Systematic Review/Meta-analysis

Prevalence of sleep disorder in irritable bowel syndrome: A systematic review with meta-analysis

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Abstract

Background/Aims: We conducted this meta-analysis to evaluate the prevalence of sleep disorder in irritable bowel syndrome (IBS) patients and study the association between IBS and sleep disorder.

Materials and Methods: A systematic search was conducted by searching PubMed, Embase, and Cochrane library databases using the following search terms: "functional gastrointestinal disorders," "Sleep disturbance," "Sleep disorder," "insomnia," "Dysomnias," "irritable bowel syndrome," and "IBS." Studies evaluating the association between IBS and sleep disorder were identified. Data analysis was conducted using meta-analysis software Comprehensive Meta-Analysis (CMA) 2.0. Heterogeneity across studies was evaluated by χ^2 and I^2 statistics. Publication bias was evaluated by funnel plot, Begg's test, and Egger's test. Sensitivity analysis was also performed by removing each single study separately.

Results: The bibliographical search yielded a total of 2866 studies. Finally, 36 studies including 63620 participants were identified. The prevalence of sleep disorder in IBS was 37.6% (95% CI: 31.4% to 44.3%) based on this meta-analysis. The pooled odds ratio was 2.618 (95% CI: 2.052% to 3.341). Publication bias was not determined. Regarding the sensitivity analysis, the outcome was stable regardless of which study was removed.

Conclusions: The prevalence of sleep disorder was higher in IBS compared to healthy controls and may be associated with the pathogenesis of IBS. The prevalence of sleep disorder in IBS may differ according to different areas, age, gender, occupation, and IBS diagnostic criteria. Further studies are needed to investigate any possible causal relationship between sleep disorder and IBS.

Keywords: Irritable bowel syndrome, meta-analysis, prevalence, sleep disorder

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INTRODUCTION

Sleep disorders are common among general population,[1,2] and are determined by self-report questionnaires, polysomnography (PSG), or actigraphy.[3] The prevalence of sleep disorders varies in different countries. A meta-analysis conducted in 2006 demonstrated a female predisposition for insomnia.[4] Sleep disorders may also contribute to various health problems.[5] An association between functional gastrointestinal disorder and sleep disturbances has been identified.[6]

Irritable bowel syndrome (IBS) is a functional bowel disorder defined by recurrent abdominal pain related to defecation or a change in the frequency or appearance of stool.[7] The prevalence varied according to

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geographical location and was higher among women than men.[8] The etiology of IBS remains unclear. Genetics and environmental factors, visceral hypersensitivity, gut microbiota, disorder of the gut brain axis, and psychological factors were thought to be involved.[9] Some studies have reported that sleep disorders were common in IBS patients. To our knowledge, the prevalence of sleep disorders among IBS varies from 7.1% to 73.9%. Moreover, sleep disorders may be associated with greater gastrointestinal symptom severity.[10] The global prevalence of sleep disorders among IBS has not been investigated. The aim of this meta-analysis was to identify the pooled coexistence rates of sleep disorder and IBS and to explore the association between IBS and sleep disorder.

MATERIALS AND METHODS

Information sources

Relevant studies were identified by searching PubMed (till March 2017), EMBASE (till March 2017), and the Cochrane Central Register of Controlled trials (Issue 3 of 12, till March 2017).

Search

The search terms used for all databases included: (Functional gastrointestinal disorders and Sleep disturbance) OR (Functional gastrointestinal disorders and Sleep disorder) OR (Functional gastrointestinal disorders and insomnia) OR (Functional gastrointestinal disorders and dyssomnias) OR (Irritable bowel syndrome and sleep disturbance) OR (Irritable bowel syndrome and sleep disorder) OR (Irritable bowel syndrome and insomnia) OR (Irritable bowel syndrome and dyssomnias) OR (IBS and sleep disturbance) OR (IBS and sleep disorder) OR (IBS and insomnia) OR (IBS and dyssomnias). The search terms were slightly modified in different databases.

Study selection

The inclusion criteria included: (1) articles reporting prevalence of sleep disorder in IBS patients and (2) available information on sleep disorder prevalence and sample size.

Data extraction

Two independent investigators extracted the data using standardized data extraction forms. Any discrepancies were resolved by consensus. The data collected included year of publication, geographic region, study design, methods for assessing sleep disorder, diagnostic criteria for IBS, prevalence of sleep disorder, mean age, occupation, and proportion of female and male participants.

