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ORIGINAL PAPER

Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis

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Abstract Irritable bowel syndrome (IBS) has been associated with high prevalence of psychological disorders. However, it remains unclear whether IBS and each of its subtypes (predominant diarrhea IBS-D, constipation IBS-C, mixed IBS-M) are associated with higher anxiety and depressive symptoms levels. This study aimed to determine the associations of IBS and each of its subtypes with anxiety and/or depression. We conducted a systematic review and meta-analysis using five electronic databases (PubMed, PsychINFO, BIOSIS, Science Direct, and Cochrane CENTRAL). We selected case–control studies comparing anxiety and depression levels of patients with IBS to healthy controls, using standardized rating scales. Outcomes were measured as random pooled standardized mean differences (SMD). Ten studies were included in our analysis (885 patients and 1,384 healthy controls). Patients with IBS had significant higher anxiety and depression levels than controls (respectively, SMD = 0.76, 95 % CI 0.47; 0.69, $p < 0.01$, $I2 = 81.7$ % and SMD = 0.80, 95 % CI 0.42; 1.19, $p < 0.01$, $I2 = 90.7$ %). This significant difference was confirmed for patients with IBS-C and -D subtypes for anxiety, and only in IBS-D patients for depression. However, other IBS subtypes had a statistical trend to be associated with both anxiety and depressive symptomatology, which suggests a lack of power due to the small number of studies included. Patients with IBS had significantly higher levels of anxiety and depression than healthy controls. Anxiety and depression symptomatology should be systematically checked and treated in IBS patients, as psychological factors are important moderators of symptom severity, symptom persistence, decisions to seek treatment, and response to treatment.

Keywords Irritable bowel syndrome · Anxiety · Depression · Psychiatric comorbidities

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Introduction

Irritable bowel syndrome (IBS) is a common, costly, and potentially disabling functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain associated with alterations in bowel habits [31]. Recent psychological studies IBS have suggested that there is evidence of an association with psychological factors, especially depression, anxiety, and somatization. Some studies have shown

that approximately up to 60 % of IBS patients have major psychosocial problems [30]. Although the etiology of IBS remains elusive, there is support for the notion that dysfunction of brain-gut pathways is a factor in the presentation of the disease [4, 25]. This biopsychological model of IBS suggests that abdominal symptoms secondarily influence anxiety and depression (bottom-up model) and that psychological factors themselves influence physiological factors such as motor functions, sensory threshold, and stress reactivity of the gut via vagal and sympathetic afferents (top-down model) [39]. There is particularly strong evidence for the role of early-life stressors such as sexual abuse and maternal separation in IBS [10, 26, 47]. Exploring the psychological aspects of IBS is thus important to the understanding of the disorder and also for developing effective treatments.

Over the last decade, numerous studies have investigated the psychological disorders of patients with IBS by comparing their levels of anxiety and depression with those of healthy controls, but these studies have reported contrasting findings. Some studies have suggested that IBS was associated with higher anxiety [1, 11, 24, 29, 36, 40] and/or depression levels [1, 11, 36, 40], whereas others did not find such an association [1, 5, 29]. In addition, conflicting results have been reported for IBS-subtypes (IBS-C "constipation," IBS-D "diarrhea," and IBS-M "mixed," i.e., with alternant diarrhea and constipation episodes). Some studies suggested that IBS-C subtype may be specifically associated with higher anxio-depressive symptomatology [33], whereas others found no differences between IBS subtypes [8, 18, 40].

In order to provide more reliable estimates of the level of anxiety and depression in IBS, we report a systematic review and meta-analysis of studies describing the associations of IBS and each of its subtypes with anxiety and/or depression in comparison with healthy controls.

Methods

Search strategy

This meta-analysis is based on the PRISMA criteria (Preferred Reporting Items for Systematic reviews and Meta-Analysis) [32]. A specific search strategy was developed for the interface PubMed (MEDLINE database), based on a combination of MeSH terms "irritable bowel syndrome," as well as indexed terms related to depression ("Depression" OR "Depressive Disorders" OR "Mood Disorders" OR "Affective Disorders," OR "Anxiety") and study design ("controlled clinical trial") to identify case–control studies from different computerized databases: PubMed (from 1966 to September 2013), Embase (from 1980 to September 2013), PsychINFO (from 1806 to September 2013), BIOSIS (from 1926 to September 2013), Science Direct (from 2006 to September 2013), and Cochrane CENTRAL (from 1993 to September 2013). Furthermore, we searched ProQuest Dissertations and Theses Full Text Database to identify unpublished dissertations.

