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Meta-analysis

The Increased Level of Depression and Anxiety in Irritable Bowel Syndrome Patients Compared with Healthy Controls: Systematic Review and Meta-analysis

Changhyun Lee,[1] Eunyoung Doo,[1] Ji Min Choi,[1] Seung-ho Jang,[2] Han-Seung Ryu,[3] Ju Yup Lee,[4] Jung Hwan Oh,[5] Jung Ho Park,[6] and Yong Sung Kim[7]*; Brain-Gut Axis Research Group of Korean Society of Neurogastroenterology and Motility

[1]Department of Internal Medicine and Healthcare Research Institute, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea; [2]Department of Psychiatry, School of Medicine, Wonkwang University, Iksan, Jeollabuk-do, Korea; [3]Department of Gastroenterology and Digestive Disease Research Institute, Wonkwang University School of Medicine, Iksan, Jeollabuk-do, Korea; [4]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea; [5]Division of Gastroenterology, Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea; [6]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; and [7]Division of Gastroenterology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo, Gyeonggi-do, Korea

Background/Aims
Irritable bowel syndrome (IBS) patients commonly experience psychiatric disorders, such as depression and anxiety. This meta-analysis sought to compare depression and anxiety levels between IBS patients and healthy controls.

Methods
We searched major electronic databases (PubMed, EMBASE, MEDLINE, and Cochrane library) to find comparative studies on IBS patients and healthy controls. The primary outcome was a standardized mean difference (SMD) of anxiety and depression levels; sub-group analyses were conducted according to IBS-subtypes.

Results
In total, 2293 IBS patients and 4951 healthy controls from 27 studies were included. In random effect analysis, depression and anxiety levels were significantly higher in IBS patients (pooled SMD = 0.76; 95% CI, 0.62-0.90; $P < 0.001$; $I^2 = 77.2\%$ and pooled SMD = 0.84; 95% CI, 0.67-1.01; $P < 0.001$; $I^2 = 85.6\%$, respectively). Both analyses' funnel plots showed symmetry. In meta-regression analysis, heterogeneity was due to the studied region and questionnaire type for both depression and anxiety. In sub-group analyses of IBS-subtype, the pooled SMDs of depression and anxiety levels (IBS with predominant constipation: 0.83 and 0.81, IBS with predominant diarrhea: 0.73 and 0.65, and IBS with mixed bowel habits: 0.62 and 0.75; $P < 0.001$, respectively) were significantly higher in all IBS-subtypes.

Conclusions
The present meta-analysis showed depression and anxiety levels to be higher in IBS patients than in healthy controls, regardless of IBS-subtype. However, the gender effect on psychological factors among IBS patients could not be determined and should be evaluated in prospective studies.
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Key Words
Anxiety; Depression; Irritable bowel syndrome; Meta-analysis

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*Correspondence: Yong Sung Kim, MD, PhD
Division of Gastroenterology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, 327 Sanbon-ro, Gunpo, Gyeonggi-do 15865, Korea
Tel: +82-31-390-2973, Fax: +82-31-390-2244, E-mail: wms89@hanmail.net
Changhyun Lee and Eunyoung Doo contributed equally to this article

Introduction

The Rome IV criteria defined functional gastrointestinal (GI) disorders (FGID) as "disorders of gut-brain interaction" because symptoms are generated not only in the gut, but also by the complex interactions among factors such as gut dysbiosis, altered gut signaling, and dysregulation of the central nervous system.[1] Irritable bowel syndrome (IBS) is the most prevalent FGID, affecting approximately 10-15% of populations; diagnosis requires recurrent abdominal pain associated with ≥ 2 of the following: (1) defecation, (2) a change in stool frequency, and (3) a change in stool form.[2,3]

Psychological problems such as anxiety and depression are common in IBS patients.[4] Overlap between depression and FGID is about 30% and anxiety disorders are the most common psychiatric comorbidity in FGID patients.[4,5] The psychosocial modifiers of IBS were emphasized in the "multi-dimensional clinical profile" introduced by the Rome IV criteria[1] because psychological factors influence IBS symptoms, modify illness behavior (eg, healthcare seeking), and contribute to poor outcomes.[1]

The brain-gut axis is the hard-wiring between the brain and gut, communicating information from the brain's emotional network (eg, from the cingulate cortex to the peripheral GI tract and vice versa). Therefore, the perception of pain is influenced by the emotional mechanism; IBS symptoms can also be affected by the psychological state.[6,7] Treatment directed towards psychiatric conditions can reduce IBS symptoms' severity.[8] Furthermore, psychosocial factors such as the psychological state, individual's traits, and life stress also affect the gut physiology through the brain–gut axis in the biopsychosocial model of IBS.[4] Psychosocial factors impair mucosal secretory and barrier function through alteration of the efferent autonomic nervous system and the stress hormone system (hypothalamo-pituitary-adrenal axis), resulting in the translocation of bacterial cell products.[1,4,9] Animal studies have demonstrated the influence of stress on colonic permeability, and mucosal and systemic inflammation's mediation by the autonomic nervous system and the hypothalamo-pituitary-adrenal axis.[4]

Several recently published studies have mapped IBS's relationship with psychological disorders[10-16] and compared depression and anxiety levels in IBS-subtypes.[15,17,18] However, the relationship between IBS and psychological disorders (depression or anxiety) was inconsistent, even in a recent meta-analysis entailing eight studies.[19] The heterogeneity of the results was too high, with no further analysis of its cause. Furthermore, IBS-subtypes failed to show statistical significance for both anxiety and depression, except IBS with predominant constipation (IBS-C) and IBS with predominant diarrhea (IBS-D) for anxiety, and IBS-D for depression, because few studies were included.

Knowledge of IBS's correlation with psychiatric disorders would enhance understanding and treatment of IBS patients, as psychological distress could exacerbate symptoms, negatively affect treatment outcomes, and affect doctor-patient relationships.[4] The aim of this meta-analysis was to compare depression and anxiety levels between IBS patients and healthy controls, also considering IBS subtypes and patient gender.

Materials and Methods

The protocol for this review was prospectively developed, detailing specific patients, healthy controls, the primary outcome, study selection criteria, and study quality checks. The checklist and flow chart of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement were referred to, to achieve the highest standard in reporting items for a systematic review and meta-analysis.