Summary measures

The data analysis was performed using the Comprehensive Meta-Analysis software, Version 2 (Biosta, Inc. USA). The proportion of individuals with sleep disorder in each trial was combined to achieve a pooled prevalence of sleep disorder. Moreover, pooled odds ratios (ORs) were calculated to evaluate the association between sleep disorder and IBS. All results are presented with 95% confidence intervals.

SYNTHESIS OF RESULTS

The degree of heterogeneity of the studies was evaluated using the χ^2 test (with a value less than 0.1 considered significant) and the I^2 test (25, 50, and 75% representing low, moderate, and high heterogeneity, respectively). If significant heterogeneity ($P < 0.1$ or $I^2 > 50\%$) was achieved, we used the random effect model to combine the effect sizes in these groups. Subgroup analyses were also performed to assess the effect of geographic region, gender, occupation, age, diagnostic criteria for IBS, and publication year. To assess the stability of the results, sensitivity analysis was also performed by excluding every single study respectively. Publication bias was assessed by egger's test and funnel plots.

RESULTS

Selection of studies

A total of 2866 studies were identified, of which 2581 studies were removed according to titles and abstracts. Then, 96 duplicate studies were excluded, leaving 189 records to be examined. On reviewing full-text articles, 67 unrelated studies, 34 reviews, 3 studies including participants with complications, and 49 studies with insufficient data were excluded. Finally, 36[11-46] studies including 63620 participants were identified [Figure 1 and Table 1].

The sample size of these studies ranged between 23 and 23445. Of the 36 studies, 34 studies were cross-sectional studies, 1 study was a case-control study, and 1 study was a cohort study. Furthermore, 26 studies investigated the prevalence of sleep disorder among IBS patients and evaluated the association between IBS and sleep disorder; the other 10 studies only explored the prevalence of sleep disorder among IBS patients. All these studies used subjective sleep measures to assess sleep quality.

Sleep disorders and irritable bowel syndrome

The pooled prevalence of sleep disorders among IBS was 37.6% (95% CI: 31.4% to 44.3%) [Figure 2]. A significant association was also identified between sleep disorders and

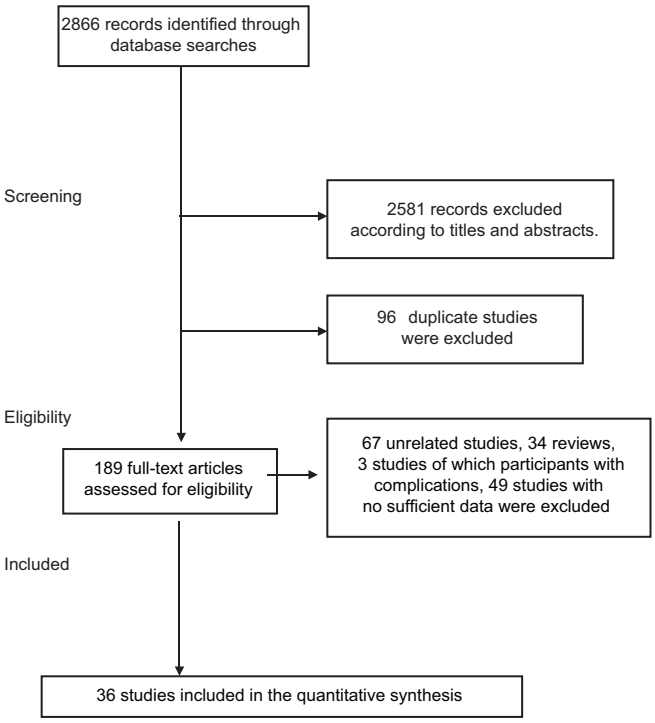

Figure 1: Flow diagram for the selection of studies

IBS. The summary odds ratio was 2.618 (95% CI: 2.052% to 3.341) [Figure 3]. The results were stable no matter which study was excluded according to sensitivity analysis [Figure 4].

Publication bias

No significant publication bias was identified by funnel plot [Figure 5]. Egger's regression test ($P = 0.34$) and Begg's test ($P = 0.69$) also did not show significant bias [Table 2].

Sleep disorders and irritable bowel syndrome based on areas

Twenty-one studies were conducted in Asia (12 in East Asia, 7 in Middle East, 1 in South Asia, and 1 in Southeast Asia). The prevalence of sleep disorders among IBS in Asia was 36.9% (95% CI: 27.7% to 47.2%). The prevalence in East Asia, Middle East, South Asia, and Southeast Asia was 38.2% (95% CI: 25.6% to 52.5%), 35.4% (95% CI: 24.5% to 48.1%), 41.1% (95% CI: 32.2% to 50.7%), and 26.2% (95% CI: 17.9% to 36.6%), respectively. The pooled OR of sleep disorders was 2.982 (95% CI: 2.250 to 3.951) among populations with IBS in Asia. The pooled ORs in East Asia, Middle East, South Asia, and Southeast Asia were 2.351 (95% CI: 1.884 to 2.934), 2.971 (95% CI: 2.068 to 4.269), 19.029 (95% CI: 11.928 to 30.357), and 2.257 (95% CI: 1.294 to 3.937), respectively.