Criteria for selecting articles

Studies were included if they met the following criteria: (1) All observational case–control studies, observational studies, and first-round data collection of observational studies addressing the difference in depressive or anxiety symptoms between adult IBS patients and healthy controls were included and (2) identification of clinically relevant depressive or anxiety symptoms based on validated scales without language restriction.

Two investigators (G.F. and L.B.) independently assessed the manuscripts generated for relevancy, and manuscripts with the following criteria were excluded: (1) Comparisons were not made between IBS patients and healthy controls, and (2) a standardized mean difference (SMD) could not be calculated after contacting the authors. As this meta-analysis involved data from published studies, an institutional review board approval was not required.

Selection of studies and data extraction

One author (J-A.M.) screened titles and abstracts of database records and retrieved full texts for eligibility assessment. Two authors independently checked the full text records for eligibility (G.F. and L.B.). Disagreements were resolved by consensus discussion.

The manuscripts of the studies were then independently reviewed by two of the authors (G.F. and L.B.). Data were independently extracted into a standard electronic form: first author name, date of publication, design, sample size, IBS diagnosis criteria. Any discrepancies were resolved by consensus with a third reviewer (J-A.M.).

Assessing the methodological quality of included studies (Table 2)

The methodological quality of included studies was assessed independently by two of the authors (G.F. and L.B.) using a validated rating scale for detecting bias in psychiatric case–control studies [28]. We adapted this scale for the subject of this meta-analysis, and we explored selection bias of cases (eight items), selection of bias of controls (four items), and information bias (one item). Any discrepancies were resolved by consensus with a third reviewer (J-A.M.).

Statistical analyses

We calculated SMD with 95 % confidence intervals (CIs) for each study, defined as the difference in means between the two groups (IBS and control) divided by the pooled standard deviation of the measurements. We used random effects models [15] which account for between-study heterogeneity by weighting studies similarly. Heterogeneity was assessed using the $I2$ statistic, which represents the percentage of variance due to between-study factors rather than sampling error [23]. We considered values of $I2 > 50$ % as indicative of large heterogeneity [48]. We used funnel plots, Rosenthal fail-safe N (i.e., which estimates the number of missing studies needed to change the results of the meta-analysis), and the Egger regression intercept (i.e., which assesses the degree of funnel plot asymmetry by the intercept from regression of standard normal deviates against precision) to estimate risk of bias [6]. Forest plots were generated to show SMD with corresponding CIs for each study and the overall random effects pooled estimate. We conducted several sensitivity or influence analyses to explore potential reasons for heterogeneity or inconsistency. Analyses were performed with comprehensive meta-analysis software (version 2.0, National Institute of Health) [6].

Results

Study selection

Seven hundred and sixty-four abstracts were initially identified through database searches. We excluded 752 articles because they did not meet the inclusion criteria. In the remaining 14 articles, 2 studies failed to have a healthy control group; one study lacked standardized assessment of depressive or anxiety symptoms; one study had the same data with one other study, which was already included. The selection process was summarized in Fig. 1. Finally, we included ten studies in our analysis, conducted between 2002 and 2012 [1, 5, 8, 11, 24, 27, 36, 40, 44, 45]. The Table 1 described the key characteristics of the included studies: study design, number of patients and controls, studied populations, mean ages, diagnosis criteria for IBS, and scales used for assessment of anxiety and depression. The Table 2 described the methodological quality of the case–control studies. The clinical setting used for recruitment and the inclusion/exclusion criteria for cases were always clear. However, the reporting was particularly poor for the other items for cases and controls. According to these criteria, five studies over the ten were globally less vulnerable to selection and information bias [1, 11, 36, 40, 45].

