	260 (55.7%)	6 (28.6%)	254 (57.0%)	0.013
Getting enough rest by sleeping	6,216 (58.3%)	220 (47.1%)	4 (19.0%)	216 (48.4%)	0.012
Skipping breakfast ≥3 times a week	1,519 (14.3%)	82 (17.6%)	5 (23.8%)	77 (17.3%)	0.391
Eating 2 h before going to bed ≥3 times a week	2,960 (27.8%)	134 (28.7%)	8 (38.1%)	126 (28.3%)	0.331
Eating snacks and sweet drinks in addition to three meals in a day	8,442 (79.2%)	415 (88.9%)	17 (81.0%)	398 (89.2%)	0.275
Eating faster than other people	4,137 (38.8%)	188 (40.3%)	9 (42.9%)	179 (40.1%)	0.823
Weight gain of ≥10 kg from the age of 20	3,712 (34.8%)	136 (29.1%)	4 (19.0%)	132 (29.6%)	0.461
State of biting and eating a meal					0.619
Can bite and eat anything	9,083 (85.2%)	373 (79.9%)	16 (76.2%)	357 (80.0%)	
Feel difficulty in biting due to teeth problems	1,470 (13.8%)	92 (19.7%)	5 (23.8%)	87 (19.5%)	
Hardly bite	47 (0.4%)	2 (0.4%)	0 (0.0%)	2 (0.4%)	
Lifestyle improvement					0.473
Already improving	2,686 (25.2%)	91 (19.5%)	2 (9.5%)	89 (20.0%)	
Willing to improve	5,852 (54.9%)	295 (63.2%)	16 (76.2%)	279 (62.6%)	
No intention to improve	2,062 (19.3%)	81 (17.3%)	3 (14.3%)	78 (17.5%)	
Willing to use opportunity to receive health instruction on lifestyle improvement	5,111 (48.0%)	229 (49.0%)	13 (61.9%)	216 (48.4%)	0.268
Heartburn	481 (4.5%)	28 (6.0%)	0 (0.0%)	28 (6.3%)	0.62
Nausea	151 (1.4%)	13 (2.8%)	2 (9.5%)	11 (2.5%)	0.099
Stomachache	631 (5.9%)	48 (10.3%)	5 (23.8%)	43 (9.6%)	0.057
Abdominal bloating/distension	812 (7.6%)	109 (23.3%)	11 (52.4%)	98 (22.0%)	0.003
Feeling stressed	2,244 (21.1%)	142 (30.4%)	12 (57.1%)	130 (29.1%)	0.005
Annoyance	1,129 (10.6%)	86 (18.4%)	8 (38.1%)	78 (17.5%)	0.038
Lack of motivation	662 (6.2%)	54 (11.6%)	7 (33.3%)	47 (10.5%)	0.007
Fatigue upon waking	1,604 (15.0%)	116 (24.8%)	10 (47.6%)	106 (23.8%)	0.014
Feeling depressed	726 (6.8%)	52 (11.1%)	6 (28.6%)	46 (10.3%)	0.024
General disinterest	239 (2.2%)	19 (4.1%)	1 (4.8%)	18 (4.0%)	0.566
<i>H. pylori</i> eradication history	1,567 (14.7%)	69 (14.8%)	7 (33.3%)	62 (13.9%)	0.024
Fecal occult blood test -positive	989 (9.3%)	62 (13.3%)	2 (9.5%)	60 (13.5%)	0.751
History of colorectal polyps	782 (7.3%)	43 (9.2%)	0 (0.0%)	43 (9.6%)	0.243
History of colorectal cancer	88 (0.8%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	1
History of cardiovascular diseases	328 (3.1%)	15 (3.2%)	1 (4.8%)	14 (3.1%)	0.504
History of cerebrovascular diseases	178 (1.7%)	14 (3.0%)	1 (4.8%)	13 (2.9%)	0.48
Chronic kidney disease (Stage G3a–G5)	1,033 (9.7%)	38 (8.1%)	0 (0.0%)	38 (8.5%)	0.241
Antihypertensive drugs	1,513 (14.2%)	55 (11.8%)	1 (4.8%)	54 (12.1%)	0.493
Hypoglycemic drugs or insulin	391 (3.7%)	21 (4.5%)	0 (0.0%)	21 (4.7%)	0.615
Antidyslipidemic drugs	1,210 (11.4%)	59 (12.6%)	1 (4.8%)	58 (13.0%)	0.497
Levothyroxine sodium hydrate	133 (1.2%)	7 (1.5%)	1 (4.8%)	6 (1.3%)	0.277
Antihistaminic drugs	254 (2.4%)	12 (2.6%)	2 (9.5%)	10 (2.2%)	0.097
Antipsychotics or antidepressants	115 (1.1%)	7 (1.5%)	0 (0.0%)	7 (1.6%)	1
Anxiolytics or sleeping pills	230 (2.2%)	18 (3.9%)	1 (4.8%)	17 (3.8%)	0.57
Iron supplements	34 (0.3%)	3 (0.6%)	0 (0.0%)	3 (0.7%)	1
Acid secretion suppressants	394 (3.7%)	21 (4.5%)	0 (0.0%)	21 (4.7%)	0.615
Laxatives	135 (1.3%)	21 (4.5%)	1 (4.8%)	20 (4.5%)	1

