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## Research Paper

# Depressive symptoms in patients with irritable bowel syndrome: a meta-analysis of comparative studies

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## Abstract

Depression is common in patients with irritable bowel syndrome (IBS), but the reported prevalence across different studies is inconsistent. This meta-analysis systematically examined the presence and severity of depressive symptoms in patients with IBS. Two investigators independently performed a literature search. The pooled depressive symptom severity was calculated using a random effects model. Subgroup, sensitivity and meta-regression analyses were conducted to examine the moderating factors of the development of depressive symptoms. Twenty four studies (n=2,837) comparing depressive symptoms between IBS patients (n=1,775) and healthy controls (n=1,062) were identified; 14 (58.3%) studies were rated as high quality. Compared to healthy controls, IBS patients had more frequent (OR=9.21, 95%CI: 4.56-18.57, P<0.001; I<sup>2</sup>=76%) and more severe depressive symptoms (n=1,480, SMD=2.02, 95%CI: 1.56-2.48, P<0.001; I<sup>2</sup>=94%). Subgroup analyses revealed that patients with all IBS subtypes had more severe depressive symptoms than controls. In addition, versions of the Hamilton Depression Rating Scale (HAM-D) and IBS diagnostic criteria were significantly associated with depressive symptom severity. Meta-regression analyses revealed that female gender, younger age and small sample size were significantly associated with more severe depressive symptoms. In conclusion, meta-analytic data showed that IBS patients had more frequent and severe depressive symptoms than healthy controls. Adequate screening and treatment for depression should be developed and implemented in this patient population.

Key words: IBS; depressive symptoms; controlled studies; meta-analysis

## Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) diseases with the prevalence of around 20% in the general population [1-3]. The Rome diagnostic criteria are the diagnostic standard for research and clinical care of IBS [4, 5]. According to the predominant stool pattern,

IBS is traditionally classified into four subtypes; IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M) and non-subtyped IBS (IBS-U) [6]. Typical symptoms of IBS include recurrent abdominal pain, bloating, change in bowel habits without detectable structural or biochemical abnormalities [7].

IBS is associated with poor quality of life, impaired social functions [8, 9] and psychological-psychiatric conditions, such as depression [10]; approximately 20-40% of IBS patients present with depressive symptoms [11, 12].

The close association between IBS and depression is supported by psychophysiological and neuro-imaging studies [13, 14], and this association might be related to the 'brain-gut axis' that is defined as the bidirectional connecting system through neural, neuroimmune and neuroendocrine pathways between the digestive system and the brain [15]. Psychosocial factors can affect the gut physiology via the brain-gut axis in IBS [10, 16]. Antidepressants are effective to some extent in treating IBS directly through the brain-gut axis independent of changes in depressive symptoms [17, 18].

The relationship between IBS and depression has not been consistent across studies. IBS has been associated with more severe depressive symptoms compared to healthy controls in some [19-22], but not all [23, 24] studies. Additionally, the association between IBS subtype and depressive symptoms is also uncertain with studies finding either an association with IBS-C [25] or IBS-D [26, 27] but not with other subtypes [25], or not at all [28, 29].

Two meta-analyses [27, 30] concluded that IBS patients had more severe depressive symptoms than healthy controls, but the association between IBS subtypes and depressive symptoms was inconsistent. These studies only covered English databases and the included studies employed self-reported scales on depressive symptoms, such as the Hospitalization Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI). As the reliability of self-reported scales are affected by impaired insight and cognitive functions that are common in depression, investigator-rated tools, such as the Hamilton Depression Rating Scale (HAMD) [31, 32] are generally thought to be more objective and suitable for research purposes.

To the best of our knowledge, no meta-analysis or systemic review on depressive symptoms in IBS using interviewer-rated tools have been published. Thus, the aim of this study was to conduct a systematic meta-analysis to compare objectively rated depressive symptoms between IBS patients and healthy controls, and examine the association between IBS subtypes and depressive symptoms.

