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Comorbid irritable bowel syndrome symptoms and headache have greater association with anxiety than depression

Annual health check-up survey results

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Abstract

High rates of co-existing irritable bowel syndrome (IBS) and headache have been reported in western countries. We investigated that comorbidity in individuals in Japan, along with anxiety and depression in subjects with and without IBS symptoms and/or headache.

This cross-sectional study was performed from April 2012 to January 2013 at the Matsue Seikyo General Hospital Health Check Center. Questionnaires concerning symptoms related to IBS (Rome III) and headache, as well as anxiety/depression score were sent to individuals scheduled to undergo an annual health check-up, then returned during the visit and analyzed in a blinded manner.

A total of 2885 individuals returned completed questionnaires and were enrolled, of whom 218 (7.6%) met the IBS criteria. The rates of co-existing headache in subjects with and without IBS symptoms were 44.0% (96/218) and 22.9% (611/2667), respectively, indicating a significantly higher rate of co-existing headache in subjects with as compared to without IBS (odds ratio [OR] 2.65, $P < .001$). Furthermore, the percentage of subjects with anxiety along with comorbid IBS symptoms and headache was significantly greater as compared to those with IBS (OR 3.01, $P = .001$) or headache (OR 2.41, $P < .001$) alone. Unlike anxiety, the percentage of subjects with depression was not significantly different among the IBS/non-headache, non-IBS/headache, and IBS/headache groups.

Subjects with IBS symptoms had a higher rate of co-existing headache as compared to those without IBS. Furthermore, those with comorbid IBS symptoms and headache had a greater association with anxiety than with depression, as compared to those with only IBS or headache.

Abbreviations: CI = confidence interval, HADS = hospital anxiety and depression scale, HIT-6 = headache impact test-6, IBS = irritable bowel syndrome, OR = odds ratio.

Keywords: anxiety, depression, headache, irritable bowel syndrome, Rome III criteria

1. Introduction

Irritable bowel syndrome (IBS) is a type of functional gastrointestinal disorder characterized by chronic abdominal pain or discomfort, and also associated with disturbed defecation, as shown in the Rome III criteria.[1] The reported prevalence of IBS in community studies conducted in Asian countries ranges from 6.1% to 13.5%.[2–5] Affected individuals frequently show multiple comorbidities, such as fibromyalgia, interstitial cystitis, chronic fatigue syndrome, sleep disturbance, depression, anxiety, and headache.[5–9] Furthermore, IBS with 1 or more comorbid

Editor: Babić Žarko.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Kawashima K, Fukuba N, Uemura Y, Ota K, Kazumori H, Sonoyama H, Oka A, Tada Y, Mishima Y, Oshima N, Yuki T, Katsube T, Kinoshita Y, Ishihara S. Comorbid irritable bowel syndrome symptoms and headache have greater association with anxiety than depression: annual health check-up survey results. Medicine 2020;99:47(e23059).

Received: 28 February 2020 / Received in final form: 26 September 2020 / Accepted: 5 October 2020

http://dx.doi.org/10.1097/MD.0000000000023059

somatic disorders has been found to reduce quality of life (QOL) and impair individual health perception as compared to that without comorbidity.[10–12]

Among the various somatic comorbidities investigated, coexistence of IBS and headache has often been reported. In studies conducted in several different countries, headache was found to be associated with IBS in 25% to 50% of the examined subjects, significantly higher as compared to healthy individuals[6–7,13–15] On the other hand, the relationship between IBS and headache in individuals in Japan has not been investigated. Many of those reports noted a significant association of IBS with psychiatric disorders, such as anxiety, panic disorder, agoraphobia, and depression.[5,15–18] Similarly, headache including migraine may also be associated with such psychiatric disorders.[19,20] Therefore, it is speculated that a relationship exists between the 2 distinct functional pain disorders IBS and headache, and that they share a similar pathogenesis. However, the clinical characteristics of individuals with comorbid IBS and headache, including psychological factors such as depression and anxiety, have not been fully elucidated.

The aim of this large-scale prospective study was to clarify the presence of anxiety and depression state in subjects in Japan with and without IBS symptoms and/or headache.