CC, chronic constipation; IBS, irritable bowel syndrome; IQR, interquartile range; BMI, body mass index; *H. pylori*, *Helicobacter pylori*. One go of Japanese sake contains approximately 22 g of ethanol.

Table 2. Stool frequency and stool form, defecation situation, and abdominal pain based on questionnaire responses

Variables	All subjects	CC	CC		<i>p</i> value (IBS vs non-IBS)
			IBS	Non-IBS	
Stool frequency					0.009
Less than once in 3 days	280 (2.6%)	137 (29.3%)	4 (19.0%)	133 (29.8%)	
Once in 3 days	655 (6.1%)	164 (35.1%)	6 (28.6%)	158 (35.4%)	
Once in 2 days	1,593 (14.9%)	111 (23.8%)	5 (23.8%)	106 (23.8%)	
Once a day	5,470 (51.3%)	42 (9.0%)	2 (9.5%)	40 (9.0%)	
Twice a day	1,860 (17.5%)	6 (1.3%)	2 (9.5%)	4 (0.9%)	
Three times a day	551 (5.2%)	3 (0.6%)	1 (4.8%)	2 (0.4%)	
More than 4 times a day	193 (1.8%)	3 (0.6%)	1 (4.8%)	2 (0.4%)	
Stool form based on BSFS					0.17
Type 1	329 (3.1%)	125 (26.8%)	3 (14.3%)	122 (27.4%)	
Type 2	350 (3.3%)	126 (27.0%)	6 (28.6%)	120 (26.9%)	
Type 3	1,335 (12.5%)	121 (25.9%)	6 (28.6%)	115 (25.8%)	
Type 4	6,706 (62.9%)	59 (12.6%)	2 (9.5%)	57 (12.8%)	
Type 5	1,546 (14.5%)	24 (5.1%)	2 (9.5%)	22 (4.9%)	
Type 6	307 (2.9%)	9 (1.9%)	2 (9.5%)	7 (1.6%)	
Type 7	21 (0.2%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	
Defecation situation					
Straining during ≥one-fourth of defecation episodes	1,700 (16.0%)	275 (58.9%)	14 (66.7%)	261 (58.5%)	0.505
Lumpy or hard stools during ≥one-fourth of defecation episodes	2,096 (19.7%)	366 (78.4%)	16 (76.2%)	350 (78.5%)	0.788
Sensation of incomplete evacuation during ≥one-fourth of defecation episodes	2,694 (25.3%)	305 (65.3%)	19 (90.5%)	286 (64.1%)	0.017
Sensation of anorectal obstruction/blockage during ≥one-fourth of defecation episodes	572 (5.4%)	149 (31.9%)	12 (57.1%)	137 (30.7%)	0.016
Manual maneuvers to facilitate defecation during ≥one-fourth of defecation episodes	304 (2.9%)	79 (16.9%)	4 (19.0%)	75 (16.8%)	0.767
Fewer than three spontaneous bowel movements per week	1,093 (10.3%)	316 (67.7%)	13 (61.9%)	303 (67.9%)	0.634
Above symptoms present for the last 3 months with symptom onset at least 6 months prior	598 (5.6%)	467 (100.0%)	21 (100.0%)	446 (100.0%)	NA
Abdominal pain occurring, on average, at least 1 day per week for the last 3 months					
Abdominal pain related to defecation	1,868 (17.5%)	148 (31.7%)	21 (100.0%)	127 (28.5%)	<0.001
Abdominal pain associated with a change in stool frequency	646 (6.1%)	81 (17.3%)	17 (81.0%)	64 (14.3%)	<0.001
Abdominal pain associated with a change in stool form (appearance)	935 (8.8%)	67 (14.3%)	14 (66.7%)	53 (11.9%)	<0.001
Above symptoms present for the last 3 months with symptom onset at least 6 months prior	156 (1.5%)	34 (7.3%)	21 (100.0%)	13 (2.9%)	<0.001

CC, chronic constipation; IBS, irritable bowel syndrome; BSFS, Bristol Stool Form Scale; NA, not applicable.