## Methods

### Search strategy

The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) guidelines [33]. Two authors (ZQE and WF) independently performed a literature search using both English (PubMed, PsycINFO, Embase, Cochrane Library) and Chinese (Wan Fang, SinoMed and Chinese National Knowledge Infrastructure (CNKI)) databases, from their inception to September 12, 2017 with the following search terms: ("irritable bowel syndrome" OR "colon diseases, functional" OR "functional bowel diseases" OR "IBS") AND ("depressive" OR "depression" OR "melancholia"). Furthermore, the references of included studies, meta-analyses and review papers were manually searched [27, 30, 34] to identify additional relevant studies.

### Selection criteria

The search results were imported into the EndNote X7 software (Thomson Reuters, Philadelphia, PA, USA). The inclusion criteria were based on the PICOS acronym: Participants (P): Patients with IBS according to any diagnostic criteria. Intervention (I): not applicable. Comparison (C): healthy controls. Outcomes (O): depressive symptoms assessed with validated interviewer-rated scales. To assess depressive symptoms more objectively, only studies using investigator-rated scales were included. Study design (S): published case-control, cohort (only baseline data were included) and cross-sectional studies. Studies were excluded if they (1) made no comparisons between patients with IBS/IBS subtype and healthy controls; (2) did not provide meta-analyzable data on depressive symptoms. If more than one publication were published based on the same dataset, only publications with complete data were included.

### Data extraction

Two reviewers (ZQE and WF) independently checked and extracted data from the studies using a pre-defined electronic Excel form: first author, year of publication, country, study design, IBS diagnostic criteria, and the assessment tools and means and standard deviations (SDs) of depressive symptoms. The first or corresponding authors were contacted for more information if relevant data were incomplete. Extracted data were analyzed independently by two reviewers (ZQE and QG). Any controversy was resolved by consensus or with the involvement of a third reviewer (WZ).

### Statistical analysis

Data analyses were performed using the Review Manager Version 5.3 software (<http://www.cochrane.org>) and the Comprehensive Meta Analysis, Version 2.2.064 (<http://www.Meta-Analysis.com>), according to the recommendation of the Cochrane

Handbook for Systematic Reviews [35]. Due to the unavoidable heterogeneity in study characteristics, the random effects model was used to synthesize the data. Heterogeneity was examined by the  $I^2$  and  $Q$  statistics. Significant heterogeneity was considered when  $I^2$  values were of  $>50\%$  or  $P < 0.1$  in the  $Q$  statistics [36, 37]. For continuous and dichotomous outcomes SMDs and odds ratios (OR), respectively were calculated to evaluate the results' effect size (ES). ES values over 0.8, 0.5-0.8 and 0.2-0.5 constituted large, medium and small effect sizes, respectively [38]. Subgroup and sensitivity analyses were conducted to explore potential sources of heterogeneity. Subgroup analyses were performed according to the following variables: 1) subtypes: IBS-C vs. IBS-D vs. IBS-M vs. IBS-U; 2) Chinese studies vs. non-Chinese studies; 3) IBS diagnostic criteria: Rome I vs. Rome II vs. Rome III; 4) treatment settings: inpatients vs. outpatients vs. mixed; 5) HAMD versions: HAMD-17 vs. HAMD-24 vs. HAMD-not reported (NR); 6) refractory vs. non-refractory IBS. Random effects meta-regression was used to evaluate the impact of continuous moderating variables, such as age, proportion of females, sample size and the Newcastle-Ottawa Scale

(NOS) scores with the primary outcome [39]. Potential publication bias was assessed with the funnel plots and Egger's regression test [40, 41].

### Assessment of study quality

Two reviewers (ZQE and WF) independently evaluated the methodological quality of each study using the NOS [42, 43], which has a score ranging from 0 to 9 points. The total NOS score of  $\geq 7$  points were rated as high quality [44, 45].

## Results

### Literature search

Out of 6,654 studies, 4,071 were identified after duplicate publications were removed. Eventually, 24 studies met full criteria and were included in the meta-analysis. The screening process according to the PRISMA flow diagram is presented in Figure 1. One study [46] reported data on both refractory and non-refractory IBS patients separately, therefore the data were extracted and analyzed as two separate arms. In order to avoid inflating the sample size in the control group, half numbers of healthy controls were assigned to each arm in the analyses.