2. Methods

2.1. Study subjects

This prospective cross-sectional study was performed from April 2012 to January 2013 at the Matsue Seikyo General Hospital Health Check Center in Japan. A total of 6223 individuals scheduled to undergo an annual health check-up examination were asked to participate, with most living in the eastern part of Shimane prefecture, a typical regional area. All questionnaires were sent by postal mail prior to the annual health check-up examination, and the recipients were asked to complete and return them at the time of their next visit. Individuals with a history of gastrointestinal tract or intracranial surgery, known neurological or digestive organic diseases, or a malignant tumor were excluded, as were those with an incomplete questionnaire. The study protocol was approved by the institutional ethics committee of Matsue Seikyo General Hospital.

2.2. Questionnaire

All prospective participants were asked to provide answers to a self-reported anonymous questionnaire concerning IBS symptoms, headache, and anxiety/depression state, in addition to age and gender. To precisely evaluate exclusion criteria, details regarding previous and present diseases, as noted above, were also queried. IBS symptoms were assessed based on the Japanese version of the Rome III diagnostic criteria,[21] and accordingly were defined as present in a subject who satisfied 2 of 3 of those criteria. Furthermore, IBS symptoms were classified into 4 subtypes; constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M), and unsubtyped (IBS-U).

Headache was evaluated using a Japanese translated version of the headache impact test-6 (HIT-6), which consists of 6 items and is used to determine the impact of headache on QOL.[22] The total HIT-6 score ranges from 36 to 76, with a higher score indicating a greater impact of headache on daily life. The presence of headache was defined as a score of 50 or greater, as previously reported.[23] Moreover, subjects with headache were classified into 3 groups according to the degree of disability; some impact (HIT-6: 50–55), substantial impact (HIT-6: 56–59), and severe impact (HIT-6: 60–78).

Anxiety and depression scoring was performed using the validated Hospital Anxiety and Depression Scale (HADS), a self-reported questionnaire comprised of 14 questions with the answers graded on a 4-point scale, as well as an anxiety subscale with 7 items and a depression subscale with 7 items.[24] To achieve high specificity, scores of 11 or more for anxiety (HADS-A) and 11 or more for depression (HADS-D) were used to indicate the presence of those conditions.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS statistical package (version 19.0, SPSS, Chicago, USA). Age is presented as the mean and standard deviation. Other parametric values are expressed as mean and standard error. Prevalence is presented as percentage with 95% confidence interval (CI). All *P*-values are 2-sided, with $P < .05$ considered to indicate statistical significance.

First, we investigated the presence of headache, and compared between subjects with and without IBS symptoms. Furthermore, the degree of disability caused by headache in subjects with and without IBS symptoms was examined. Statistical analysis was performed using a chi-square test or Student's t-test for categorical data.

For assessments of anxiety and depression, the subjects were divided into 4 groups; without IBS or headache (non-IBS/non-headache), with IBS and without headache (IBS/non-headache), without IBS and with headache (non-IBS/headache), and with IBS and headache (IBS/headache). The rates for presence of anxiety and depression were compared among those 4 groups using a chi-square test or ANOVA test for categorical data. Differences regarding anxiety and depression rates among the groups are expressed as odds ratios (OR) with 95% CI.

3. Results

3.1. Clinical characteristics of enrolled subjects

Of the 6223 individuals sent a questionnaire prior to the health check-up, 3017 returned that at the time of their visit for an overall response rate of 48.5%. Of those, 132 were excluded due to incomplete status or other exclusion criteria, thus 2885 (1535 males, 1350 females; mean age 50.4 ± 10.9 years) were enrolled as subjects for this study. Their clinical characteristics are shown in Table 1. The rates for presence of IBS symptoms, headache, anxiety, and depression were 7.6% (95% CI 6.7–8.6%), 24.5% (95% CI 23.0–26.1%), 8.5% (95% CI 7.6–9.6%), and 14.0% (95% CI 12.8–15.3%), respectively. Of the 218 with IBS symptoms, 39 (17.9%) were classified as IBS-C, 70 (32.1%) as IBS-D, 21 (9.6%) as IBS-M, and 88 (40.4%) as IBS-U. As for gender difference, the presence of IBS was noted in 106 of the 1535 males (6.9%, 95% CI 5.7–8.2%) and 112 of the 1350 females (8.3%, 95%CI 6.9–9.9%).

3.2. Relationship between IBS and headache

As shown in Figure 1, the presence of headache was noted in 96 of 218 subjects with IBS symptoms (44.0%, 95%CI 37.3–50.9%) and 611 of 2667 of those without IBS symptoms (22.9%, 95%CI

Table 1

Clinical characteristics of enrolled subjects.