Discussion

We conducted this study to examine the difference in characteristics of subjects who met the criteria for CC by dividing the subjects into IBS and non-IBS. Our results showed that IBS subjects with CC had sleep disorders, complex symptoms, dyschezia sensation, and higher stool frequency among subjects with CC.

We found that the proportion of IBS subjects was 4.5% among the subjects with CC. The prevalence of IBS in our study was lower than a previous report that the prevalence of IBS diagnosed by the Rome III criteria among the subjects with CC diagnosed by the modified Rome III criteria was 17%.⁽⁸⁾ It is reported that the prevalence of IBS diagnosed by the Rome IV criteria is generally lower than that diagnosed by the Rome III criteria in a systematic review and meta-analysis.⁽⁹⁾ Moreover, the prevalence of CC can widely range from 0.7% to 79% depending on the definition used and population studied,⁽¹⁰⁾ and there are few reports about the prevalence of CC diagnosed by the Japanese evidence-based clinical practice guidelines for chronic constipation in 2017. A low prevalence of IBS in our study may be attributed to these reasons.

The pathophysiology of IBS is heterogeneous, and various factors seem to be involved, such as abnormal gastrointestinal motility, visceral hypersensitivity, disturbances in brain–gut interaction, psychosocial distress, and altered gut microbiome.^(11–17) IBS is typically accompanied by other functional disorders, such

as constipation and diarrhea, due to abnormal gastrointestinal motility.⁽¹⁸⁾ Moreover, the proportion of subjects with IBS-C/M was 76.2% among the IBS subjects with CC, indicating that IBS subjects with CC did not always have a stiff stool form. Of note, IBS subjects had significantly less time of sleep and insufficient rest by sleep among their lifestyle habits. This is consistent with previous reports that have shown that the prevalence of sleep disorder is higher in IBS patients,^(19,20) which may be because sleep disorders are associated with dysregulation of the autonomic nervous system that causes IBS.^(21,22) Abdominal pain, a component of the diagnostic criteria of IBS, and abdominal bloating/distension were more common in IBS patients, which might be due to the abnormal visceral hypersensitivity and disturbances in brain–gut interaction. In addition to abdominal pain and abdominal bloating/distension, troublesome symptoms of daily life, such as feeling stressed, annoyance, lack of motivation, fatigue upon waking, feeling depressed, were significantly more common in IBS subjects than in non-IBS subjects. It is known that psychological and psychiatric comorbidities, such as anxiety, depression, and paranoia, are common among IBS patients.^(23–26) Therefore, these symptoms may result from psychosocial distress and psychiatric comorbidities in IBS patients. Kawamura *et al.*⁽²⁷⁾ reported that IBS subjects with predominant constipation complained of more severe symptoms than FC subjects, resulting in impairment of QOL. Furthermore, IBS subjects had more *H. pylori* eradication histories than non-IBS subjects. As there are reports that *H. pylori* infection is involved in triggering

Table 3. Multivariate ordinal logistic regression analysis of factors associated with a higher stool frequency or a looser stool form among subjects with chronic constipation