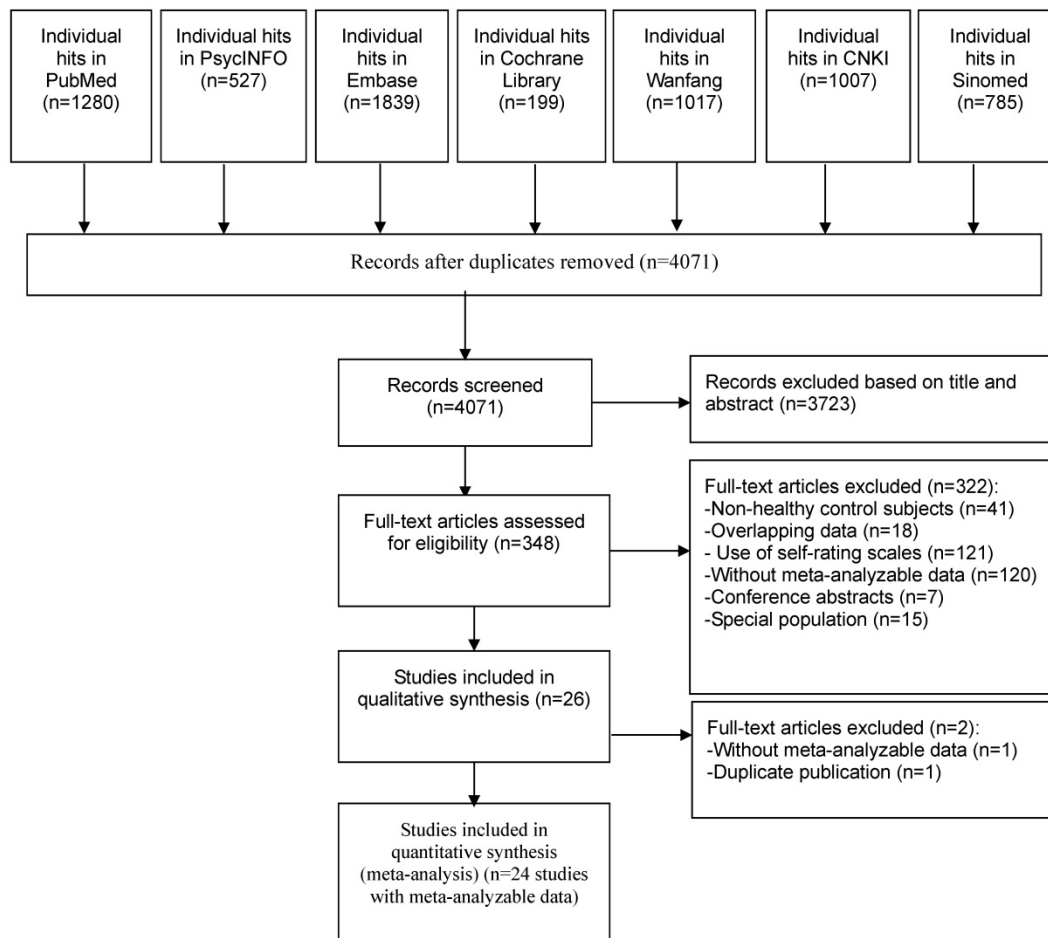


Figure 1. PRISMA flow diagram

**Table 1.** Characteristics of the studies included in the meta-analysis

Authors	Country	N	Design, n (IBS/control)	Assessment scales on depressive symptoms	Patients with IBS			Healthy controls			NOS scores	
					IBS diagnostic criteria	Subject type	Mean age (yrs)	Male (%)	Subject type	Mean age (yrs)		Male (%)
Akkus et al, 2004	Turkey	82	Case control, 32/50	HAMD-17	Rome I	Outpatients	44.8	59.4	Hospital staff; Healthy volunteers	47.6	44.0	7
Chen and Wang et al, 2007	China	60	Case control, 30/30	HAMD	Rome II	Inpatients; Outpatients	NR	40.0	Health examination population; Healthy volunteers	NR	43.3	8
Chen and Zou et al, 2007	China	54	Case control, 27/27	HAMD-24	Rome II	Outpatients	40.3	44.4	Health examination population	37	48.2	6
Gonçalves de Medeiros et al, 2012	United Kingdom	27	RCT, 21/8	HAMD	Rome II	Outpatients	39.9	23.8	Healthy volunteers	32.3	75.0	6
Hao et al, 2015	China	50	Case control, 30/20	HAMD	Rome III	Inpatients	38 <sup>c</sup>	53.3	Health examination population	42 <sup>c</sup>	55.0	8
Jin et al, 2004	China	58	RCT, 36/22	HAMD-17	Rome II	Inpatients; Outpatients	42.7	44.4	Health examination population	41.1	59.1	5
Kilkens et al, 2013	Netherlands	46	Case control, 23/23	HAMD-17	Rome II	Outpatients	32.9	39.1	Healthy volunteers	28.6	39.1	8
Li and Chen et al, 2015	China	140	Case control, 70/70	HAMD-24	Rome III	Outpatients	51.0	48.6	Health examination population	49	50.0	7
Li et al, 2015	China	64	Case control, 32/32	HAMD-24	Rome III	Inpatients; Outpatients	40.8	34.4	Health examination population; Healthy volunteers	39	31.3	8
Liu et al, 2013	China	801	Cross-sectional, 601/100	HAMD-17	Rome III	Outpatient	38.3	49.5	Health examination population	39.7	45.0	7
Mao et al, 2010	China	96	Case control, 56/40	HAMD	Rome III	Inpatients	35.2	32.1	Health examination population	32.2	35.0	6
Mu et al, 2003	China	60	Case control, 30/30	HAMD	Rome II	Outpatients	NR	33.3	Hospital staff	NR	40.0	5