Ten studies were conducted in America (9 studies in North America and 1 in South America). The prevalence of sleep disorders among IBS in America was 40.1% (95% CI: 30.6% to 50.4%). The prevalence in North America and South America was 37.3% (95% CI: 28.3% to 47.4%) and 67.1% (95% CI: 56.4% to 76.2%), respectively. The pooled OR of sleep disorders was 2.268 (95% CI: 1.123 to 4.582) among populations with IBS in America. The pooled ORs in North America and South America were 2.363 (95% CI: 1.081 to 5.165) and 1.666 (95% CI: 0.886 to 3.132).

Five studies were conducted in Europe (2 in Nordic Europe, 1 in Central Europe, 1 in Southern Europe, and 1 multicenter study). The prevalence of sleep disorders among IBS in Europe was 35.9% (95% CI: 24.2% to 49.6%). The prevalence in Nordic Europe, Central Europe, and Southern Europe was 47.1% (95% CI: 34.1% to 60.4%), 21.6% (95% CI: 18.0% to 25.8%), and 42.3% (95% CI: 34.4% to 50.5%), respectively. Only 2 studies conducted in Europe evaluated the association between sleep disorders and IBS (1 study conducted in Nordic Europe and 1 multicenter study). The pooled OR of sleep disorders was 1.721 (95% CI: 1.438 to 2.060) among populations with IBS in Europe.

Sleep disorders and irritable bowel syndrome based on gender

Data regarding gender were available from 10 studies. The prevalence of sleep disorders among female IBS was 43.6% (95% CI: 33.5% to 54.2%). The pooled OR of sleep disorders was 1.884 (95% CI: 1.456 to 2.438) among females with IBS. The prevalence of sleep disorders among males with IBS was 34.4% (95% CI: 27.3% to 42.3%). The pooled OR of sleep disorders was 1.601 (95% CI: 1.308 to 1.960) among males with IBS.

Sleep disorders and irritable bowel syndrome based on occupation

Data regarding occupation were available from 11 studies. Eight studies were conducted among students, 2 were conducted among nurses, and 1 was conducted among veterans. The prevalence of sleep disorders among IBS in students, nurses, and veterans were 32.2% (95% CI: 24.8% to 40.5%), 51.0% (95% CI: 42.3% to 59.7%), and 7.1% (95% CI: 3.2% to 15.0%), respectively. The pooled ORs in students, nurses, and veterans were 2.939 (95% CI: 1.676 to 5.153), 2.435 (95% CI: 1.584 to 3.742), and 0.513 (95% CI: 0.173 to 1.520), respectively.

Sleep disorders and irritable bowel syndrome based on age

Data regarding age were available from 35 studies. Thirty-two studies were conducted among adults and 3 studies were conducted among children and adolescents. The prevalence of sleep disorders was 36.4% (95% CI: 28.6% to 45.0%) among adult IBS patients and 42.4% (95% CI: 34.9% to 50.2%)

Table 1: Characteristics of included studies of quadruple regimens versus other regimens