Searching Strategy

The following inclusion criteria were applied: (1) articles published from January 2000 to July 2016 in peer-reviewed journals, (2) comparative studies on IBS patients and healthy controls, (3) adults ≥ 18 years, and (4) depression and anxiety levels presented or extracted as mean ± SD. Our search terms were "((irritable bowel syndrome) OR irritable bowel syndrome[MeSH Terms]) AND (((depression) OR depression[MeSH Terms]) OR depressive disorders[MeSH Terms])) AND (((anxiety) OR anxiety disorders[MeSH Terms]) OR anxiety[MeSH Terms]))) AND "2000/01/01"[Date - Publication] : "2016/07/31"[Date - Publication]" for PubMed; "'irritable bowel syndrome' AND ('depressive disorder' OR 'depression') AND ('anxiety disorder' OR 'anxiety') AND 'article'/it AND [1-1-2000]/sd NOT [31-7-2016]/sd AND [embase]/lim" for Embase; ""irritable bowel syndrome' AND ('depressive disorder' OR 'depression') AND ('anxiety disorder' OR 'anxiety') AND [2000-2016]/py NOT [31-7-2016]/sd AND 'article'/it AND [medline]/lim" for Medline; ""irritable bowel syndrome" in Title, Abstract, Keywords and "anxiety disorder" OR "anxiety" in Title, Abstract, Keywords and "depression" OR "depressive disorder" in Title, Abstract, Keywords" in Cochrane Reviews for Cochrane library.

Study Selection

The results from the database search were imported into EndNote X7 software (Thomson Reuters, Philadelphia, PA, USA) and combined to remove duplicates. Two authors (C.L. and E.D.) independently assessed the titles and abstracts of all the studies identified through the search outlined above. Full texts of studies fulfilling the inclusion criteria were obtained and reviewed. Exclusion criteria were (1) studies did not present depression or anxiety scores, (2) studies that could not determine the mean and SD, (3) studies with no healthy controls, (4) studies with only one IBS-subtype or only post-infectious IBS, (5) studies with low quality scores, and (6) duplicated study data. Disagreements were resolved through discussion; otherwise the co-author, Y.S.K., was consulted.

Assessing Methodological Quality

Two independent authors (C.L. and E.D.) assessed article quality according to the Newcastle-Ottawa Scale for "case-control studies."[20] The quality scale ranges from 0 to 9 points, with ≤ 4 indicating poor article quality, and warranting its exclusion.

Data Extraction

Two authors (C.L. and E.D.) independently analyzed articles and extracted data using a pre-defined data extraction worksheet. The following information was extracted from each article: title, first author, publication year, country of origin, IBS criteria, type of questionnaire for depression, type of questionnaire for anxiety, the number of IBS patients, the number of healthy controls, the proportion of females in the IBS group, the mean and SD of depression levels, and the mean and SD of anxiety levels. To determine depression and anxiety levels in IBS-subtypes, the following information was also extracted: the number of IBS-subtype patients and means and SDs of depression and anxiety levels among these. In this meta-analysis, the standardized mean difference (SMD) was used for comparing IBS patients' and healthy controls' anxiety and depression levels because various types of questionnaires were used to assess these variables. We estimated SD from the standard error (SE) of the mean, using the formula $SD = SE \times \sqrt{N}$, and calculated SD from a 95% confidence interval (CI) using the formula $SD = \sqrt{N} \times (\text{Upper limits} - \text{Lower limits}) \div 3.92$.

Statistical Analysis and Risk of Bias Assessment

Meta-analysis was conducted using STATA ver. 14.1 (Stata Corp, College Station, TX, USA). We used the STATA "metan" command for calculating SMD with 95% confidence intervals. If the studies showed substantial heterogeneity ($I^2 > 50\%$), we used random effects models. We also used the STATA "metan" command to create the forest plot. Publication bias was assessed through the Egger's test, using the "metabias" command, and presented graphically with funnel plots, using the "metafunnel" command. The cause of heterogeneity was analyzed using the "metareg" command.

Results

Search Results

Through a database search, 1737 records were identified (PubMed, n = 637; Embase, n = 579; Medline library, n = 517; Cochrane library, n = 1; other sources,[21-23] n = 3) and 837 records remained after duplicates were removed. Initial screening of the title and abstracts resulted in 786 records being excluded. Full texts of the remaining 51 records were reviewed in detail. A total of 27 articles were included in this systemic review and meta-analysis,[10-13,15-17,21-40] and 24 articles were excluded with specific reasons; (1) 8 studies without depression or anxiety scores,[41-48] (2) 3 studies from which the mean and SD could not be determined,[49-51] (3) 4 studies with no healthy controls,[14,52-55] (4) 2 studies with only one IBS-subtype or post-infectious IBS,[56,57] (5) 5 studies with low quality scores (Newcastle-Ottawa Scale ≤ 4),[58-62] and (6) 2 studies with duplicated data.[63,64] The selection process according to the PRISMA flow diagram is shown in Figure 1.

Baseline Characteristics of Included Studies

A total of 2293 IBS patients and 4951 healthy controls were included from 27 studies.[10-13,15-17,21-40] The baseline characteristics of included studies are shown in Table 1 and the major findings were listed in Supplementary Table. Eight studies were conducted in East Asia,[11-13,16,26,31,37,40] 7 in the USA,[10,17,21-23,30,33] 7 in Europe,[15,27,29,32,34-36] and 5 in the other regions.[24,25,28,38,39] Three studies were cross-sectional,[22,24,31] 11 were age-sex matched case-control studies,[11,12,15,16,21,25-27,37,40] 9 were unmatched case-control studies,[10,13,23,28,29,34,35,38,39] and 4 were case-control studies that enrolled female participants only.[17,30,32,33] IBS was diagnosed using the Rome III criteria in 10 studies,[10-13,15,16,32,35,39,40] Rome II criteria in 11 studies,[17,21,24,28,29,31,33,34,36-38] Bowel Disease Questionnaire in 3 studies,[22,23,30] Manning's criteria in 2 studies,[25,27] and the Rome I criteria in 1 study.[26] The level of depression was assessed using the Hospitalization Anxiety and Depression Scale (HADS) in 14 studies,[10,15-17,21,25,27,28,32,34,37-40] Beck Depression Inventory (BDI) in