Shi et al, 2012	China	90	Case control, 60/30	HAMD-24	Rome III	Inpatients; Outpatients	NR	30.0	Health examination population	NR	66.7	8
Shi and Zhang et al, 2012	China	57	Case control, 32/25	HAMD-17	Rome III	Outpatients	40.0	40.6	NR	39.2	56.0	6
Song et al, 2015	China	204	Case control, 102/102	HAMD-24	Rome III	Outpatients	48.1	38.2	Health examination population	42.3	42.2	7
Tian et al, 2011	China	30	Case control, 20/10	HAMD	Rome III	NR	45 <sup>c</sup>	55.0	Health examination population	42 <sup>c</sup>	60.0	7
Tosic-Golubovic et al, 2010	Serbia	60	Case control, 30/30	HAMD	Rome II	Outpatients	43.9	50.0	Community	41.6	50.0	8
Wan et al, 2005	China	50	Case control, 30/20	HAMD	Rome II	Outpatients	37.0	0	Hospital staff; Patient's relative; Students	38	0	6
Wang et al, 2012	China	116	Case control, 56/60	HAMD-24	Rome II	Inpatients; Outpatients	NR	NR	Health examination population; Patient's relative	NR	NR	6
Wang et al, 2014	China	260	Case control, 150/110	HAMD	Rome III	NR	NR	41.3	Health examination population; Patient's relative	NR	NR	8
Xu et al, 2012	China	134	Case control, 69/65	HAMD-24	Rome III	Inpatients; Outpatients	NR	42.0	Hospital staff; Patient's relative	NR	50.8	8
Xu et al, 2014	China	215	Case control, 112/103	HAMD-24	Rome III	Outpatients	63.7	69.6	Healthy volunteers	56.3	57.3	5
Xu et al, 2017	China	66	Cross-sectional, 46/20	HAMD-24	Rome III	Outpatients	34.2	49.1	Healthy volunteers	29.5	60.0	8
Zhang et al, 2007	China	115	Case control, 80/35	HAMD	Rome II	NR	20-73	55.0	NR	20-60	45.7	5

<sup>a</sup> Only data from IBS subjects and healthy control groups were extracted if there were multiple study arms.

<sup>b</sup> Rome I/II/III are standard criteria for diagnosis of IBS.

<sup>c</sup> median age.

HAMD=Hamilton Depression Rating Scale; IBS= irritable bowel syndrome; NR=not reported; NOS=Newcastle-Ottawa Scale; yrs=years; RCT=randomized controlled trial.