Author-year	Country	Study design	IBS		Control		Age	Diagnostic criteria for IBS
			Sleep disorder	Total	Sleep disorder	Total		
Lee-2017	Korean	Cross-sectional study	154	374	842	3055	Adult	Rome II criteria
Baniasadi-2017	Iran	Cross-sectional study	28	123			Adult	Rome III criteria
Ibrahim-2016	Saudi Arabia	Cross-sectional study	22	33	79	196	Adult	Rome III Criteria
Wang-2016	China	Cross-sectional study	74	101			Adult	Rome III Criteria
Acay-2016	Turkey	Cross-sectional study	16	112	5	106	Adult	Rome III Criteria
Tuteja-2016	USA	Cross-sectional study	6	84	9	69	Adult	Rome III Criteria
Simian-2016	Chile	Cross-sectional study	57	85	44	80	NA	Rome III Criteria
Tack-2015	European	Cross-sectional study	142	525			Adult	Rome III Criteria
Guo-2015	China	Case-control	30	78	6	79	Adult	Rome III Criteria
Yamamoto-2015	Japan	Cross-sectional study	8494	17882			Children and adolescents	Rome III Criteria
Lee-2015	Taiwan	Cohort study	153	4689	258	18756	Adult	ICD-9-CM code 564.1
Liu-2014	China	Cross-sectional study	91	255	91	512	Adult	Rome III Criteria
Heitkemper-2014	USA	Conference abstract	18	46	6	24	Adult	Rome III Criteria
Lackner-2013	USA	Cross-sectional study	34	175			Adult	Rome III Criteria
Yildirim-2013	Turkey	Cross-sectional study	35	97	7	39	Adult	Rome III Criteria
Zhou-2012	China	Cross-sectional study	108	290	224	1252	Children and adolescents	Rome III Criteria
Rajindrajith-2012	Sri Lanka	Cross-sectional study	44	107	57	1610	Children and adolescents	Rome III Criteria
Yang-2012	China	Cross-sectional study	151	245			Adult	Rome III Criteria
Tang-2012	China	Cross-sectional study	223	452			Adult	Rome III Criteria
Okami-2011	Japan	Cross-sectional study	233	628	336	1140	Adult	Rome II criteria
Gulewitsch-2011	Germany	Cross-sectional study	92	425	269	1771	Adult	Rome III Criteria
Bellini-2011	Italy	Cross-sectional study	60	142			Adult	Rome III Criteria
Nojkov-2010	USA	Cross-sectional study	72	147	59	252	Adult	Rome III Criteria
Nojkov-2010	USA	Cross-sectional study	68	147	84	252	Adult	Rome III Criteria
Shinozaki-2008	Japan	Cross-sectional study	58	196	18	161	Adult	Rome II criteria
Faresjö-2007	Sweden	Cross-sectional study	185	347	392	1041	Adult	ICD-10-P code K-58-p
Heitkemper-2005	USA	Cross-sectional study	20	36	4	38	Adult	Rome II criteria
Akkus-2004	Turkey	Cross-sectional study	11	32	12	50	Adult	Rome I criteria
Vege-2004	USA	Cross-sectional study	112	335	77	1396	Adult	Rome II criteria
Tan-2003	Malaysia	Cross-sectional study	22	84	61	449	Adult	Rome I criteria
Lu-2003	Taiwan	Cross-sectional study	185	447	357	1571	Adult	Rome II criteria
Canataroğlu-2001	Turkey	Cross-sectional study	32	78	9	70	Adult	The criteria of Manning
Fass-2000	USA	Cross-sectional study	153	305	113	205	Adult	The criteria of Manning

Contd...

Table 1: Contd...

Author-year	Country	Study design	IBS		Control		Age	Diagnostic criteria for IBS
			Sleep disorder	Total	Sleep disorder	Total		
Jarrett-2000	USA	Cross-sectional study	20	82	4	35	Adult	Rome I criteria
Sperber-1999	Israel	Cross-sectional study	25	54	11	49	Adult	Rome I criteria
Goldsmith-1993	USA	Cross-sectional study	17	23			Adult	The criteria of Manning
Svedlund-1985	Sweden	Cross-sectional study	40	101			Adult	By definition