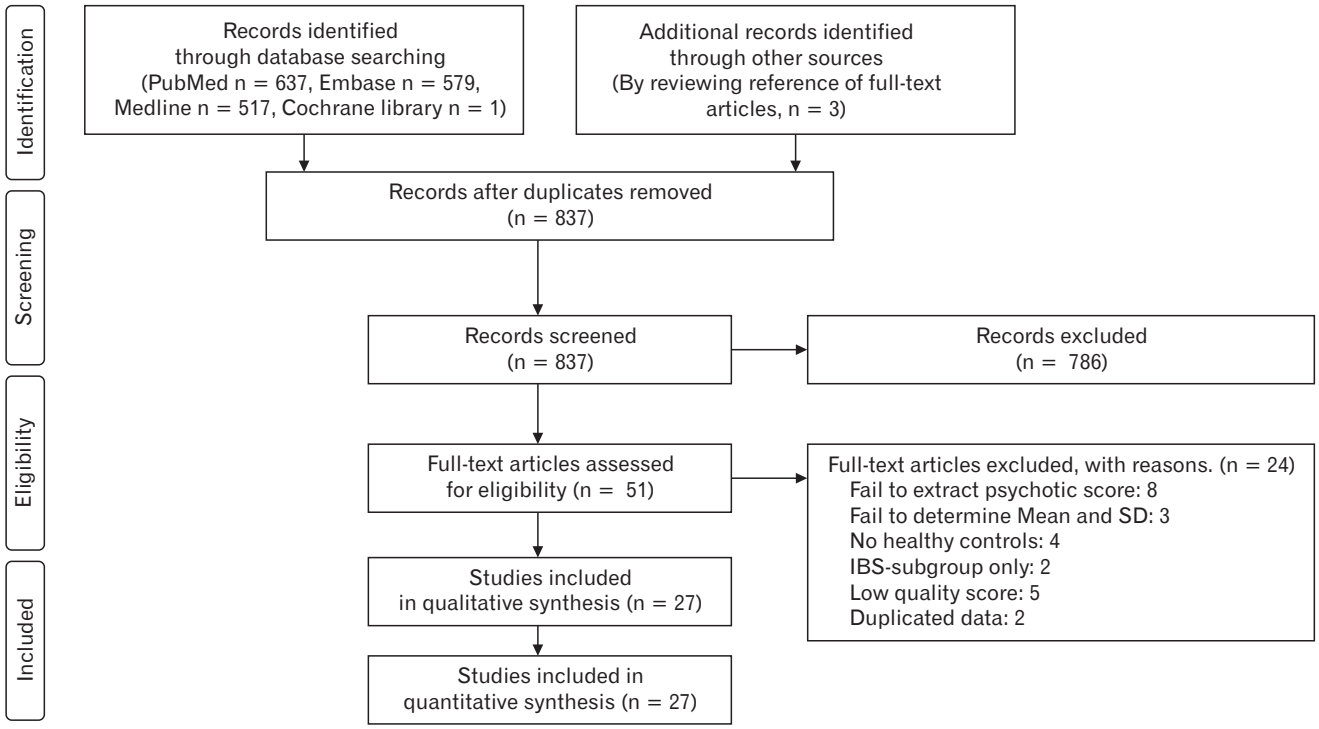

Figure 1. PRISMA flow diagram of the meta-analysis. IBS, irritable bowel syndrome.

5 studies,[26,27,30,33,35] Self-Rating Depression Scale (SDS) in 4 studies,[11-13,31] Symptom Checklist (SCL)-90 in 3 studies,[22,23,29] and the Sphere score in 1 study.[24] The anxiety score was assessed using the HADS in 15 studies,[10,15-17,21,25,28,32,34-40] State and Trait Anxiety Inventory (STAI) in 5 studies,[11,13,26,27,33] Self Rating Anxiety Scale (SAS) in 2 studies,[12,31] SCL-90 score in 3 studies,[22,29] Sphere score in 1 study,[24] and the Beck Anxiety Inventory (BAI) in 1 study.[30]

The Depression Level in Irritable Bowel Syndrome Patients

Depression levels in IBS patients were higher than in healthy controls (Pooled SMD, 0.76; 95% CI, 0.62-0.90; $P < 0.001$; Fig. 2A). We used the random effect analysis because this result showed medium heterogeneity ($I^2 = 77.2\%$). Egger's test ($P = 0.287$) showed no small-study effects and the funnel plot showed no asymmetry, except for 8 outlier studies (Fig. 2B).[11,13,22,25,28,29,34,36] However, 4 of 8 outlier studies were age-sex (hyphen) unmatched.[13,28,29,34]

The Anxiety Level in Irritable Bowel Syndrome Patients

Anxiety levels in IBS patients were also higher than in healthy controls (Pooled SMD, 0.84; 95% CI, 0.67-1.01; $P < 0.001$; Fig. 3A). We also used random effect analysis because this result showed high heterogeneity ($I^2 = 85.6\%$), Egger's test ($P = 0.313$) showed no small-study effects, and the funnel plot showed no asymmetry, except 9 outlier studies (Fig. 3B).[10,11,13,22,25,28,29,35,36]

Meta-regression Analysis and Sub-group Analysis

Meta-regression analysis was conducted due to medium and high heterogeneity. The result of meta-regression is shown in Table 2. In the meta-regression analysis, the heterogeneity of pooled SMD in the level of depression was due to the studied region (East Asia, USA, Europe, and others; $P = 0.007$) and type of depression questionnaire used (HADS, BDI, SDS, and others; $P < 0.001$). The heterogeneity of pooled SMD in the level of anxiety was also due to the studied region (East Asia, USA, Europe, and others; $P = 0.002$) and type of anxiety questionnaire used (HADS, STAI, SAS, and others; $P = 0.007$). Pooled SMD according to subgroup analyses is also shown in Table 2. Wherein depression levels are assessed through a subgroup analysis, studies using the HADS (pooled SMD, 1.02; 95% CI, 0.83-1.21; $I^2 = 66.3\%$) and the BDI (pooled SMD, 0.71; 95% CI, 0.52-0.90; $I^2 = 0\%$) showed higher SMD than other questionnaires. Furthermore, studies conducted in East Asia showed the lowest pooled SMD (pooled