## Study characteristics

There were 2,837 subjects (1,775 IBS patients and 1,062 healthy controls) in the 24 studies (Table 1). Twenty studies were conducted in China (n=2,620) [46-65], and one each in Serbia (n=60) [66], The Netherlands (n=46) [67], United Kingdom (n=29) [68] and Turkey (n=76) [69]. IBS was diagnosed using the Rome I criteria in one [69], Rome II criteria in 10 [50, 56, 58-60, 62, 65-68], and Rome III criteria in 13 studies [46-49, 51-55, 57, 61, 63, 64]. The severity of depressive

symptoms was assessed using the Hamilton Depression Rating Scale (HAMD-17) in 5 studies [46, 61, 65, 67, 69] and HAMD-24 in 9 studies [50-53, 55, 57, 60, 63, 64], but HAMD versions that were not reported (HAMD-NR) in 10 studies [47-49, 54, 56, 58, 59, 62, 66, 68]. One study included female subjects only [56]. The mean age ranged from 32.9 to 63.7 years, and the proportion of males ranged from 0% to 69.6% in the patient group.



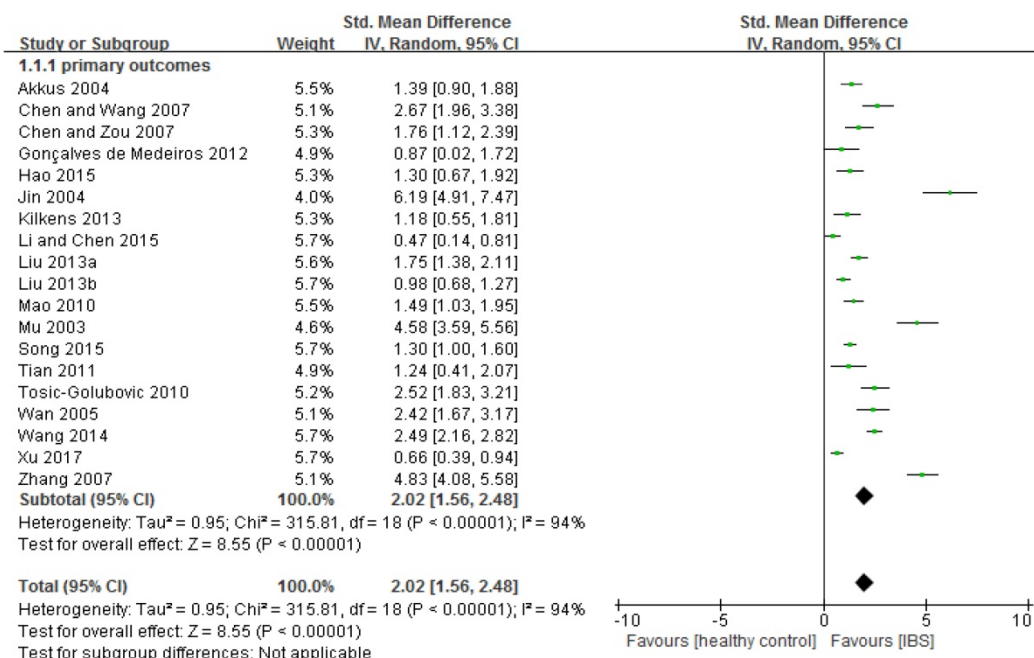


Figure 2. Depressive symptoms in IBS: forest plot of HAMD total scores

### Quality assessment

The NOS score assessing quality of the studies ranged from 4 to 8 points (Supplemental Table 1); 58.3% of studies (n=14) [46, 48-50, 52-55, 57, 63, 64, 66, 67, 69] were assessed as “high quality” (NOS≥7).

### Primary outcome

Compared to healthy controls, IBS patients had more severe depressive symptoms (n=1,480, SMD=2.02, 95%CI: 1.56-2.48, P<0.001; Figure 2). The funnel plot showed asymmetry, while Egger’s regression test showed publication bias (P=0.005). Sensitivity analysis revealed that the significance in bias remained (n=1,334, SMD=1.51, 95%CI: 1.16-1.86, P<0.001) after excluding three outlying studies (i.e., SMD>3) [59, 62, 65]. Subgroup analyses further revealed that the significance remained in all of the 18 subgroup analyses (Table 2; Supplemental figure 3). In addition, IBS diagnostic criteria (p=0.01) and HAMD versions (p=0.002) were significantly associated with more severe depressive symptoms compared with the control group (Table 2). In meta-regression analyses younger age (slope=-0.033, p<0.001), proportion of female gender (slope=0.021, p<0.001) and small sample size (slope=-0.002, p<0.001) were significantly associated with more severe depressive symptoms. NOS scores did not have significant impact on the primary outcome (slope =0.095, P=0.08).