Number	2885
Gender	
Male	1535 (53.2%)
Female	1350 (46.8%)
Age, years (mean ± SD, range)	50.4 ± 10.9 (18–83)
IBS symptoms	
Absence	2667 (92.4%)
Presence	218 (7.6%)
IBS with constipation (IBS-C)	39/218 (17.9%)
IBS with diarrhea (IBS-D)	70/218 (32.1%)
Mixed IBS (IBS-M)	21/218 (9.6%)
Unsubtyped IBS (IBS-U)	88/218 (40.4%)
Headache	
Absence (HIT-6: 36–49)	2178 (75.5%)
Presence (HIT-6: 50–78)	707 (24.5%)
Some impact (HIT-6: 50–55)	371 (12.9%)
Substantial impact (HIT-6: 56–59)	140 (4.9%)
Severe impact (HIT-6: 60–78)	196 (6.8%)
Anxiety	
HADS-A (mean ± SE)	5.29 ± 0.065
Absence (HADS-A: ≤10)	2639 (91.5%)
Presence (HADS-A: ≥11)	246 (8.5%)
Depression	
HADS-D (mean ± SE)	6.58 ± 0.064
Absence (HADS-D: ≤10)	2482 (86.0%)
Presence (HADS-D: ≥11)	403 (14.0%)

IBS = irritable bowel syndrome, HADS = hospital anxiety and depression score, SD = standard deviation, SE = standard error.

21.4–24.5%), showing a significantly higher rate for the presence of headache in subjects with as compared to without IBS symptoms (OR 2.65; 95% CI 2.00–3.51, $p < 0.001$). Furthermore, the average HIT-6 score for subjects with IBS symptoms was 47.9 ± 0.61, significantly higher than that for those without IBS symptoms (43.9 ± 0.15) ($p < 0.001$). Findings showing the degree of disability from headache in subjects with and without IBS symptoms are shown in Table 2. The degree of disability caused by headache in subjects with IBS symptoms was significantly more severe as compared to those without IBS symptoms ($p < 0.001$).

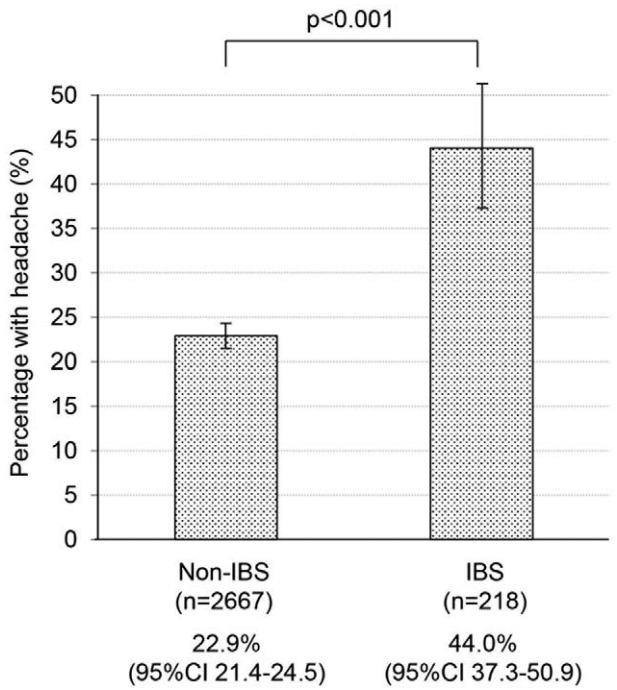

Figure 1. Percentages of subjects with headache symptoms with and without IBS. Error bar: 95% CI.

3.3. Anxiety and depression in subjects with and without IBS and/or headache

The average HADS score, as well as rates for presence of anxiety and depression in subjects with and without IBS symptoms and/or headache are shown in Table 3. There were 2056 subjects in the non-IBS/non-headache group, 122 in the IBS/non-headache group, 611 in the non-IBS/headache group, and 96 in the IBS/headache group.