Study characteristics

Overall, 885 patients and 1,384 healthy controls were included. The studies were conducted in outpatients' populations, except one, which included volunteer students, and one that was conducted in general population. Three studies were conducted in Asia, three in North America, and four in Europa.

IBS was diagnosed in nine studies using the Rome criteria for GI disorder [1, 5, 8, 11, 24, 27, 40, 44, 45]. The presence of IBS was indicated if participants had abdominal pain or discomfort during at least 3 weeks (at least once a week) in the last 3 months and two of the following three symptoms: (1) pain or discomfort getting better or stopping after a bowel movement, (2) a change in the number of bowel movements when the pain or discomfort starts, and (3) either softer or harder stools than usual when the pain or discomfort starts. One study used the Bowel Disorder Questionnaire (BDQ) [36], a validated and reliable questionnaire that was used to determine the presence of IBS symptoms during the past year [42, 43].

All the studies used validated scale to assess anxiety and depression, measuring similar constructs. Eight studies used the Hospitalization Anxiety and Depression Scale (HADS) to evaluate anxiety and depression levels [1, 5, 8, 11, 27, 40, 44, 45]. Score for each subscale (anxiety and depression) can range from 0 (minimal) to 21 (severe). One study used the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory-2nd Edition (BDI-II) [36]: The BAI and BDI-II scores can range from 0 (minimal) to 63 (respectively severe anxiety and depression) [3]. One study used the stress symptom rating scales (SSR) [24], in which anxiety level ranges from 0 (minimal) to 10 (severe anxiety). One study used the ten anxiety items and the 16 depression items of the Symptom Checklist 90 (SCL-90) [14, 45].

Anxiety and depression levels in IBS patients

Overall, the anxiety and depression scores were significantly higher in IBS patients compared to healthy controls (respectively, SMD = 0.76, 95 % CI 0.47; 0.69, $p < 0.01$, $I2 = 81.7$ % and SMD = 0.80, 95 % CI 0.42; 1.19, $p < 0.01$, $I2 = 90.7$ %) (Figs. 2 and 4). On the associated funnel plots, the studies were reasonably symmetrical, except for three outliers studies [40, 44, 45] (Appendix: the two funnel plots). Because the p values of the Egger's regression intercept were, respectively, 0.20 and 0.13, the asymmetry is considered to be statistically nonsignificant. The Rosenthal's fail-safe N value was higher than 230. Given that we identified ten studies that looked at the level of anxiety and depression in IBS, it is highly unlikely that nearly 220 studies were missed.