### Secondary outcomes

The Hamilton Depression Rating Scale (HAM-D) contains six separate factors, namely factor I

(anxiety/somatization), factor II (weight), factor III (cognitive disturbance), factor IV (diurnal variation), factor V (psychomotor retardation) and factor VI (sleep disturbances) [70-73]. Compared to healthy controls, IBS patients had significantly higher scores in most HAM-D factors (SMD=4.03 to 13.54, 95%CI: 1.28-22.45, P<0.001; I<sup>2</sup>=41% to 99%, Supplemental Figure 2): anxiety/somatization (SMD=4.03), weight (SMD=4.78), psychomotor retardation (SMD=4.23) and sleep disturbances (SMD=13.54).

Prevalence of depressive symptoms (HAM-D total score > 7) in IBS patients was higher than in healthy controls (OR=9.21, 95%CI: 4.56-18.57, P<0.001; I<sup>2</sup>=76%, Figure 3). In addition, there was higher prevalence of mild depressive symptoms (HAM-D total score: 8-19) (OR=2.69, 95%CI: 1.21-5.95, P=0.01; I<sup>2</sup>=74%, Figure 3) as well as moderate to severe depressive symptoms (HAM-D total score ≥ 20) (OR=10.45, 95%CI: 4.45-24.50, P<0.001; I<sup>2</sup>=0%, Figure 3) in the IBS group than in the control group.

### Discussion

This was the first meta-analysis on the frequency and severity of depressive symptoms measured by rater-administered scales in IBS. In psychiatric research the HAM-D is the most widely used scale of depressive symptoms with good psychometric properties [74, 75]. All studies in this meta-analysis measure the presence and severity of depressive symptoms using HAM-D scales, which significantly decreases the heterogeneity attributed to different assessment instruments.



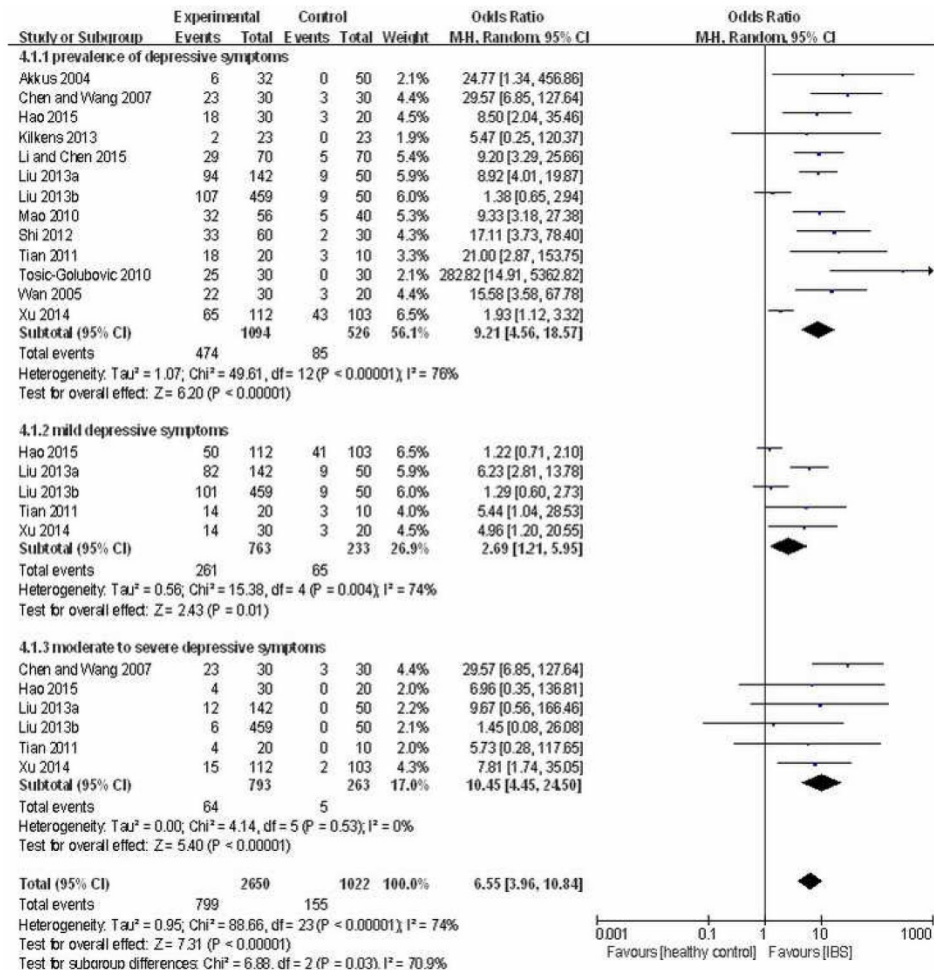
**Table 2.** Subgroup analyses of moderating variables of the primary outcome