Variables	Higher stool frequency		Looser stool form	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.02 (1.00–1.04)	0.118	0.99 (0.97–1.00)	0.123
Male sex (reference: female sex)	1.97 (1.20–3.23)	0.007	2.47 (1.50–4.06)	<0.001
BMI	1.02 (0.95–1.08)	0.638	1.05 (0.99–1.12)	0.107
Alcohol intake (≥ 5 days a week)	1.14 (0.64–2.01)	0.661	1.22 (0.70–2.13)	0.482
Smoking habit (current smoker)	0.88 (0.52–1.49)	0.621	2.36 (1.38–4.03)	0.002
Exercise for ≥ 30 min at least twice a week for ≥ 1 year	1.80 (1.05–3.07)	0.033	1.83 (1.08–3.08)	0.024
Walking (or an equal amount of exercise) for ≥ 1 h a day	0.94 (0.64–1.39)	0.753	0.83 (0.56–1.21)	0.323
Walking faster than other people of the same age and sex	1.20 (0.84–1.71)	0.313	0.79 (0.56–1.12)	0.19
Getting enough rest by sleeping	0.99 (0.70–1.40)	0.951	0.91 (0.64–1.29)	0.595
Skipping breakfast ≥ 3 times a week	0.92 (0.57–1.48)	0.732	0.93 (0.58–1.48)	0.757
Eating 2 h before going to bed ≥ 3 times a week	1.02 (0.69–1.52)	0.924	1.43 (0.96–2.14)	0.081
Eating snacks and sweet drinks in addition to three meals in a day	1.22 (0.67–2.22)	0.516	0.74 (0.40–1.37)	0.338
Eating faster than other people	0.81 (0.57–1.16)	0.249	1.00 (0.71–1.42)	0.987
Weight gain of ≥ 10 kg from the age of 20	1.14 (0.71–1.85)	0.586	0.72 (0.45–1.16)	0.175
IBS	2.46 (1.00–6.05)	0.049	1.69 (0.74–3.89)	0.214
<i>H. pylori</i> eradication history	1.28 (0.76–2.15)	0.359	1.45 (0.88–2.40)	0.148
History of cardiovascular diseases	1.40 (0.49–4.00)	0.526	0.86 (0.33–2.30)	0.769
History of cerebrovascular diseases	1.32 (0.44–3.92)	0.623	1.38 (0.48–3.92)	0.551
Chronic kidney disease (Stage G3a–G5)	0.70 (0.35–1.40)	0.313	1.83 (0.94–3.56)	0.076
Antihypertensive drugs	1.28 (0.65–2.55)	0.478	1.22 (0.62–2.41)	0.571
Hypoglycemic drugs or insulin	0.44 (0.17–1.20)	0.109	0.68 (0.27–1.74)	0.417
Antidyslipidemic drugs	1.06 (0.54–2.07)	0.87	0.81 (0.45–1.47)	0.489
Levothyroxine sodium hydrate	0.53 (0.13–2.23)	0.387	0.91 (0.23–3.50)	0.885
Antipsychotics or antidepressants	1.46 (0.37–5.76)	0.588	0.81 (0.20–3.24)	0.768
Anxiolytics or sleeping pills	0.72 (0.29–1.81)	0.481	0.44 (0.16–1.18)	0.103
Iron supplements	0.25 (0.02–2.67)	0.251	0.75 (0.11–5.23)	0.775

OR, odds ratio; CI, confidence interval; BMI, body mass index; IBS, irritable bowel syndrome; *H. pylori*, *Helicobacter pylori*.

visceral hypersensitivity in IBS patients⁽²⁸⁾ and *H. pylori* eradication treatment alters gut microbiota that is closely related to gastrointestinal health status,^(29,30) there may be some association between *H. pylori* and IBS. In defecation situations, IBS subjects had significantly more episodes of sensation of incomplete evacuation and sensation of anorectal obstruction/blockage during defecation. These sensations may be due to the hypersensitivity of rectum and anus.

Multivariate ordinal logistic regression analysis revealed that male sex, exercise for more than 30 min at least twice a week for more than 1 year, and IBS were independently associated with a higher stool frequency among subjects with CC. As more IBS subjects complained of abdominal pain associated with a change in stool frequency and sensation of difficulty during defecation, these uncomfortable symptoms might have increased the stool frequency in patients with IBS even if they were experiencing CC. On the other hand, looser stool form was associated with male sex, current smoking status, and exercise for more than 30 min at least twice a week for more than 1 year. Nicotine binds to nicotinic acetylcholine receptors to stimulate parasympathetic nerves and interferes with water absorption, resulting in a looser stool form.^(31,32) Exercise for more than 30 min at least twice a week for more than 1 year was significantly associated with both higher stool frequency and looser stool form among subjects with CC. It has been reported that regular exercise with moderate physical activity shortens the intestinal transit time and reduce the risk of constipation.^(33,34)

Regular exercise habits or medication therapy, such as osmotic

laxatives, stimulant laxatives, chloride channel activators, guanylate cyclase activators, and 5-hydroxytryptamine receptor 4 agonists, may be helpful to relieve constipation symptoms for CC patients. When treating IBS patients with CC, more multi-faceted therapeutic approach will be necessary. The effects of chloride channel activators and guanylate cyclase activators on those patients have been proven in a systematic review and meta-analysis,^(35,36) and the use of these drugs are recommended in the American College of Gastroenterology clinical guidelines.⁽³⁷⁾ Sleeping pills, anxiolytics, and antidepressants will be effective for their sleep disorders, anxiety, and depressive symptoms.^(38,39) Moreover, gut-directed psychotherapy, including cognitive-behavior therapy, hypnotherapy, mindfulness treatment, and stress management is suggested to restore their mental health.^(39,40)