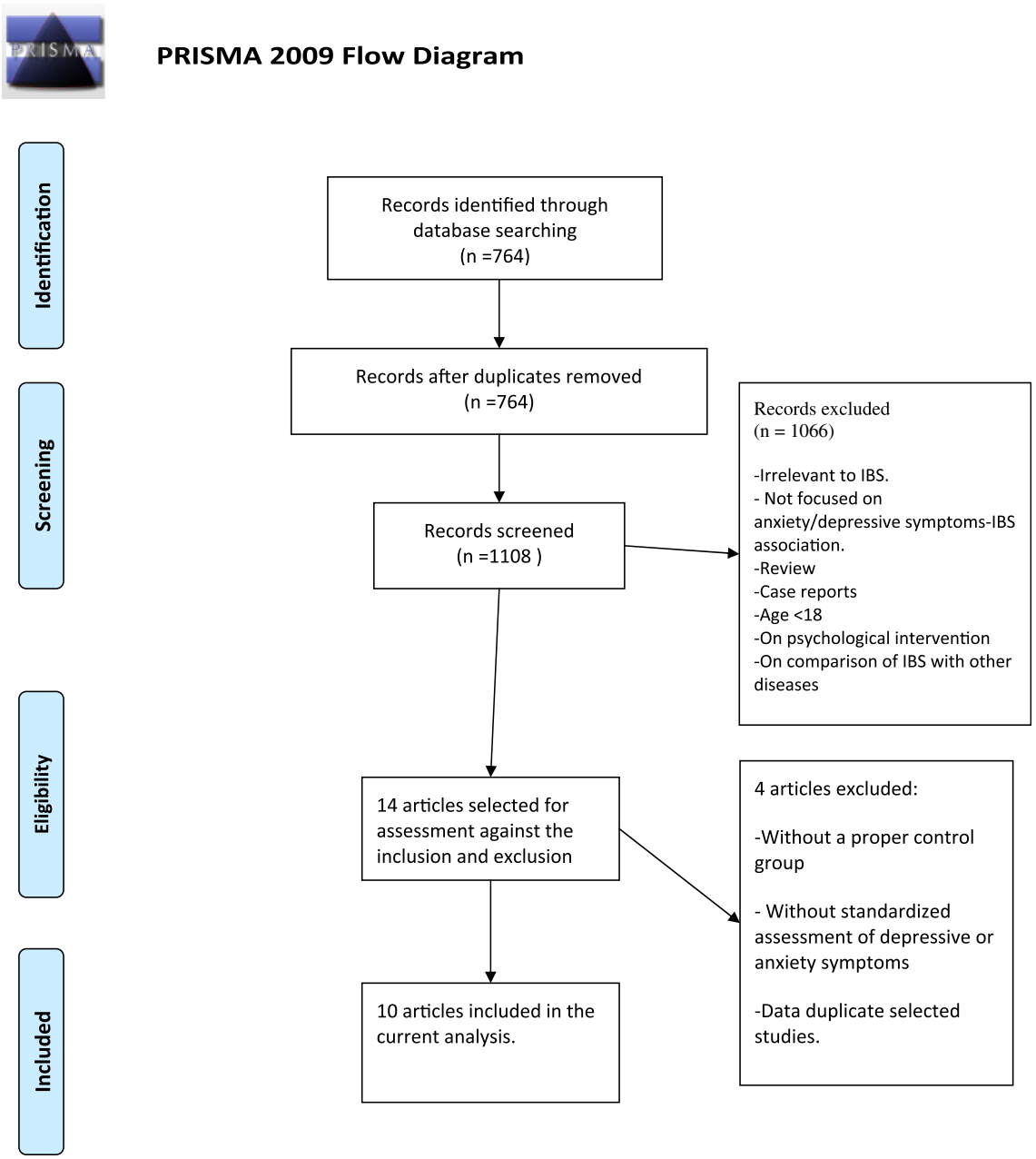

Fig. 1 PRISMA 2009 flow diagram

The higher anxiety and depression level in IBS patients remained significant after (1) excluding outliers study [40, 44, 45] (respectively, SMD = 0.75, 95 % CI 0.58–0.92, $p < 0.01$, and SMD = 0.84, 95 % CI 0.69–0.99, $p < 0.01$), (2) excluding six studies with high risk of bias [5, 8, 24, 27, 44] (respectively, SMD = 0.55, 95 % CI 0.27–0.83, $p < 0.01$, and SMD = 0.60, 95 % CI 0.24–0.96, $p < 0.01$), and (3) excluding one study on adolescent sample [40] (respectively, SMD = 0.84, 95 % CI 0.47–1.20, $p < 0.01$, and SMD = 0.90, 95 % CI 0.52–1.28, $p < 0.01$).

Anxiety and/or depression levels in IBS subtypes

We identified eight studies comparing anxiety levels of IBS patients to those of healthy controls [5, 11, 24, 27, 36, 40, 44, 45]. Patients with IBS had significant higher anxiety

Table 1 Psychiatric comorbidities of irritable bowel syndrome (IBS): summary of the major findings of the 8 studies included in our quantitative review