Table 1. Characteristics of Studies Included in the Meta-analysis

Study author	Year	Country	Criteria for IBS	Newcastle-Ottawa Scale	Questionnaire score		Sample size		Female proportion in IBS group (%)
					Depression	Anxiety	IBS	Control	
Boyce et al[24]	2000	Australia	Rome II	6	Sphere	Sphere	201	2512	68.7
Pinto et al[25]	2000	India	Manning	6	HADS	HADS	30	30	33.3
Su et al[26]	2000	Taiwan	Rome I	5	BDI	STAI	69	52	49.0
Patacchioli et al[27]	2001	Italy	Manning	6	BDI	STAI	55	28	61.0
Locke et al[23]	2004	USA	BDQ	5	SCL-90	SCL-90	69	119	73
Liebregts et al[28]	2007	Australia	Rome II	5	HADS	HADS	55	36	60.0
Van der veek et al[29]	2008	Netherlands	Rome II	6	SCL-90	SCL-90	101	40	73.0
Choung et al[22]	2009	USA	BDQ	8	SCL-90	SCL-90	106	355	49.1
Savas et al[30]	2009	USA	BDQ	6	BDI-II	BAI	93	140	100
Shen et al[31]	2009	China	Rome II	6	SDS	SAS	77	414	54.5
Elsenbruch et al[32]	2010	Germany	Rome III	5	HADS	HADS	15	12	100
Heymen et al[33]	2010	USA	Rome II	5	BDI	STAI	27	21	100
Jerndal et al[34]	2010	Sweden	Rome II	6	HADS	HADS	306	60	76.7
Seminowicz et al[17]	2010	USA	Rome II	5	HADS	HADS	55	48	100
Tosic-Golubovic et al[36]	2010	Serbia	Rome II	5	HADS	HADS	30	30	50
Piche et al[35]	2010	France	Rome III	5	BDI	HADS	40	20	30
Cho et al[37]	2011	Korea	Rome II	6	HADS	HADS	124	91	49.2
Berman et al[21]	2012	USA	Rome II	6	HADS	HADS	11	11	54.5
Goncalves de Medeiros et al[38]	2012	Brazil	Rome II	5	HADS	HADS	21	8	76.2
Hartono et al[39]	2012	Malaysia	Rome III	5	HADS	HADS	62	62	55
Lee et al[40]	2012	Taiwan	Rome III	6	HADS	HADS	17	17	64.7
Orand et al[10]	2015	USA	Rome III	5	HADS	HADS	277	382	75.2
Komuro et al[11]	2016	Japan	Rome III	5	SDS	STAI	142	142	56.3
Qi et al[12]	2016	China	Rome III	7	SDS	SAS	32	31	19.4
Sasaki et al[13]	2016	Japan	Rome III	5	SDS	STAI	111	142	57.7
Thijssen et al[15]	2016	Netherlands	Rome III	6	HADS	HADS	154	137	70.0
Wong et al[16]	2016	Singapore	Rome III	5	HADS	HADS	13	11	53.8

IBS, irritable bowel syndrome; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; HADS, Hospitalization Anxiety and Depression Scale; SAS, Self-Rating Anxiety Scale; SCL-90, Symptom Checklist-90; SDS, Self-Rating Depression Scale; STAI, State and Trait Anxiety Inventory.

SMD, 0.50; 95% CI, 0.32-0.69; $I^2 = 56.3\%$). Wherein anxiety levels were assessed through a subgroup analysis, studies using the STAI and the SAS showed low heterogeneity ($I^2 = 48.5\%$ and $I^2 = 0.0\%$, respectively); those conducted in East Asia also showed the lowest pooled SMD (pooled SMD, 0.51; 95% CI, 0.29-0.73; $I^2 = 68.5\%$).

Depression and Anxiety in Irritable Bowel Syndrome-subtype

Depression and anxiety levels in IBS-subtype patients were also analyzed. A total of six studies were included.[15,17,18,37,38,65] In those studies, healthy-control groups were used for multiple comparisons with the three IBS-subtypes; we divided the healthy-control group into three groups for meta-analysis of three IBS-subtypes alongside healthy controls. Depression levels were significantly higher in IBS-C (SMD = 0.83; 95% CI, 0.61-1.06; $I^2 = 0\%$; $P < 0.001$), IBS-D (SMD = 0.73; 95% CI, 0.51-0.96; $I^2 = 0\%$; $P < 0.001$), and IBS with mixed bowel habits (SMD = 0.62; 95% CI, 0.39-0.84; $I^2 = 0\%$; $P < 0.001$) (Fig. 4A). Egger's test ($P = 0.323$) showed no small-study effects and the funnel plot showed symmetry (Fig. 4B). Anxiety levels were also significantly higher in IBS-C (SMD = 0.81; 95% CI, 0.59-1.04; $I^2 = 0\%$; $P < 0.001$), IBS-D (SMD = 0.65; 95% CI, 0.43-0.87; $I^2 = 0\%$; $P < 0.001$), and IBS with mixed bowel habits (SMD = 0.75; 95% CI, 0.52-0.97; $I^2 = 0\%$; $P < 0.001$) (Fig. 5A). Egger's test ($P = 0.830$) showed no small-study effects and the funnel plot showed symmetry (Fig. 5B).