Rates for the presence of anxiety and depression in subjects with and without IBS symptoms and/or headache are shown in Figure 2, and differences for those rates among the 4 groups are presented as OR and 95% CI in Table 4. The rate of anxiety was greater in the IBS/non-headache, non-IBS/headache, and IBS/headache groups as compared to the non-IBS/non-headache group. In particular, anxiety in subjects in the IBS/headache group showed a significantly greater rate as compared to subjects with only IBS (OR 3.01; 95% CI 1.54–5.90, $p = 0.001$) or headache (OR 2.41; 95% CI 1.49–3.89, $p < 0.001$). The rate of depression was also greater in the IBS/non-headache, non-IBS/headache, and IBS/headache groups as compared to the non-IBS/non-headache group. However, unlike anxiety, there was no significant increase in presence of depression observed in the IBS/headache group as compared to the non-IBS/headache and IBS/non-headache groups. Thus, subjects with comorbid IBS symptoms and headache showed a greater association with anxiety than depression, as compared to those with only IBS symptoms or headache. The average HADS scores for anxiety and depression in subjects with and without IBS symptoms and/or headache were significantly different among the 4 groups ($P < .001$), and highly similar to the results regarding presence of anxiety and depression.

4. Discussion

In this prospective large-scale study of results from an annual health check-up survey conducted in Japan, a high rate of comorbidity of IBS symptoms and headache based on Rome III criteria was demonstrated. Furthermore, comorbid headache in subjects with IBS symptoms was associated with a significantly greater degree of disability as compared to those without IBS symptoms. The most important finding is that IBS symptoms and headache comorbidity had a greater association with anxiety than depression in our cohort as compared to only IBS symptoms or headache, though the present investigation was not a hospital-based study.

The coexistence of IBS symptoms and headache has been reported in studies that analyzed epidemiological data.[6,15,25] Among several kinds of headache, migraine has been shown to be strongly related to IBS, because of possible common pathogenetic mechanisms as well as clinical characteristics.[25–27] In particular, dysregulation of the brain-gut axis plays a major role in the pathophysiology of IBS and migraine.[25,28–33] In individuals with IBS, visceral hypersensitivity has been primarily observed in the

Table 2

The degree of disability from headache in subjects with and without IBS symptoms.

	Absence of headache (HIT-6: 36–49)	Some impact (HIT-6: 50–55)	Substantial impact (HIT-6: 56–59)	Severe impact (HIT-6: 60–78)	*P* value
Subjects without IBS symptoms (n = 2667)	2056 (77.1%)	328 (12.3%)	118 (4.4%)	165 (6.2%)	<.001
Subjects with IBS symptoms (n = 218)	122 (56.0%)	43 (19.7%)	22 (10.1%)	31 (14.2%)	

IBS = irritable bowel syndrome.

Table 3

Anxiety and depression state in subjects with and without IBS and/or headache.

	Number	HADS-A (mean ± SE)	Presence of anxiety (percentage, 95% CI)	HADS-D (mean ± SE)	Presence of depression (percentage, 95% CI)
Non-IBS/non-headache	2056	4.60 ± 0.07	5.0 (4.1–6.0)	6.16 ± 0.07	10.9 (9.6–12.3)
IBS/non-headache	122	6.23 ± 0.32	13.1 (7.7–20.4)	7.40 ± 0.31	17.2 (11.0–25.1)
Non-IBS/headache	611	6.84 ± 0.15	15.9 (13.0–19.0)	7.64 ± 0.14	22.4 (19.2–25.9)
IBS/headache	96	8.94 ± 0.44	31.3 (22.2–41.5)	7.84 ± 0.38	21.9 (14.1–35.1)

IBS = irritable bowel syndrome, HADS = hospital anxiety and depression score, CI = confidence interval.

enteric nervous system, while various central and peripheral factors may enhance pain sensitivity.[32,33] As for migraine, activation and sensitization of the trigeminovascular pain pathway has been shown to lead to an interictal headache.[34] Chang, et al. proposed that both of these distinct chronic pain disorders share many similarities among multiple aspects and may be considered to lie within the same spectrum of pain-centered disorders, such as also noted with central sensitization syndromes.[25] In this regard, serotonin is an important neurotransmitter related to both disorders, though the mechanisms differ for each disease.[30,31,35] In individuals with IBS, serotonin induces excessive bowel movements and massive digestive secretion, as well as visceral hypersensitivity in the gut or central nervous system.[29–33] Thus, serotonin type 3 receptor antagonists are widely used to treat patients with the diarrhea-predominant subtype of IBS. Likewise, defective serotonin activity in the central nervous system may lead to an interictal headache such as migraine, as some types of serotonin agonists have been shown effective to treat patients affected by migraine.[36] Furthermore, strong familial aggregation and genetic polymorphisms, such as the serotonin reuptake transporter gene, have been found in subjects with both IBS and migraine.[30,37,38] Recently, Lackner demonstrated that the presence of a tension headache in subjects with IBS led to a reduction in QOL and psychological distress.[10] Therefore, it may be important to take into account both comorbid tension headache and migraine when considering the pathophysiology of comorbid IBS and headache.