Psychiatric disorder	Study	Design	*N* (mean age)	Clinical evaluation support (for IBS and psychiatric disorders)	Major findings
MDD anxiety	[44]	Case–control	30 IBS (43.9) 30 HCs (41,6)	Rome II HAD	Patients with IBS had significantly higher depression and anxiety scores than healthy controls ($p < 0.00001$)
MDD anxiety	[45]	Case–control	101 IBS (42 ± 13.9) 40 HCs (39.7 ± 15)	Rome II SCL-90	Levels of anxiety and depression were significantly increased in IBS patients versus controls
Anxiety	[5]	Case control	11 IBS (40.5 ± 12.9) 11 HCs (37.3 ± 10.6)	Rome II HADS	IBS patients had a higher symptom-related anxiety (VSI) ($p < 0.0001$), neuroticism (trait anxiety) scores ($p = 0.009$) and higher plasma noradrenaline levels than HCs.
MDD anxiety	[40]	Case control College students	*N* tot = 1,087 Aged 19.7 (SD 1.8) *N* = 206 IBS *N* = 881 HCs	Rome II HADS ASI	Individuals with IBS had higher ASI and HADS-A scores ($p < 0.001$).
MDD anxiety	[29]	Case–control	17 IBS (35.9 ± 10.8) 17 HCs (37.4 ± 10.2)	Rome III HADS	HAD anxiety subscores was significantly higher in IBS (8.8 SD 3.6 IBS vs. 5.8 SD 3.2 HC, $p = 0.04$), but no difference was found in depression subscores (6.3 SD 2.7 IBS vs. 4.5 SD 2.9 HC)
MDD anxiety	[11]	Case control	124 IBS IBS-M = 31 IBS-C = 30 IBS-M = 31 91 HCs	Rome II HADS	Anxiety and depression were observed in 47(38.6 %) and 38.6 % of IBS patients, respectively, and in 22(24.2 %) and 15(16.5 %) of healthy subjects, respectively ($p < 0.05$ for both). The mean HADS scores for anxiety and depression in IBS patients were 6.8 ± 4.5 and 7.1 ± 4.4, respectively. Both anxiety and depression were associated with self-reported symptom severity ($p < 0.012$ and $p < 0.001$, respectively). After adjustment with sex, age, marital status, education level, symptom severity was the most important factor in the prediction of anxiety and depression.
MDD anxiety	[36]	Case control Women veterans	93 IBS 104 HCs	BDQ BAI BDI	Women with IBS reported higher mean scores of anxiety (IBS: 24 vs. 12, $p < 0.0005$), depression (IBS: 22 vs. 11, $p = 0.0005$). Age- and ethnicity-adjusted logistic regression analyses showed a 3- to 46-fold increase in odds of IBS among women with anxiety, depression, or PTSD.
MDD anxiety	[1]	Case–control	141 FGID (45.7 ± 14.3) 97 HCs (52.4 ± 15.4)	Rome III HADS	Significantly more anxiety in FGID group ($p = 0.002$) but not MDD.
MDD anxiety	[8]	Case–control	122 IBS 41 HCs	Rome II BDQ HADS	IBS was associated with body mass index, somatic symptoms, and anxiety and depression scores. Colonic transit (32 %) is the most prevalent physiological abnormality in IBS.
Anxiety	[24]	Case–control	40 IBS (42.6 ± 2.7) 36 HCs (36.7 ± 2.1)	Rome I SSR	IBS patients reported higher anxiety ($p = 0.005$), fatigue ($p = 0.04$), and lower arousal ($p = 0.003$) There were no differences in stress either in IBS patients according to bowel habit predominance.

HCs healthy controls, *IBS-C* IBS with predominant constipation, *IBD* inflammatory bowel disorder, *IBS-D* IBS with predominant diarrhea, *IBS-C* IBS with predominant constipation, *IBS-M* IBS with mixed/alternative constipation and diarrhea, *DSM* diagnostic and statistical manual, *ASI* Anxiety Sensitivity Index, *MDD* major depressive disorder, *SD* standard deviation, *HADS* Hospitalization Anxiety and Depression Scale, *BDI* Beck Depression Inventory, *FGID* functional gastrointestinal disorder, *BDQ* Bowel Disease Questionnaire, *BAI/BDI* Beck Depression and Anxiety Inventories, *HAD* Hamilton anxiety and Depression Scale

Table 2 Methodological quality of the case–control studies ($N = 10$ [1])