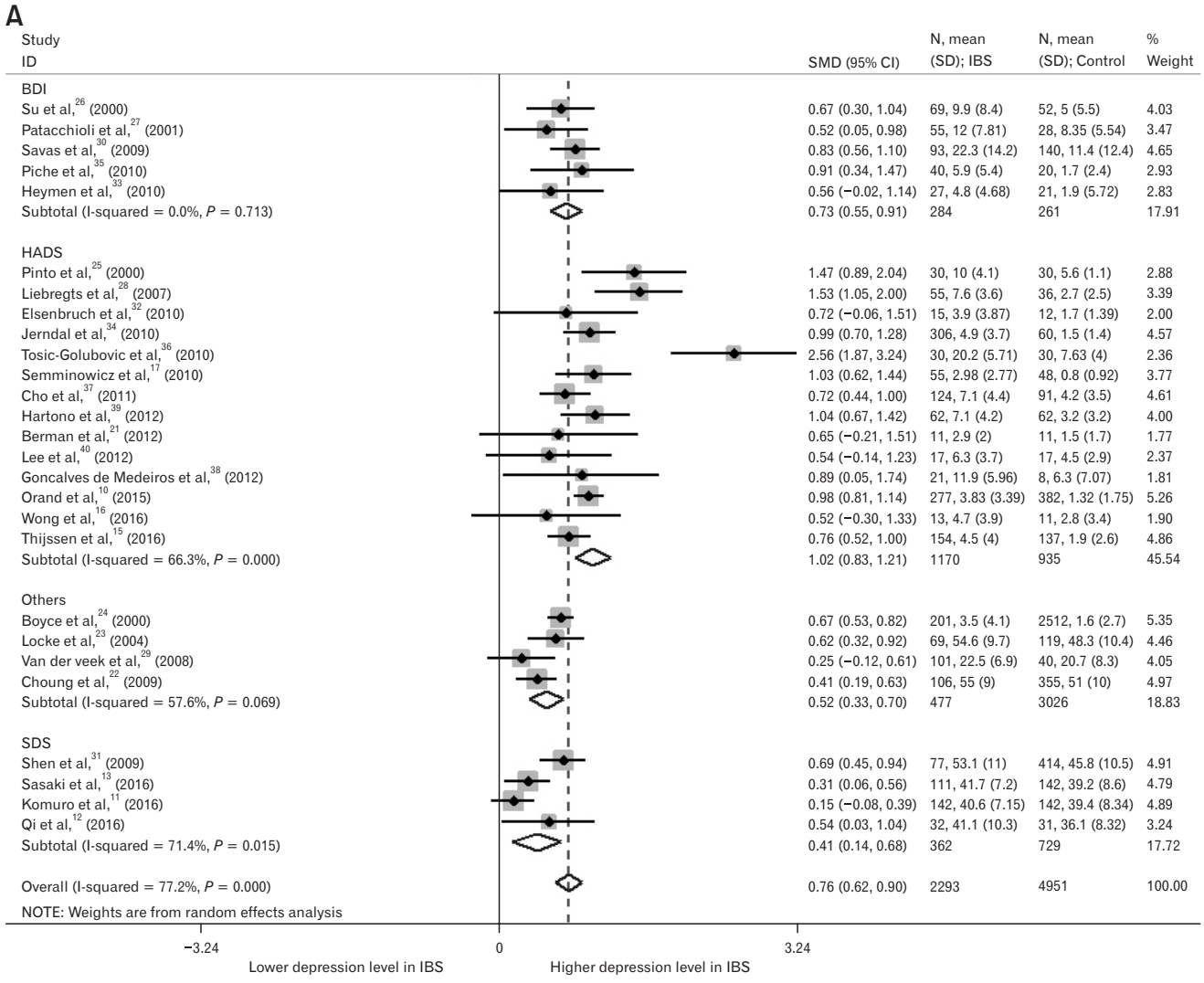

Figure 2. Forest plot and funnel plot of depression levels in irritable bowel syndrome (IBS) patients. (A) Forest plot of depression levels in IBS patients, divided by the type of questionnaire assessing depression levels. (B) Funnel plot of depression levels in IBS patients, divided by the type of questionnaire assessing depression levels. SMD, standard mean difference; BDI, Beck Depression Inventory; HADS, Hospitalization Anxiety and Depression Scale; SDS, Self-Rating Depression Scale; Others included sphere and Symptom Checklist-90; SE, standard error.