Although the present study did not distinguish among kinds of headache due to assessment using HIT-6, a strong point is evaluation of headache as a cause of disability. In previous population-based investigations conducted in several countries,

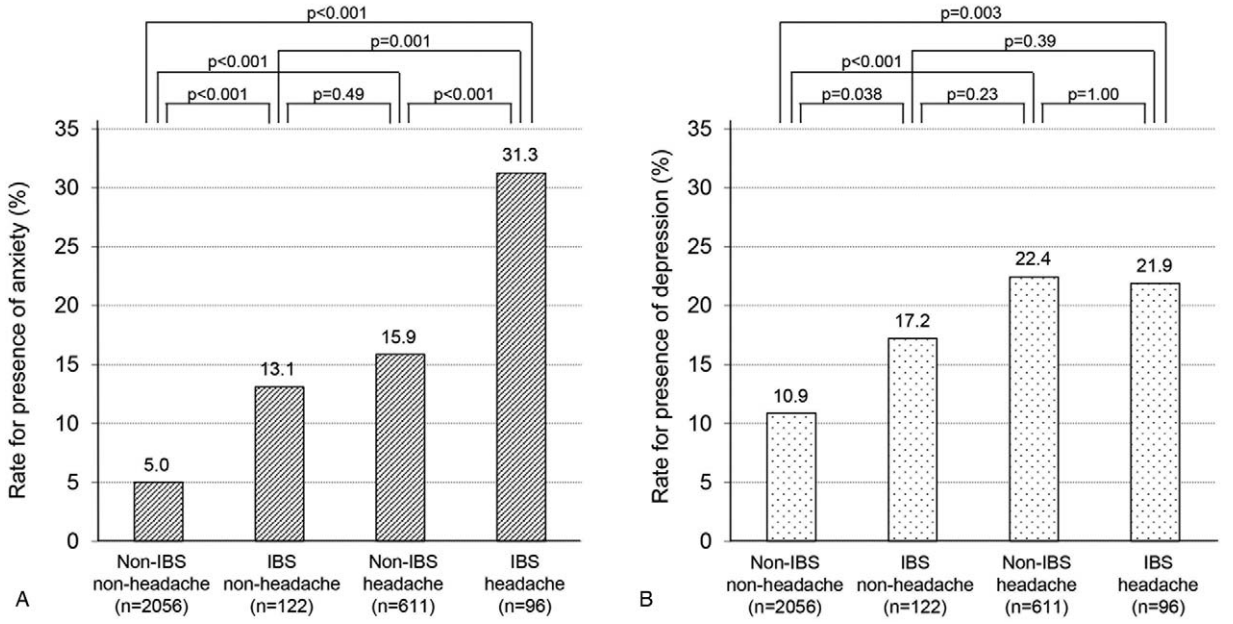

Figure 2. Rates for presence of (A) anxiety and (B) depression in subjects with and without IBS and/or headache.

Table 4

Differences regarding presence of anxiety and depression among subjects with and without IBS and/or headache.

Psychiatric	Groups	OR	95% CI	*P* value
Anxiety	IBS/non-headache vs non-IBS/non-headache	2.86	1.64–4.99	<.001
	Non-IBS/headache vs non-IBS/non-headache	3.58	2.70–4.80	<.001
	IBS/headache vs non-IBS/non-headache	8.62	5.38–13.80	<.001
	IBS/non-headache vs non-IBS/headache	0.80	0.46–1.40	.49
	IBS/headache vs IBS/non-headache	3.01	1.54–5.90	.001
	IBS/headache vs non-IBS/headache	2.41	1.49–3.89	<.001
Depression	IBS/non-headache vs. non-IBS/non-headache	1.70	1.05–2.77	.038
	Non-IBS/headache vs non-IBS/non-headache	2.36	1.87–2.99	<.001
	IBS/headache vs. non-IBS/non-headache	2.29	1.39–3.77	.003
	IBS/non-headache vs. non-IBS/headache	0.72	0.44–1.19	.23
	IBS/headache vs IBS/non-headache	1.35	0.69–2.63	.39
	IBS/headache vs non-IBS/headache	0.97	0.58–1.62	1.00