	Yes N	No N	Unclear N
Cases			
Was the clinical setting used for recruitment made clear?	9	1	0
Was the denominator from which cases were recruited described?	3	7	0
Was duration of illness adequately described?	2	8	0
Was medication use adequately described?	0	10	0
Was adequate information given on the total number of patients approached?	3	7	0
Was information given on participants and non-participants?	1	9	0
Was information given on the differences between participants and refusers?	0	10	0
Were the inclusion and exclusion criteria described well enough to be replicable?	9	1	0
Controls			
Were controls selected from an explicit sampling frame?	4	5	1
Were similar exclusion criteria applied for controls as for cases?	5	0	5
Was information given on number of controls approached?	3	7	0
Was adequate information given on differences between controls refusing and agreeing?	0	10	0
Information bias			
Were the investigators who rated the exposure masked to participants' status?	9	1	0

levels than controls (random pooled SMD = 0.66, 95 % CI 0.42–0.90, $p < 0.001$). This significant difference was confirmed for patients with IBS-C and IBS-D subtypes issued from four studies (respectively, 1.42, 95 % CI 0.04–2.79, $p = 0.043$; and 0.91, 95 % CI 0.29–1.53, $p = 0.013$), but not for patients with IBS-M (2.45, 95 % CI −0.07 to 4.96, $p = 0.056$).

We also identified 8 studies comparing depression levels of IBS patients to healthy controls [1, 5, 11, 24, 27, 36, 40, 44]. As for anxiety, patients with IBS had significant higher depression levels than controls (SMD = 0.66, 95 % CI 0.31–1.02, $p < 0.001$). This difference was confirmed in patients with IBS-D issued from three studies (1.75, 95 % CI 0.20–3.31, $p = 0.027$), contrary to IBS-C and IBS-M, which were not significant (respectively, 1.80, 95 % CI −0.12 to 3.72, $p = 0.066$; and 2.61, 95 % CI −1.42 to 6.63, $p = 0.204$).

These results are illustrated in forest plots (Figs. 2, 3, 4, and 5).

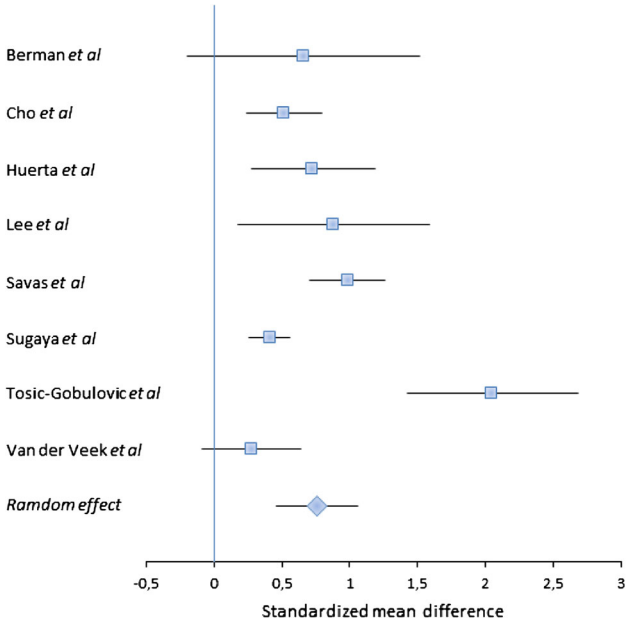

Fig. 2 Meta-analysis of eight studies about anxiety in IBS

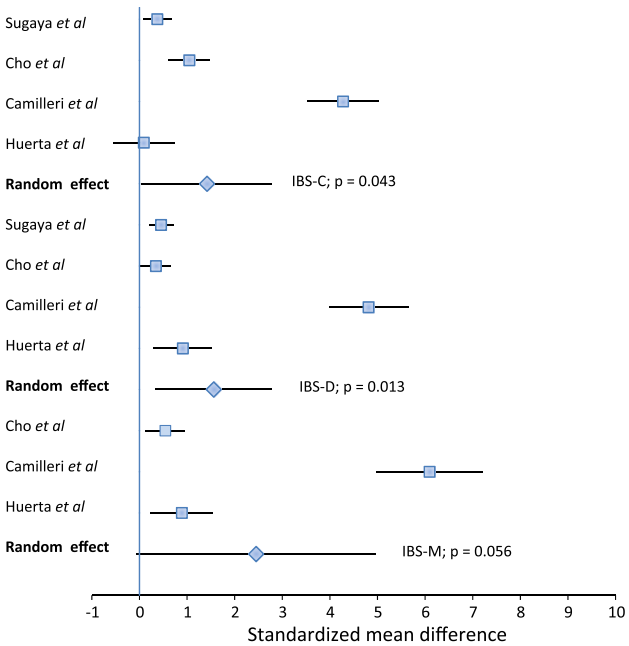

Fig. 3 Meta-analysis of four studies about anxiety in IBS subtypes

Discussion

To our knowledge, this study is the first meta-analysis aiming to estimate the anxiety and depression levels in adults with IBS compared to healthy controls. Following a broad search in various databases, we found 11 studies with an overall sample size of 885 patients and 1,384 healthy controls for this meta-analysis.