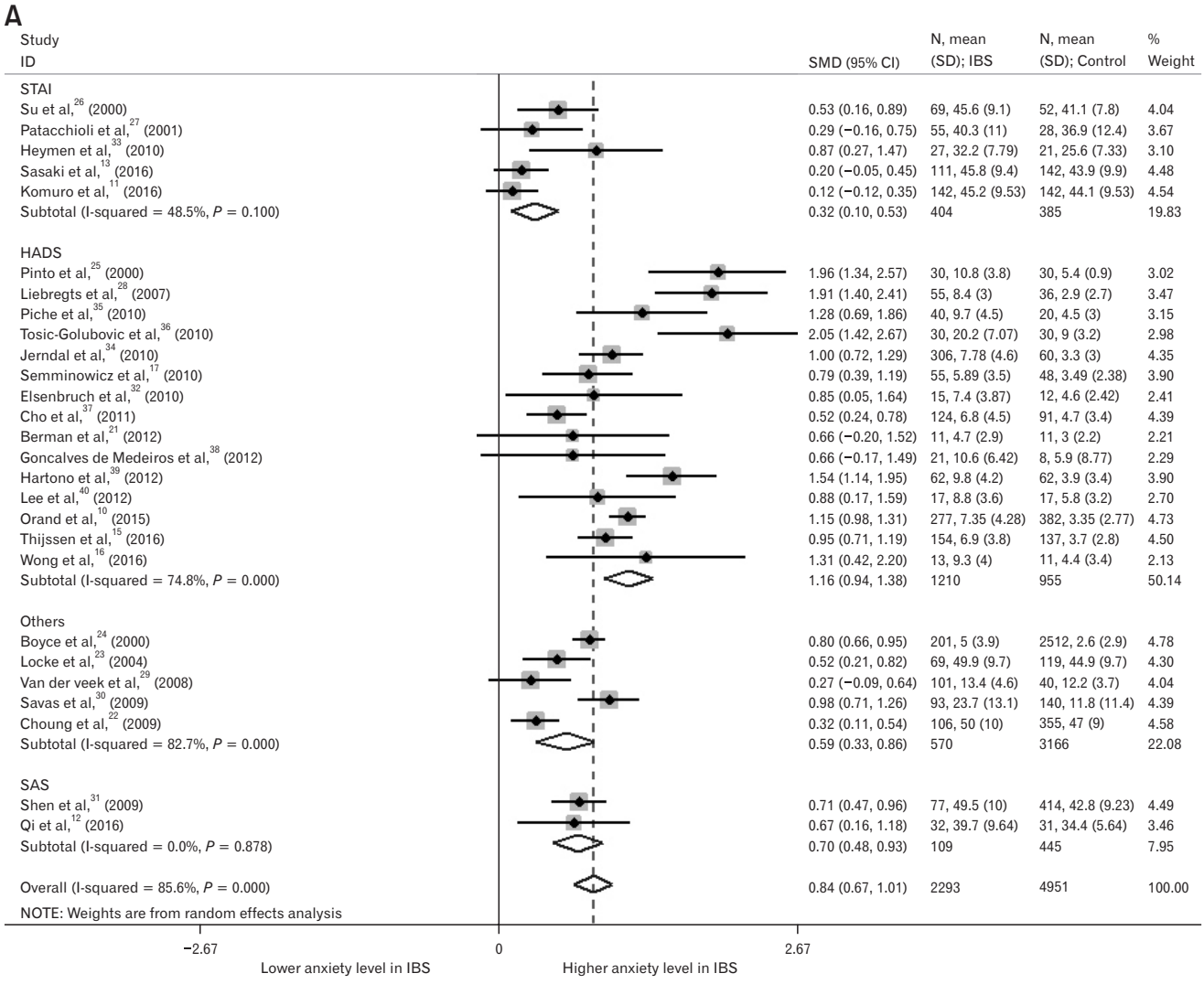

Figure 3. Forest plot and funnel plot of anxiety levels in irritable bowel syndrome (IBS) patients. (A) Forest plot of anxiety level in IBS patients, divided by the type of questionnaire assessing anxiety levels. (B) Funnel plot of anxiety levels in IBS patients, divided by the type of questionnaire assessing anxiety levels. SMD, standard mean difference; STAI, State and Trait Anxiety Inventory; HADS, Hospitalization Anxiety and Depression Scale; SAS, Self-Rating Anxiety Scale; Others included sphere, Symptom Checklist-90 and BAI; SE, standard error.

Table 2. The Result of Meta-regression Analysis and the Pooled Standard Mean Difference for Depression and Anxiety Levels According to Subgroup Analysis

	Subgroup	No. of studies	SMD (95% CI)	*P*-value	Heterogeneity		Meta-regression
					I^2 (%)	P_h[a]	*P*-value
Depression	Overall	27	0.76 (0.62-0.90)	< 0.001	77.2	< 0.001	
	Studied region						0.007
	East Asia	8	0.50 (0.32-0.69)	< 0.001	56.3	0.025	
	USA	7	0.74 (0.52-0.96)	< 0.003	77.2	0.003	
	Europe	7	0.91 (0.52-1.30)	< 0.001	83.9	< 0.001	
	Others[b]	5	1.10 (0.70-1.49)	< 0.001	78.6	0.001	
	IBS criteria						0.197
	Rome II	11	0.91 (0.60-1.15)	< 0.001	80.0	< 0.001	
	Rome III	10	0.65 (0.40-0.90)	< 0.001	80.4	< 0.001	
	Others[c]	6	0.70 (0.46-0.93)	< 0.001	65.4	0.013	
	The type of depression questionnaire						< 0.001
	HADS	14	1.02 (0.83-1.21)	< 0.001	66.3	< 0.001	
	BDI	5	0.73 (0.55-0.91)	< 0.001	0.0	0.713	
	SDS	4	0.41 (0.14-0.68)	< 0.001	71.4	0.015	
	Others	4	0.52 (0.33-0.70)	< 0.001	57.6	0.069	
Anxiety	Overall	27	0.84 (0.67-1.01)	< 0.001	85.6	< 0.001	
	Studied region						0.002
	East Asia	8	0.51 (0.29-0.73)	< 0.001	68.5	0.002	
	USA	7	0.76 (0.45-1.07)	< 0.001	85.0	< 0.001	
	Europe	7	0.92 (0.55-1.29)	< 0.001	74.8	< 0.001	
	Others[b]	5	1.38 (0.81-1.95)	< 0.001	88.9	< 0.001	
	IBS criteria						0.997
	Rome II	11	0.90 (0.66-1.14)	< 0.001	79.2	< 0.001	
	Rome III	10	0.86 (0.51-1.21)	< 0.001	90.1	< 0.001	
	Others[c]	6	0.72 (0.36-1.07)	< 0.001	85.3	< 0.001	
	The type of anxiety questionnaire						0.007
	HADS	15	1.16 (0.94-1.38)	< 0.001	74.8	< 0.001	
	STAI	5	0.32 (0.10-0.53)	0.004	48.5	0.100	
	SAS	2	0.70 (0.48-0.93)	< 0.001	0.0	0.878	
	Others	5	0.59 (0.33-0.86)	< 0.001	82.7	< 0.001	

[a]*P*-value of heterogeneity analysis.
[b]Two studies in Australia, 1 in Brazil, 1 in India, and 1 in Malaysia.
[c]Three studies using the Bowel Disease Questionnaire, 2 studies using Manning's criteria and 1 study using Rome I criteria.
SMD, standard mean difference; IBS, irritable bowel syndrome; BDI, Beck Depression Inventory; HADS, Hospitalization Anxiety and Depression Scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; STAI, State and Trait Anxiety Inventory.

Discussion

We found that depression and anxiety levels in IBS patients were significantly higher than in healthy controls, even in the subgroup analyses with IBS-subtypes. Our studies also showed significant heterogeneity of these findings (depression, $I^2 = 77.2\%$; anxiety, $I^2 = 85.6\%$), however, we found the study region and type of questionnaire used to assess depression or anxiety levels to be the main causes of heterogeneity, using meta-regression analysis.