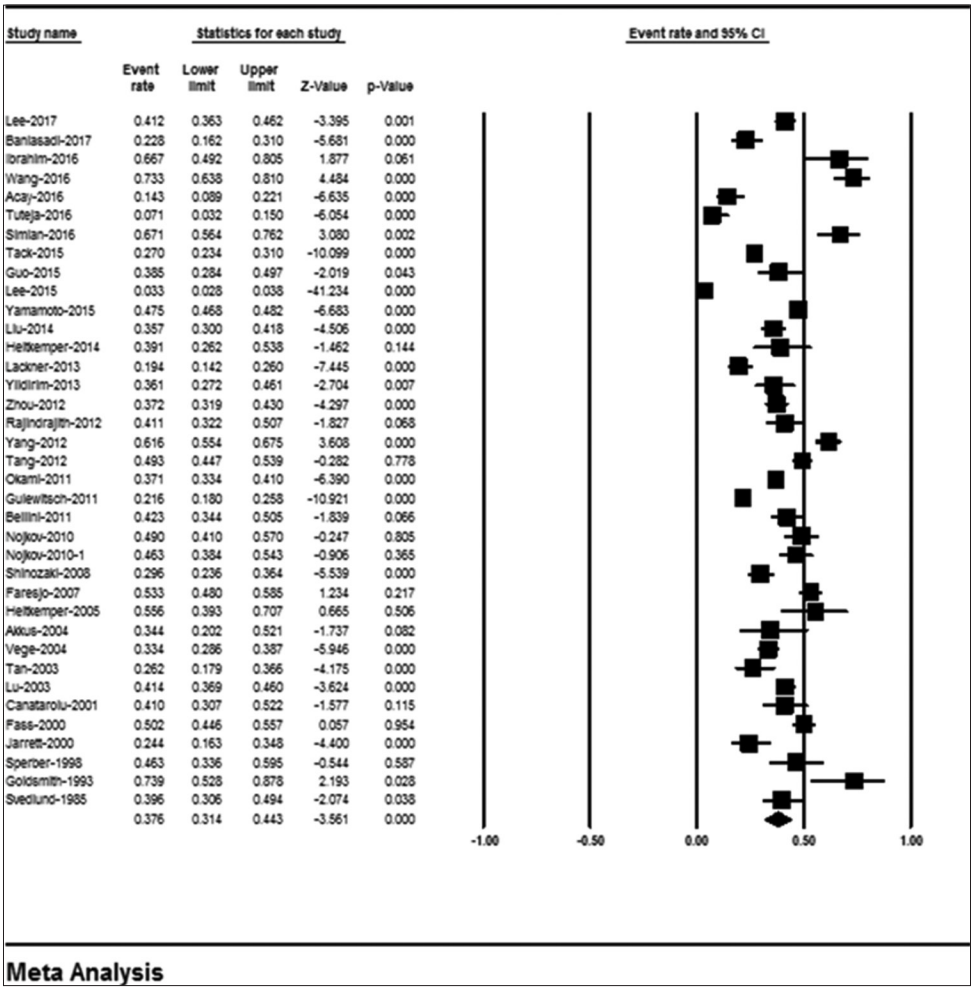

Figure 2: The pooled prevalence of sleep disorders among IBS

among children and adolescent IBS patients. The pooled ORs were 2.403 (95% CI: 1.914 to 3.017) and 7.131 (95% CI: 1.061 to 47.922), respectively.

Sleep disorders and irritable bowel syndrome based on diagnostic criteria for irritable bowel syndrome

Among 36 identified studies, 20 used Rome III criteria, 6 used Rome II criteria, 4 used Rome I criteria, 3 used Manning criteria, and the remaining 3 did not mention specific diagnostic criteria. The prevalence of sleep disorders among IBS diagnosed by Rome III criteria, Rome II criteria, Rome I criteria, and manning criteria were 38.9% (95% CI: 33.3% to 44.8%), 37.9% (95% CI: 33.7% to 42.3%), 32.0% (95% CI: 22.8% to 42.8%), and 51.8% (95% CI: 39.0% to 64.3%), respectively. The pooled ORs were 2.741 (95% CI: 1.802 to 4.168), 3.178 (95% CI: 1.830 to 5.519), 2.303 (95% CI: 1.551 to 3.422), and 1.884 (95% CI: 0.340 to 10.448), respectively.