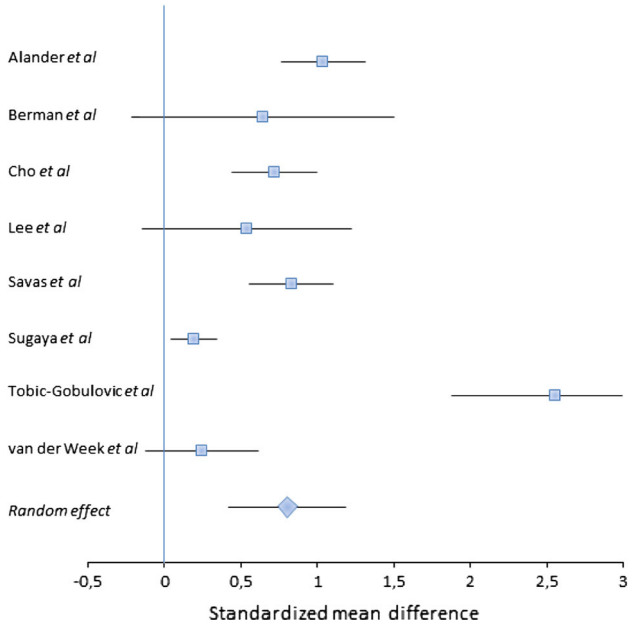

Fig. 4 Meta-analysis of eight studies about depression in IBS

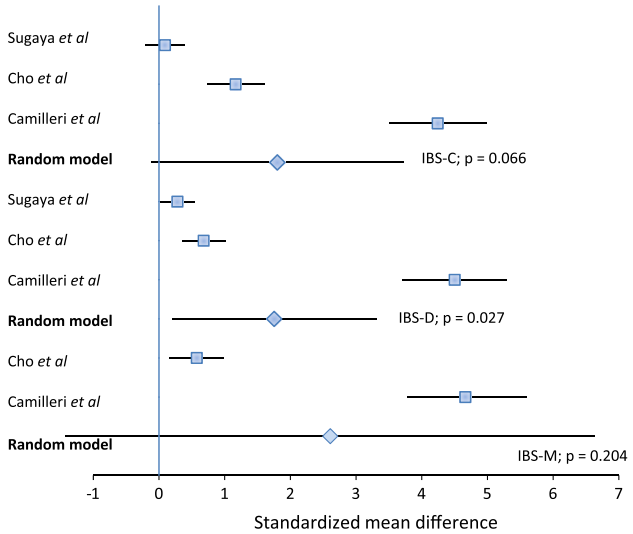

Fig. 5 Meta-analysis of three studies about depression in IBS subtypes

The first important finding of our study is the confirmation of the higher levels of anxiety and depression patients with IBS than in healthy controls. This result is not really surprising considering the scientific literature as a whole, but it can be considered as an additional argument in favor of the biopsychological model of IBS and dysfunctions of brain–gut pathways. Dysfunctional brain–gut interactions have been found in maternally separated rodents—an often studied model of early-life stress in IBS (for review see [20]) but not in humans yet. It can then be hypothesized that checking and treating IBS symptoms in patients with anxiety and depressive disorders may also improve psychiatric symptomatology of these patients. Therapies targeting microbiota could thus constitute a new field of research and development in anxiety and depressive disorders.