We studied the level of depression and anxiety, not prevalence, because of the continuing dispute on the threshold of questionnaires in patients with a medical illness. Patients with medical symptoms may record a high score that inappropriately suggests depression. Only the HADS has been reported to be suitable for measuring depression in patients with a known medical illness, because it was specially designed to overcome the said difficulty by omitting somatic symptoms.[66] The other questionnaires might overestimate the

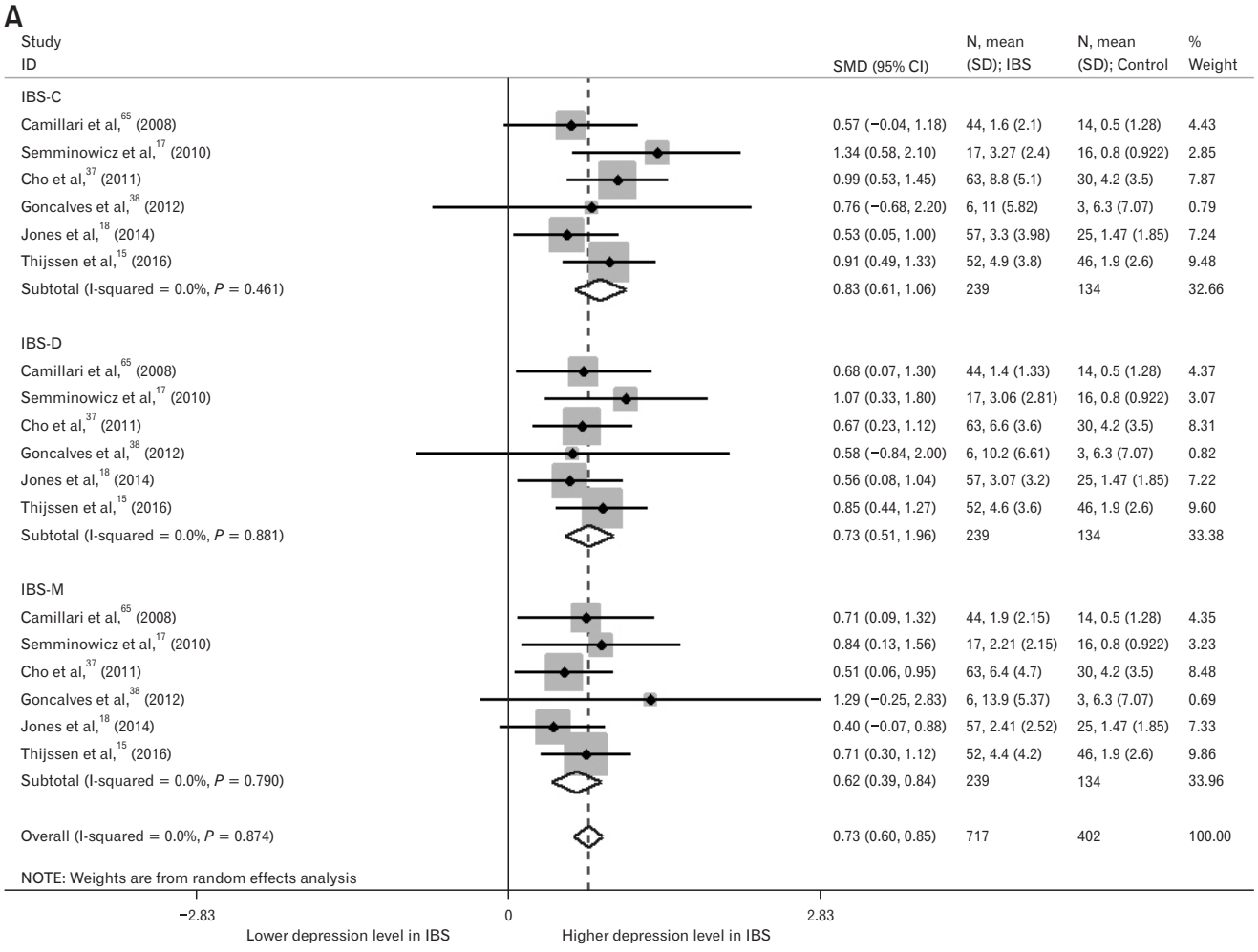

Figure 4. Forest plot and funnel plot of depression levels in subtypes of irritable bowel syndrome (IBS). (A) Forest plot of depression levels in IBS-subtype patients (B) Funnel plot of depression levels in IBS-subtype patients. SMD, standard mean difference; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; SE, standard error.