Sleep disorders and irritable bowel syndrome based on publication year

Five studies were published before 2000, 9 were published

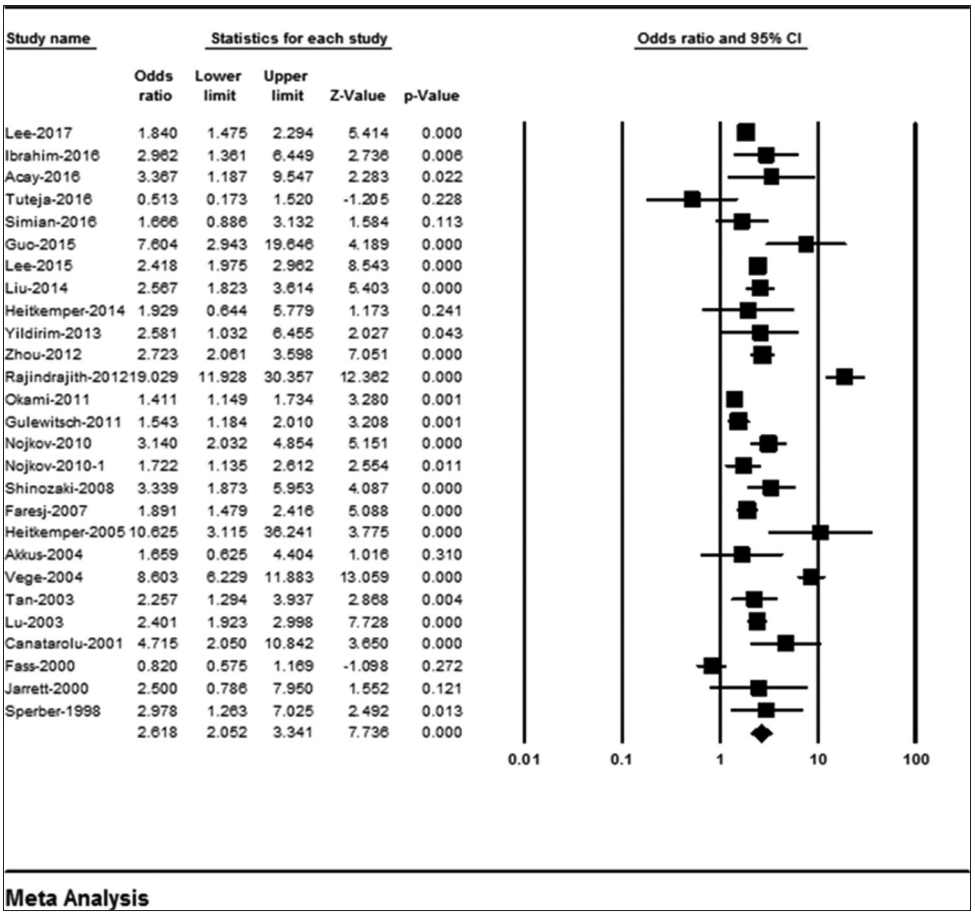

Figure 3: The summary odds ratio of sleep disorders among IBS

between 2001 and 2010, and 22 were published between 2011 and 2017. The prevalence of sleep disorders among IBS during these years were 44.8% (95% CI: 33.1% to 57.1%), 40.8% (95% CI: 34.8% to 47.0%), and 34.6% (95% CI: 25.7% to 44.7%), respectively. The pooled ORs were 1.677 (95% CI: 0.635 to 4.428), 3.093 (95% CI: 2.100 to 4.557), and 2.542 (95% CI: 1.827 to 3.536), respectively.

DISCUSSION

This is the first meta-analysis examining the prevalence of sleep disorders among IBS patients. The results of this meta-analysis involving 36 studies showed that sleep disorders were common in IBS and the prevalence rate was 37.6% (95% CI: 31.4% to 44.3%). The pooled ORs revealed that sleep disorders were significantly associated with IBS.

The reason why sleep disorders are associated with IBS remains unclear. The gut–brain axis plays an important role in the pathogenesis of IBS. Central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), and hypothalamic pituitary adrenal (HPA) axis are thought to be involved.[47] Several studies found that sleep deprivation led to modification of the ANS activity indicating that sleep disorder may be associated with autonomic dysregulation.[48,49] The HPA axis has been reported to be inhibited by sleep and sleep disorder may result in a 24hour increased secretion of ACTH and cortisol.[50] Moreover, the symptoms of IBS, such as abdominal pain, may activate sympathetic nervous system and reduce sleep efficiency.[51] The impact of altered microbiota on the development of IBS has been considered more seriously. Similar mechanism may exist between sleep and gut microbiota. Gut microbes may affect sleep status via degradation products such as muramyl peptides (MPs), lipopolysaccharide (LPS),[52] and melatonin.[53] These degradation products could activate immune cells leading to the release of cytokines, which could affect sleep. A recent study found short chain fat acids and microbiota metabolites might have a potential impact on central and hepatic circadian rhythm.[54] In return, circadian disorganization has been reported to alter the composition of gut microbiota under high-fat, high-sugar diet conditions in mice.[55] Chronic sleep disruption can also cause reversible changes in gut microbiota.[56] Sleep quality assessed by Pittsburgh sleep quality index was also found to be related to the composition of the gut microbiome in healthy older adults.[57] However, the results were controversial. A study reported