However, it remains unclear whether microbiota dysbiosis initiates anxiety and depressive symptoms (by increased gut permeability, endotoxin and/or neuropeptides' secretion, mucosal and general inflammation, nutrients absorption modifications, and autonomic nervous system modulation) or whether anxiety and depressive disorders induce gastrointestinal disorders (mostly by the autonomic nervous system dysfunction that has been well described in depressive disorders, but also by stress hormones secretion and immune dysfunction that have been described in these disorders) [9, 19]. Cohort studies are few in numbers, with very heterogeneous designs, and only two studied the temporal relationship between IBS and anxio-depressive symptoms: Talley et al. [41] identified in a birth cohort study of 1,037 subjects that IBS symptoms at age 26 were associated with psychopathology at age 18 and 21, suggesting that psychiatric symptoms preceded IBS symptoms, and Goodwin et al. [21] recently found in a large sample of the general population ($N = 17{,}415$) that IBS symptoms at age 42 were related to psychopathology at age 24 and 34. Anxio-depressive symptoms seem then to precede IBS symptoms.

We found mixed results regarding associations between each IBS subtypes and, respectively, anxiety and depression. Given that some of associations (IBS-D and IBS-C with anxiety, IBS-D with depression) are statistically significant and that the others nearly reach significance, it seems reasonable to suggest that each IBS subtypes may be associated with higher anxiety and depression levels and that nonsignificant results are due to lack of power given the few numbers of studies (four for anxiety, and three for depression). The deltas seem also similar in both anxiety and depression. Future studies should, however, explore this issue on large sample and confirm the similarity of psychological profiles between IBS subtypes.

These results may have important clinical implications. Patients with IBS are at high risk of anxiety and/or depression symptomatology. These comorbidities should be systematically checked and treated. Psychological factors appear to play particularly important roles as moderators of symptom severity, symptom persistence, decisions to seek treatment, and response to treatment [17]. Some studies have suggested that psychological intervention may improve the management of the gastrointestinal disorder evolution (according to the top-down hypothesis) as well as the quality of life of the patients, even in when patients are in remission but keep residual symptoms like fatigue [22, 37]. Examining which psychological factors had the

highest impact on IBS symptoms severity, van Tilburg et al. found that anxiety had an indirect effect on IBS symptoms through catastrophizing, as well as somatization. Anxiety, in turn, was predicted by neuroticism and stressful life events [46]. However, although the role of psychological therapies has been analyzed in multiple studies [7, 38], the methodological design of most of these studies was inadequate [35], and the efficiency of these therapies should be rigorously explored in future studies. Moreover, prospective cohort studies would be helpful in exploring the questions being raised, such as the direction of causality in the reported association.

Although our overall results go in the same direction, confirming the strong association of IBS, anxiety, and depression, our results should be weighted by (1) the methodological quality of the studies: We found in this review that the methodological level was poor, and many manuscripts failed to include sufficient information to allow a judgment about the potential selection biases (Table 2). The recruitment of cases was often not well described (e.g., description of nonparticipants, refuses, participation rate…), and the generalizability of the findings cannot be certain to the whole population of IBS patients, and (2) the use of the HADS for anxiety and depression assessment. Five of the ten included papers included HADS. This is a clear limitation as Norton and colleagues recently re- and meta-analyzed data from 21 previous studies and advised against using the HADS in clinical practice when the objective was to provide a specific analysis of anxiety or depression [34]. Some authors even recommend to abandon HADS in the evaluation of depression and anxiety [13], but the subject is controversial [12, 16]. However, other more consensual depression scales should be used in further studies. (3) An important issue was that GI side effects from selective serotonin reuptake inhibitors prescribed for depression may confound IBS cases as no treatment data were recorded in the included studies. (4) Another point is that because of probable cultural and socioeconomic differences in IBS presentation, the inclusion of studies performed in other countries may have modified our results [2]. Further studies should take these issues into account. Moreover, the number of total studies included in this meta-analysis may be considered as small, and this is particularly relevant when interpreting the associations between IBS subtypes and anxiety and depression levels. Future works are needed to provide more precise estimates of these associations.

Conclusion

This review confirms the higher levels of anxiety and depression in patients with IBS; however, no specific subtype has been identified to be associated with higher psychiatric comorbidities compared to the others. The potential contribution of addressing psychological factors in IBS would benefit from further examination in large clinical trial.

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Conflict of interest No conflicts to disclose.

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