This study has some limitations. First, it was conducted at a single medical check-up institution, and the characteristics of the subjects might have been biased. The subjects who underwent a medical check-up were highly conscious of their health, and their overall health status was generally good. Moreover, very elderly and very young individuals usually do not receive medical check-ups. Second, the questionnaire used in this study was based on self-reported measures by subjects, and issues such as missed reporting and providing inaccurate information were unavoidable. Third, some subjects who did not meet the diagnostic criteria for CC because they took laxatives may meet the criteria for CC if they discontinue the laxatives. It is ideal to assess defecation situation after discontinuing laxatives. However, it is undesirable to discontinue the laxatives just for diagnosing CC.

In conclusion, it is suggested that IBS subjects have unique characteristics in subjects with CC as they suffer from sleep disorders, are more symptomatic, have more episodes of sensation of incomplete evacuation and anorectal obstruction/blockage during defecation, and have a higher stool frequency. It is necessary to be aware of these various features of IBS subjects in the treatment of CC, and we hope that these study findings will help to relieve their troublesome symptoms.

Author Contributions

KO designed, analyzed the data, and drafted the paper; TW supervised the study and revised the paper; KTakahashi analyzed the data; MO, YNadatani, SFukunaga, SH, NK, FT, YNagami, KTaira, TK, SFukumoto, and YF reviewed the manuscript and provided valid inputs on the study.

References

- Wald A, Scarpignato C, Kamm MA, *et al.* The burden of constipation on quality of life: results of a multinational survey. *Aliment Pharmacol Ther* 2007; **26**: 227–236.
- Chang L. Review article: epidemiology and quality of life in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 2004; **20 Suppl 7**: 31–39.
- Chang JY, Locke GR 3rd, McNally MA, *et al.* Impact of functional gastrointestinal disorders on survival in the community. *Am J Gastroenterol* 2010; **105**: 822–832.
- Research Society for the Diagnosis and Treatment of Chronic Constipation/Affiliated to The Japanese Society of Gastroenterology. *Evidence-based Clinical Practice Guidelines for Chronic Constipation* 2017. Tokyo: Nankodo, 2017.
- Bharucha AE, Pemberton JH, Locke GR 3rd. American Gastroenterological Association technical review on constipation. *Gastroenterology* 2013; **144**: 218–238.
- Chiba T, Kudara N, Sato M, *et al.* Colonic transit, bowel movements, stool form, and abdominal pain in irritable bowel syndrome by treatments with calcium polycarbophil. *Hepatogastroenterology* 2005; **52**: 1416–1420.
- Locke GR 3rd, Zinsmeister AR, Fett SL, Melton LJ 3rd, Talley NJ. Overlap of gastrointestinal symptom complexes in a US community. *Neurogastroenterol Motil* 2005; **17**: 29–34.
- Rey E, Balboa A, Mearin F. Chronic constipation, irritable bowel syndrome with constipation and constipation with pain/discomfort: similarities and differences. *Am J Gastroenterol* 2014; **109**: 876–884.
- Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 908–917.
- Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol* 2011; **25**: 3–18.
- Dupont HL. Review article: evidence for the role of gut microbiota in irritable bowel syndrome and its potential influence on therapeutic targets. *Aliment Pharmacol Ther* 2014; **39**: 1033–1042.
- Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; **123**: 2108–2131.
- Cashman MD, Martin DK, Dhillon S, Puli SR. Irritable bowel syndrome: a clinical review. *Curr Rheumatol Rev* 2016; **12**: 13–26.
- Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015; **313**: 949–958.
- Chang JY, Talley NJ. An update on irritable bowel syndrome: from diagnosis to emerging therapies. *Curr Opin Gastroenterol* 2011; **27**: 72–78.
- Mayer EA, Naliboff BD, Chang L. Basic pathophysiologic mechanisms in irritable bowel syndrome. *Dig Dis* 2001; **19**: 212–218.
- Hauser G, Pletikosc S, Tkalcic M. Cognitive behavioral approach to understanding irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 6744–6758.
- Mearin F, Lacy BE, Chang L, *et al.* Bowel disorders. *Gastroenterology* 2016. DOI: 10.1053/j.gastro.2016.02.031.
- Wang B, Duan R, Duan L. Prevalence of sleep disorder in irritable bowel

Abbreviations

BMI	body mass index
BSFS	Bristol Stool Form Scale
CC	chronic constipation
CI	confidence interval
FC	functional constipation
IBS	irritable bowel syndrome
IBS-C/M	IBS with predominant constipation or mixed bowel habits
OR	odds ratio
QOL	the quality of life

Conflict of Interest

No potential conflicts of interest were disclosed.