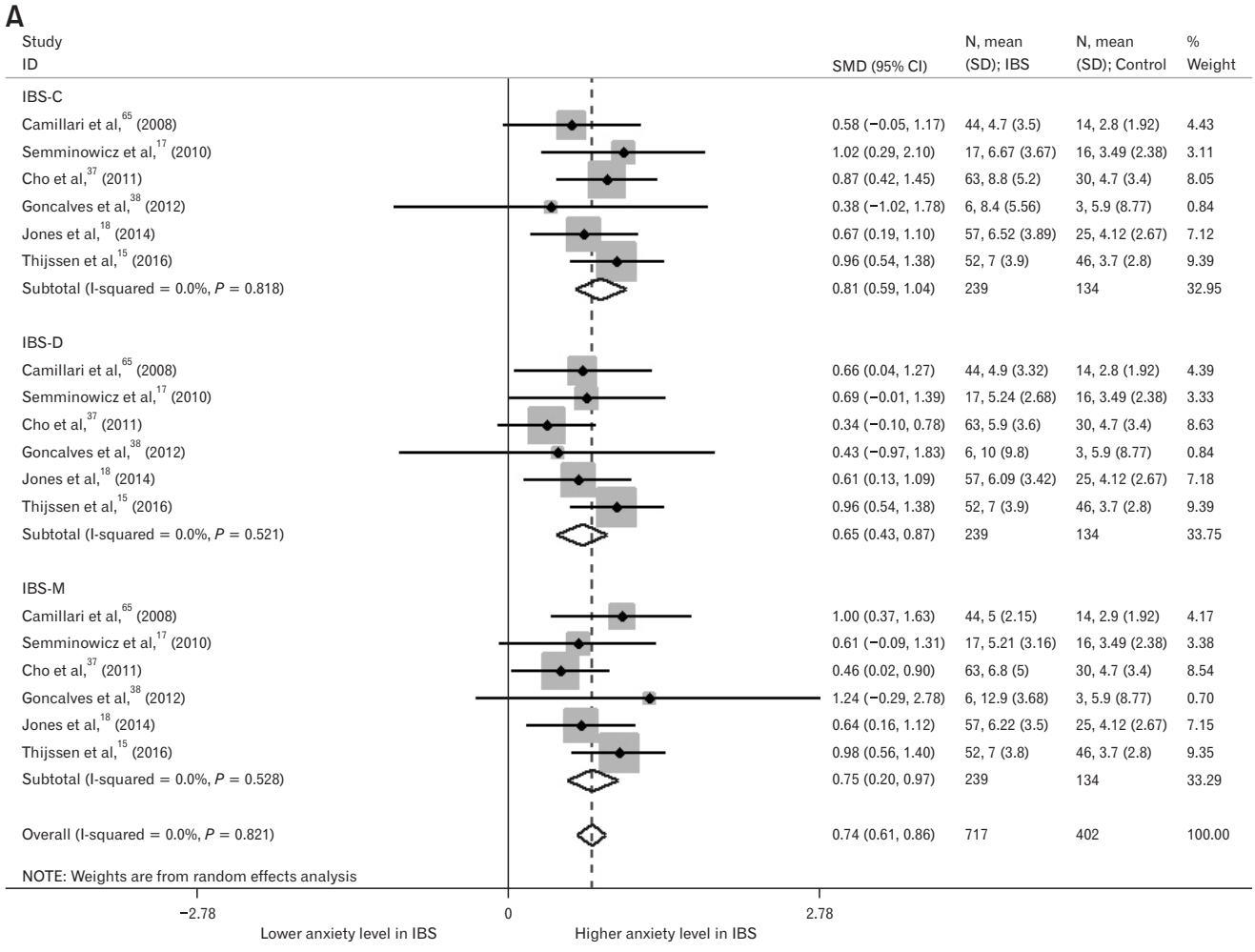

Figure 5. Forest plot and funnel plot of depression levels in subtypes of irritable bowel syndrome (IBS). (A) Forest plot of anxiety levels in IBS-subtype patients. (B) Funnel plot of anxiety levels in IBS-subtype patients. SMD, standard mean difference; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; SE, standard error.

symptoms of depression because they do not rule out somatic questions. However, the HADS is a symptom-screening questionnaire, and not a diagnostic measure for depression. Furthermore, pooled SMD of the HADS was higher than other questionnaires in meta-regression analysis of our study. There is still no consensus on this issue.

The studied regions contributed to the significant heterogeneity found in this meta-analysis. The prevalence of IBS, anxiety, and depression varies according to the cultural region. This diversity in prevalence may be due to actual differences in prevalence, discrepancies in measurement, due to translation, and limited validation of questionnaires in question in each cultural region, or all of them.[67] Cross-cultural factors are considered important, not only in the diagnosis of anxiety and depression, but also in IBS, as symptoms are also vague and there are no objective findings to confirm the diagnoses. Furthermore, the translation of words used to describe symptoms into another language introduces complexities, because there are sometimes no exact equivalents. Therefore, the translated questionnaires used to diagnose IBS and the questionnaires used to assess anxiety and depression levels would contribute towards heterogeneity in this meta-analysis.

The newly revised Rome IV highlights this importance of cross-cultural competence in clinical medicine and research.[68] The English version of diagnostic questionnaire for IBS in the Rome IV criteria has been translated into other languages and is being validated; this should make it possible to carry out cross-cultural and global epidemiologic studies.[69] However, Rome IV criteria were not used in enrolled studies. Several types of diagnostic criteria for IBS were used in studies selected in this meta-analysis, but the types of IBS criteria did not significantly influence heterogeneity.

There are also cultural differences in the prevalence and diagnosis of anxiety and depression in different regions. Low prevalence rates of common mental disorders such as anxiety and depression in East Asia have been reported in a recent meta-analysis.[70] In this meta-analysis, studies conducted in East Asia also showed lower pooled SMD in both depression and anxiety levels. The results of the WHO World Health Survey depression study also showed East Asia to have the lowest prevalence estimates.[71] Reasons for the low prevalence of depression and anxiety in East Asia are still unknown, but both protective cultural factors and underestimation due to cultural differences could be possible explanations.[70] Therefore, it is important to understand culture-specific ways to express mental symptoms.[72] Consensus or guidelines must be proposed for the estimation of depression and anxiety levels in IBS patients from different cultural backgrounds, so cultural heterogeneity can be overcome.

In general, higher prevalence among women was not limited to IBS, but pertained to anxiety and depression as well.[73] Therefore, women were considered to have more impaired quality of life with IBS, due to the correlation between somatic symptoms and a gender-related increase in anxiety and depression prevalence.[73] To know the gender effect on psychological factors among IBS patients, we tried to get the gender specific score of anxiety and depression. However, it is not possible to get the gender specific data in this meta-analysis. As an alternative, we studied the heterogeneity of the results according to the proportion of female patients. Interestingly, the proportion of female patients did not affect heterogeneity in this meta-analysis. In the meta-analysis, most studies, except 3,[12,25,35] enrolled more than 49% of female patients; so, the proportion of female patients did not differ across studies. However, this finding means only that the proportion of female patients did not affect pooled SMD among the studies. The gender effect on psychological factors in IBS patients is still unknown because the data of either depression or anxiety levels between male and female patients in enrolled studies could not be acquired. A direct comparison between male and female patients was not possible in this study. The gender effect in IBS with psychological distress should be evaluated in prospective studies.

In the meta-analysis on IBS-subtype, both depression and anxiety levels were higher in all IBS-subtypes. In our study, IBS-C patients showed the highest SMD for depression (SMD = 0.83; 95% CI, 0.61-1.06) and anxiety (SMD = 0.81; 95% CI, 0.59-1.04). One possible explanation for this finding is a change in the intestinal serotonin (5-hydroxytryptamine, 5-HT) system. Excess 5-HT could contribute to diarrhea through the 5-HT receptor; moreover, increased postprandial release of 5-HT in patients with IBS-D has been reported.[74] On the other hand, the IBS-C subtype may be considered an imbalance of 5-HT secretion, and high levels of depression and anxiety in IBS-C subtype may be associated with low responsiveness of 5-HT in both the central and peripheral regions.[75] However, all subtypes showed significantly higher depression and anxiety levels in our meta-analysis.

This review has some limitations. First, we included English-language studies only; so some articles may have been missed despite extensive database searches. Second, high heterogeneity may be attributable to the assessment methods and regions under study in the primary studies. This makes it difficult to draw consistent conclusions about anxiety and depression levels among IBS patients. There is a need for consensus about the evaluation methods of depression and anxiety in IBS patients.

In conclusion, the present meta-analysis showed that depression and anxiety levels were higher in IBS patients than in healthy controls, regardless of IBS-subtype. However, the gender effect on psychological factors among IBS patients could not be determined. Further prospective studies are needed to evaluate and compare the mechanisms of those relationships.

Supplementary Material

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm16220.

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