OR = odds ratio, CI = confidence interval, IBS = irritable bowel syndrome.

chronic headache was found in 25–50% of IBS subjects,[12–16] while a recent meta-analysis revealed that subjects with IBS had an overall estimated odds ratio of 2.66 for headache/migraine comorbidity.[25] In Japan, employers are required by law to provide annual health check-up examination for all employees, thus most of the present eligible subjects were company workers. This is the first study to examine the presence of comorbid IBS symptoms and headache in individuals in Japan, and we found that 44.0% of the present subjects with IBS symptoms also had headache symptoms, with an odds ratio of 2.65 for IBS subjects with headache comorbidity. These results are quite similar to those of previous studies conducted in several different countries.

It is widely known that either IBS or headache is strongly correlated with psychiatric disorders, such as anxiety and depression. However, the mental burden in subjects with comorbid IBS and headache has not been fully investigated. A recent report noted that the prevalence of both anxiety and depression is increased with an increasing number of coexistent functional gastrointestinal disorder.[18] In a hospital-based study of migraine patients, comorbidity with IBS also had a significant association with anxiety and depression.[27] In contrast to those results, the present findings demonstrated that subjects with both IBS symptoms and headache had a greater association with anxiety than depression, as compared to those with only IBS symptoms or headache. This result may be because the subjects of our study were chosen from individuals scheduled to undergo an annual health check-up, who may have a different mental state as compared to those who visit a hospital for treatment of either IBS or headache. It is also possible that individuals with depression as well as those with comorbid IBS and headache might not choose to undergo an annual health check-up examination, thus selection bias should be considered when interpreting the present results.

Regarding treatment of anxiety disorder, available serotonin receptors are generally type 1 and 2, and similarly are very important for treating patients with migraine. In clinical practice, serotonin receptor type 1B/1D agonists are often used for migraine treatment, while, as noted above, serotonin type 3 and 4 receptors are considered to be important for management of IBS.[35,36] Among the present subjects, those with comorbid IBS and headache had a greater association with anxiety than depression. In other words, anxiety state was shown likely to have a strong causal relationship with comorbid IBS symptoms and headache as compared to depression, though this was not a hospital-based study. In addition, the present findings also have important clinical implications. It is considered that anxiety probably precedes IBS onset and a psychiatric disorder cannot be regarded as a response to IBS. When examining a patient with comorbid IBS symptoms and headache in daily practice, it is important to consider not only other pain disorders but also subclinical psychiatric disorders, particularly anxiety.

This study has several limitations. First, the type of headache experienced by each subject was not determined. Paradoxically, the present evaluation that categorized all types of headache as headache disability might be a strong point, as some individuals are affected by both migraine and tension headaches. Second, concomitant use of medications was not investigated, though that is an important factor. It is possible that subjects receiving a non-steroidal anti-inflammatory drug for headache treatment also experienced abdominal pain induced by such administration. Third, the presence of IBS symptoms and headache was determined based on findings obtained with questionnaires, and organic diseases may not have been completely excluded. However, a previous reported noted that the prevalence of organic colonic diseases in patients who met the Rome III criteria was similar to that in those who did not meet those criteria, indicating that the criteria are adequately specific for a diagnosis of IBS without colonoscopy results.[39] Finally, for determining the presence of IBS symptoms in the present cohort, the Rome III criteria were used. In 2016, those criteria were updated to Rome IV for diagnosis of IBS and in future studies it will be necessary to utilize current diagnostic criteria.[40]

In conclusion, using results obtained in an annual health check-up survey conducted in Japan, we found that a high rate of adult subjects with IBS symptoms were affected by comorbid headache as compared to those without IBS. Furthermore, subjects with comorbid IBS and headache had a greater association with anxiety as compared to depression than those with only IBS or headache.

Acknowledgments

The authors thank the nurses and medical staff of the Matsue Seikyo General Hospital Health Check Center for their kind help with the present study.

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