subgroups	Study arms (subjects)	SMDs (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub> <sup>a</sup>	P-value for each subgroup	P-value across subgroups
Overall	18 (1480)	2.02 (1.56, 2.48)	94	<0.001	<0.001	NA
Subtypes						
IBS-C	6 (145)	2.38 (1.10, 3.67)	95	<0.001	0.0003	0.81
IBS-D	7(253)	2.08 (1.46, 2.70)	86	<0.001	<0.001	
IBS-M	3(27)	2.50 (1.86, 3.14)	26	0.26	<0.001	
IBS-U	2(33)	2.21 (1.69, 2.72)	0	0.66	<0.001	
Study setting						
China	14 (1374)	2.17 (1.62, 2.71)	95	<0.001	<0.001	0.12
Other countries <sup>b</sup>	4 (106)	1.50 (0.86, 2.15)	74	0.008	<0.001	
IBS diagnosis criteria						
Rome I	1 (32)	1.39 (0.90, 1.88)	NA	NA	<0.001	
Rome II	9 (307)	2.95 (1.95, 3.95)	93	<0.001	<0.001	
Rome III	8 (1141)	1.30 (0.85, 1.74)	92	<0.001	<0.001	
Patients						
Inpatients	2 (86)	1.42 (1.05, 1.79)	0	0.62	<0.001	0.15
Outpatients	11 (1078)	1.57 (1.14, 1.99)	91	<0.001	<0.001	
Mixed	2 (66)	4.39 (0.94, 7.84)	95	<0.001	0.01	
NR	3 (250)	2.85 (1.16, 4.54)	95	<0.001	0.0009	
HAM-D version						
HAMD-17	4 (692)	2.06 (1.19, 2.94)	94	<0.001	<0.001	0.002
HAMD-24	4 (311)	1.00 (0.51, 1.49)	87	<0.001	<0.001	
NR	10 (477)	2.42 (1.74, 3.10)	92	<0.001	<0.001	
IBS severity						
Refractory IBS	3 (208)	3.43 (1.50, 5.36)	96	<0.001	0.0005	0.11
Non-refractory IBS	16 (1272)	1.80 (1.32, 2.27)	94	<0.001	<0.001	

<sup>a</sup> P-value of heterogeneity analysis.

<sup>b</sup> One study each in Turkey, Serbia, Netherlands, and in the United Kingdom.

NA=Not applicable; NR=Not reported; SMDs=Standard mean differences; IBS-C=Constipation-predominant Irritable Bowel Syndrome; IBS-D=Diarrhea-predominant irritable bowel syndrome; IBS-M=Mixed Irritable Bowel Syndrome; IBS-U=Un-subtyped Irritable Bowel Syndrome; Rome I/II/III=A standardize criteria for diagnosis of IBS; HAM-D=Hamilton Depression Rating Scale.