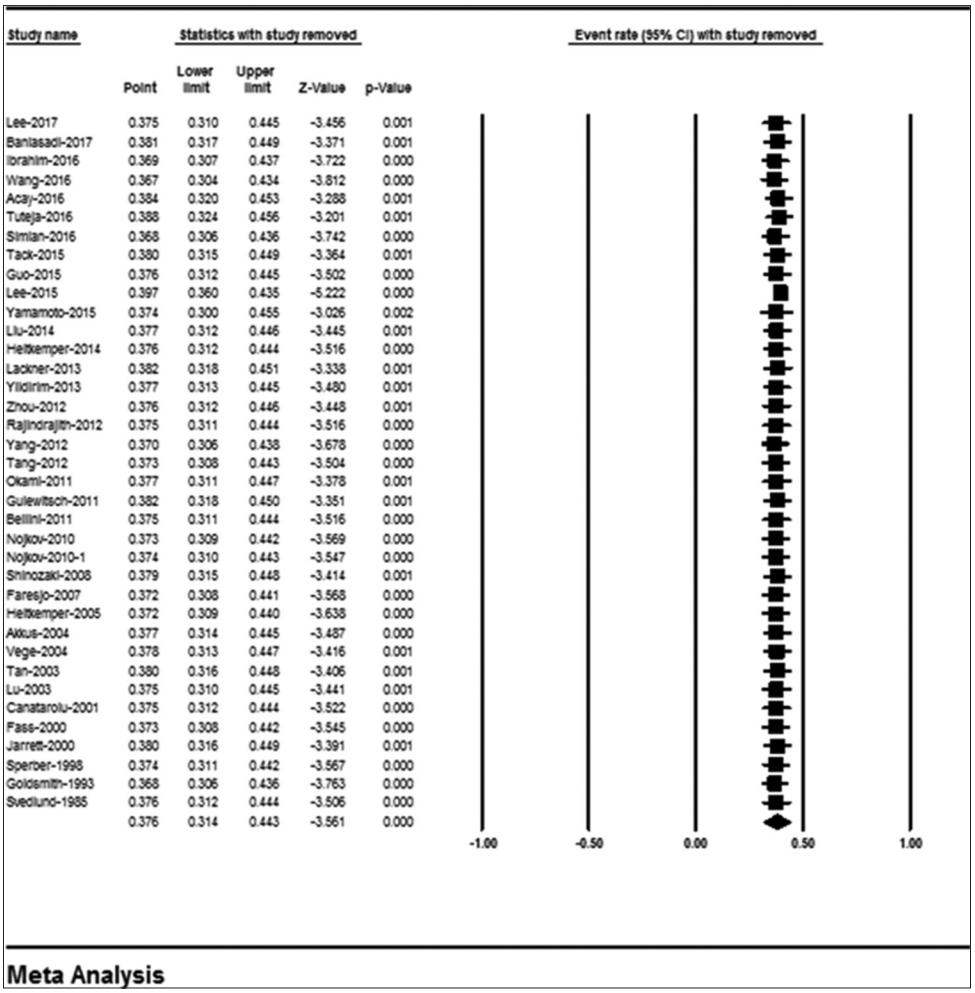

Figure 4: Sensitivity analysis

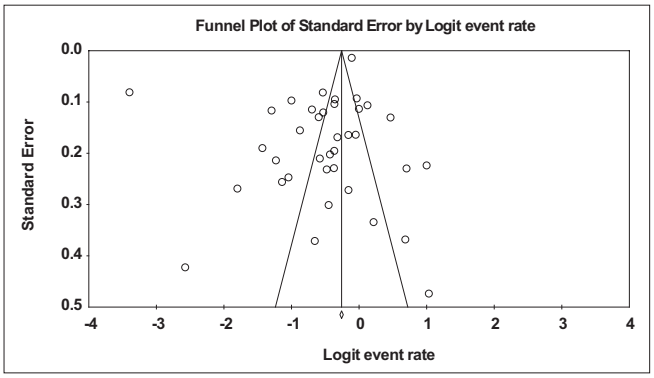

Figure 5: Funnel plot

the overall composition of gut microbiota maintained after several consecutive days of sleep restriction.[58] Overall, although the reason for sleep disorders seen commonly among IBS patients is obscure, gut–brain–microbiota axis disorder may underlie this association.

According to subgroup analysis, the prevalence of sleep disorders among IBS varied slightly in different geographical locations. We also found that the prevalence of sleep disorders among female IBS patients was higher than male IBS patients, however, the difference was not significant. Higher risk of sleep disorder and IBS in females compared with males has been reported by many studies. Sex hormones,[59] difference in visceral and somatic pain sensitivity, central processing of visceral stimuli, genetics, and immunologic/microbiome[60] may be causal factors. Occupation subgroup analysis showed that nurses with IBS might have a higher risk of suffering from sleep disorders. Part of the reason may be the demanding, stressful working conditions. Age subgroup analysis revealed that the prevalence of sleep disorders among children and adolescents with IBS was higher than that among adults, but with no statistically significant difference. Academic stress may be an explanatory factor for this observation. Different IBS diagnostic criteria may lead to differences in prevalence based on subgroup analysis. The prevalence of sleep disorders among IBS seemed to be declining on the basis of publication year subgroup analysis, however, these differences were not statistically significant.