- syndrome: a systematic review with meta-analysis. *Saudi J Gastroenterol* 2018; **24**: 141–150.
- Grover M, Kolla BP, Pamarthy R, *et al.* Psychological, physical, and sleep comorbidities and functional impairment in irritable bowel syndrome: results from a national survey of U.S. adults. *PLoS One* 2021; **16**: e0245323.
- Miglis MG. Autonomic dysfunction in primary sleep disorders. *Sleep Med* 2016; **19**: 40–49.
- Tobaldini E, Costantino G, Solbiati M, *et al.* Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. *Neurosci Biobehav Rev* 2017; **74 (Pt B)**: 321–329.
- Radovanovic-Dinic B, Tesic-Rajkovic S, Grgov S, Petrovic G, Zivkovic V. Irritable bowel syndrome - from etiopathogenesis to therapy. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2018; **162**: 1–9.
- Blewett A, Allison M, Calcraft B, Moore R, Jenkins P, Sullivan G. Psychiatric disorder and outcome in irritable bowel syndrome. *Psychosomatics* 1996; **37**: 155–160.
- Drossman DA. Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? *Am J Med* 1999; **107**: 41S–50S.
- Drossman DA, McKee DC, Sandler RS, *et al.* Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. *Gastroenterology* 1988; **95**: 701–708.
- Kawamura Y, Yamamoto S, Funaki Y, *et al.* Internet survey on the actual situation of constipation in the Japanese population under 70 years old: focus on functional constipation and constipation-predominant irritable bowel syndrome. *J Gastroenterol* 2020; **55**: 27–38.
- Gerards C, Leodolter A, Glasbrenner B, Malfertheiner P. *H. pylori* infection and visceral hypersensitivity in patients with irritable bowel syndrome. *Dig Dis* 2001; **19**: 170–173.
- Cornejo-Pareja I, Martín-Núñez GM, Roca-Rodríguez MM, *et al.* *H. pylori* eradication treatment alters gut microbiota and GLP-1 secretion in humans. *J Clin Med* 2019; **8**: 451.
- Takagi T, Naito Y, Inoue R, *et al.* Differences in gut microbiota associated with age, sex, and stool consistency in healthy Japanese subjects. *J Gastroenterol* 2019; **54**: 53–63.
- Mandl P, Kiss JP. Role of presynaptic nicotinic acetylcholine receptors in the regulation of gastrointestinal motility. *Brain Res Bull* 2007; **72**: 194–200.
- Hajek P, Gillison F, McRobbie H. Stopping smoking can cause constipation. *Addiction* 2003; **98**: 1563–1567.
- Bingham SA, Cummings JH. Effect of exercise and physical fitness on large intestinal function. *Gastroenterology* 1989; **97**: 1389–1399.
- Matsuzaki J, Suzuki H, Masaoka T, Tanaka K, Mori H, Kanai T. Influence of regular exercise on gastric emptying in healthy men: a pilot study. *J Clin Biochem Nutr* 2016; **59**: 130–133.
- Li F, Fu T, Tong WD, *et al.* Lubiprostone is effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2016; **91**: 456–468.
- Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. *Neurogastroenterol Motil* 2014; **26**: 499–509.

- 37 Lacy BE, Pimentel M, Brenner DM, *et al.* ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol* 2021; **116**: 17–44.
- 38 Pace F, Maurano A, Ciacci C, *et al.* Octatropine methyl bromide and diazepam combination (Valpinax) in patients with irritable bowel syndrome: a multicentre, randomized, placebo-controlled trial. *Eur Rev Med Pharmacol Sci* 2010; **14**: 155–162.
- 39 Ford AC, Lacy BE, Harris LA, Quigley EMM, Moayyedi P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol* 2019; **114**: 21–39.
- 40 Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: a systematic review and meta-analysis. *Clin Psychol Rev* 2017; **51**: 142–152.



This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).