**Figure 3.** Forest plot of the prevalence of depressive symptoms in IBS patients versus healthy controls

In this study, compared to healthy controls IBS patients had more severe depressive symptoms overall (SMD=2.02) and also in specific domains, namely anxiety/somatization (SMD=4.03), weight (SMD=4.78), psychomotor retardation (SMD=4.23) and sleep disturbances (SMD=13.54). Further, depressive symptoms were more frequent in IBS patients (OR=9.21), particularly moderate to severe depressive symptoms (OR=10.45). Both frequency and severity of depressive symptoms were higher in this study than in other meta-analyses [27, 30], which may be due to several reasons. First, this study focused more broadly on depressive symptoms rather than major depressive disorder. Second, studies of this meta-analysis only used the HAMD scales, which maintained the homogeneity of assessment compared to other meta-analyses that covered studies employing different self-reported tools to evaluate depressive symptoms [27, 30]. It is likely that patients who had severe to very severe depressive symptoms were unable to complete self-reported scales and were therefore excluded from studies included in previous meta-analyses. Using rater-administered scales is more likely to include patients with wider range of severity which could lead to a larger effect size in this study.

In this study all IBS subtypes were associated with increased risk of the development of depressive symptoms. Patients with IBS-M showed the largest effect size (SMD = 2.50; 95% CI, 1.86-3.14), which is different from studies that found IBS-C/IBS-D with the largest effect size [18, 25, 26]. Possible factors for this discrepancy may relate to the different number of included studies and measures of depressive symptoms across meta-analyses.

Subgroup and meta-regression analyses found that HAM-D versions (HAMD-17, HAMD-24 and HAMD-NR), IBS diagnostic criteria (ROME I, ROME II and ROME III), younger age, female gender and small sample size were significantly associated with more severe depressive symptoms. In terms of gender differences, earlier studies [76] found that women with IBS had more severe IBS symptoms and lower quality of life than men, regardless of diagnostic criteria used. In addition, the prevalence of IBS in women is approximately 1.5 to 3 fold higher than in men [77-80]. Further, in IBS patients with severe symptoms (>3 Manning criteria), 80% are women. The consensus in the literature is that women have more anxiety and depressive symptoms than men with IBS [81], which is supported by the current study, but not others [30].

IBS occurs in all age groups [82] although around half of those with IBS develop initial symptoms before age of 35 years [83]. As the prevalence of IBS and

severity of pain usually decrease after the age of 50 years [84], there may be less depressive symptoms in older patients, which is consistent with our findings. Different sample sizes could influence the power to detect significant results [38], which could account for the association between sample size and the prevalence of depressive symptoms. The findings of clinical trials with small sample size are usually not stable, thus results of small studies should be interpreted with caution [85].

A previous study [30] showed no significant association between IBS diagnostic criteria and severity of depressive symptoms. However, in this study patients diagnosed according to Rome II or Rome III criteria had more severe depressive symptoms than healthy controls, while no significant difference was found between those diagnosed with Rome I criteria and controls. Reasons for the discrepancy may include the different depression scales used (self-reported scales vs. interviewer-rated scales) and the differences between the three diagnostic criteria in terms of the frequency and severity of IBS symptoms. For example, more IBS symptoms and stringent severity were adopted in Rome II than Rome III criteria, while Rome III criteria contain more items on the socioeconomic burden of IBS than Rome II [86]. Further, only one study using Rome I was included in this meta-analysis.

The results of this meta-analysis should be interpreted with caution due to several methodological limitations. First, studies included in the meta-analysis focused on depressive symptoms, but not major depressive disorder. The prevalence studies of major depressive disorder in IBS needs more sophisticated methodology. Second, there was publication bias in the meta-analysis. Third, high heterogeneity remained in some subgroup analyses. Fourth, relevant variables related to IBS, such as pharmacotherapy, were not examined due to incomplete information. Finally, most studies were conducted in China, which may lead to selection bias.

In conclusion, patients with IBS of all subtypes had more frequent and severe depressive symptoms than healthy controls, particularly female and younger patients. Regular screening on depressive symptoms and effective interventions should be developed for this patient population.

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## Supplementary Material

Supplementary figures and table.

<http://www.ijbs.com/v14p1504s1.pdf>

## Competing Interests

The authors have declared that no competing interest exists.

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