Table 2. Results of meta-analyses/subgroup analyses

Meta-analyses/subgroup analyses	Number of studies	Prevalence	OR	I^2
All studies	36	37.6% (95% CI: 31.4% to 44.3%)	2.618 (95% CI: 2.052-3.341)	98.215
Subgroup based on areas				
Asia	21	36.9%(95% CI: 27.7% to 47.2%)	2.982 (95% CI: 2.250-3.951)	98.85
East Asia	12	38.2%(95% CI: 25.6% to 52.5%)	2.351 (95% CI: 1.884-2.934)	99.338
Middle East	7	35.4%(95% CI: 24.5% to 48.1%)	2.971 (95% CI: 2.068-4.269)	86.07
South Asia	1	41.1%(95% CI: 32.2% to 50.7%)	19.029 (95% CI: 11.928-30.357)	0
Southeast Asia	1	26.2% (95% CI: 17.9% to 36.6%)	2.257 (95% CI: 1.294-3.937)	0
America	10	40.1%(95% CI: 30.6% to 50.4%)	2.268 (95% CI: 1.123-4.582)	91.935
North America	9	37.3%(95% CI: 28.3% to 47.4%)	2.363 (95% CI: 1.081-5.165)	91.103
South America	1	67.1%(95% CI: 56.4% to 76.2%)	1.666 (95% CI: 0.886-3.132)	0
Europe	5	35.9%(95% CI: 24.2% to 49.6%)	1.721 (95% CI: 1.438-2.060)	95.976
Nordic Europe	2	47.1%(95% CI: 34.1% to 60.4%)		82.788
Central Europe	1	21.6%(95% CI: 18.0% to 25.8%)		0
Southern Europe	1	42.3%(95% CI: 34.4% to 50.5%)		0
Subgroup based on gender				
Female IBS patients	10	43.6%(95% CI: 33.5% to 54.2%)	1.884 (95% CI: 1.456-2.438)	94.385
Male IBS patients	6	34.4%(95% CI: 27.3% to 42.3%)	1.601 (95% CI: 1.308-1.960)	76.482
Subgroup based on occupation				
Students	8	32.2%(95% CI: 24.8% to 40.5%)	2.939 (95% CI: 1.676-5.153)	96.44
Nurses	2	51.0%(95% CI: 42.3% to 59.7%)	2.435 (95% CI: 1.584-3.742)	54.145
Veterans	1	7.1%(95% CI: 3.2% to 15.0%)	0.513 (95% CI: 0.173-1.520)	0
Subgroup based on age				
Adults	32	36.4%(95% CI: 28.6% to 45.0%)	2.403 (95% CI: 1.914-3.017)	97.947
Children and adolescents	3	42.4%(95% CI 34.9% to 50.2%)	7.131 (95% CI: 1.061-47.922)	85.209
Subgroup based on diagnostic criteria for IBS				
Rome III criteria	20	38.9%(95% CI: 33.3% to 44.8%)	2.741 (95% CI: 1.802-4.168)	95.194
Rome II criteria	6	37.9%(95% CI: 33.7% to 42.3%)	3.178 (95% CI: 1.830-5.519)	71.033
Rome I criteria	4	32.0%(95% CI: 22.8% to 42.8%)	2.303 (95% CI: 1.551-3.422)	64.354
Manning criteria	3	51.8%(95% CI: 39.0% to 64.3%)	1.884 (95% CI: 0.340-10.448)	72.485
Subgroup based on publication year				
Before 2000	5	44.8%(95% CI: 33.1% to 57.1%)	1.677 (95% CI: 0.635-4.428)	83.597
Between 2001 and 2010	9	40.8%(95% CI: 34.8% to 47.0%)	3.093 (95% CI: 2.100-4.557)	83.838

There are some limitations of our meta-analyses. First, significant heterogeneity was found when data were pooled. Reasons for this heterogeneity may be different characteristics among identified studies. The random-effects model was used to provide a more conservative result. We hope our meta-analyses could show an epidemiologic and global perspective of the prevalence of sleep disorders among IBS patients. Second, most identified studies (34 of 36) in this meta-analysis were cross-sectional studies. We could only describe the association between sleep disorders and IBS but could not determine the cause. More case-control and cohort studies are needed to investigate the substantial causal relationship. Third, all included studies assessed sleep disorders using a subjective questionnaire. Objective measures may be more convincing.

In conclusion, this meta-analysis demonstrated a global prevalence of sleep disorders among IBS and identified an underlying association between them. Different geographical locations, age, gender, occupations, and IBS diagnostic criteria may affect the prevalence of sleep disorders in IBS. Further case-control and cohort studies are needed to elucidate a substantial causal relationship.

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Conflicts of interest

There are no conflicts of interest.

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