Psychological disorders in gastrointestinal disease: epiphenomenon, cause or consequence?

Eric Shah[a], Ali Rezaie[a], Mark Riddle[b], Mark Pimentel[a]

Cedars-Sinai Medical Center, Los Angeles, CA, USA; Naval Medical Research Center, Silver Spring, Maryland, USA

Abstract	
	Background Psychological disorders have been associated with irritable bowel syndrome (IBS) for decades in the absence of other objective etiology. However, such associations are also evident in other chronic diseases with more clearly defined pathogenesis such as ulcerative colitis. In this study, we examined the prevalence and severity of psychological disorders among IBS and ulcerative colitis (UC) patients relative to healthy controls.
	Methods A review was conducted of English-language literature to identify case-control studies reporting the prevalence of depression or anxiety in IBS and UC populations relative to healthy controls. Our primary endpoint was the pooled prevalence or average score of depression or anxiety in an IBS or UC population relative to healthy control.
	Results Seven case-control studies evaluating IBS and three evaluating UC were included. All IBS and UC studies reported excess prevalence and severity of depression as well as anxiety, relative to healthy controls. The prevalence of depression in excess of healthy controls was 39% in UC case-control trials and 33% in IBS studies, and excess anxiety was present in UC (42%) and IBS (19%) case-control trials as well. Anxiety and depression scores were higher (representing more severe symptoms) in both UC and IBS patients compared to healthy controls.
	Conclusions Anxiety and depressive disorders are associated with both IBS and UC. The non-specific association between these psychological and gastrointestinal disorders could suggest that chronic gastrointestinal illness might affect psychosocial behavior.
	Keywords Mood disorders, irritable bowel syndrome, colitis, ulcerative

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Introduction

Disorders of unknown etiology have historically been linked to psychosomatic causes. In gastroenterology, one example is ulcerative colitis (UC) before the advent of flexible endoscopy. Historically, UC was linked to Freudian anal

[a]GI Motility Program Cedars-Sinai Medical Center, Los Angeles, CA (Eric Shah, Ali Rezaie, Mark Pimentel); [b]Enteric Diseases Department, Naval Medical Research Center, Silver Spring, Maryland (Mark Riddle), USA

Correspondence to: Mark Pimentel, MD, FRCP(C), Director, GI Motility Program, Cedars-Sinai Medical Center, 8730 Alden Drive, Suite 201E, Los Angeles, California, 90048 USA, Tel.: +1 310 423 6143, Fax: +1 310 423 8356, e-mail: pimentelm@cshs.org

regression caused by a difficult dilemma facing the patient [1]. The psychosomatic hypothesis in UC remained prominent for many decades. Evaluations were conducted to assess the psychosomatic theory [2]almost concurrently with classic evaluations of immunomodulating agents [3]. As recent as twenty years ago, a well-conducted systematic review failed to find an association between psychological factors and UC [4]. As UC was slowly legitimized as an organic disease process, the role of stress and psychological contributions took a back seat to theories of immune dysfunction and potential environmental factors [5].

It is well-known that irritable bowel syndrome (IBS) and psychological illnesses are often co-morbid conditions [6,7]. A prior systematic review also revealed that IBS is common in patients with chronic fatigue syndrome, pelvic pain, temporomandibular joint disorder which are all theorized to have some psychological component in their manifestation [8]. Despite these findings, a true prospective study has yet to prove that IBS is actually caused by, rather than merely associated with, psychological stressors. Emerging data are beginning to characterize potential pathophysiologic mechanisms of IBS such as post-infectious IBS or altered gut microbiota

which argue against a mainly psychological root cause [9,10]. Moreover, the role of microinflammation in the bowel wall in IBS is becoming clear which may explain overlapping IBS-like symptoms in IBD patients [11].

The effects of illness and disability on the psychological wellbeing of humans are well documented in the literature [12-15]. Psychological illnesses can worsen disease through factors separate from the pathophysiology of the medical condition, such as non-adherence to therapy and follow up [16,17] as well as lifestyle choices known to worsen the underlying condition [18,19]. Regardless of cause, the resulting combination of co-morbid medical and psychological conditions leads to poor outcomes [20,21]. Co-morbid psychological illness may potentiate or predict the presence of a medical disorder but does not necessarily have to cause the medical condition [22].

We postulated that the association between IBS and psychological factors might be attributed to the general psychological stress of suffering from chronic and often debilitating disease or a derangement of the gut-microbiome-brain axis involving dysbiosis of neurocognitive function. Based on this, it would be reasonable to consider a similar association with psychological disorders in other disease literature as well. Therefore, we aimed to identify the severity of depression and anxiety symptoms measured with scoring symptoms using validated patient questionnaires of IBS patients relative to healthy controls, and to compare these data with similar data in the UC literature on the basis of both illnesses being traditionally classified as colonic diseases.

Methods

Study design

We conducted a PubMed literature search (7 May 2013) to identify relevant case-control studies evaluating co-morbid psychological factors in two populations of patients with two gastrointestinal (GI) illnesses typically classified as colonic diseases: patients with IBS or UC compared to a healthy population. Search terms are shown in the *supplement*. Due to our pooled endpoint, IBS studies were limited to those evaluating Rome criteria to increase the homogeneity of IBS patient populations. Inclusion criteria were then applied (Table 1) to identify relevant studies for this analysis. Data were extracted by ES and reviewed by ES and MP.

Extracted data included methodology of recruiting and enrolling patients, eligibility criteria for case or control groups, sex distribution of enrolled patients, and criteria for determining presence or severity of depression and anxiety.

Endpoints and statistical analysis

Our primary endpoint was the percentage of patients identified as having co-morbid depression or anxiety with the

respective GI illness, relative to a healthy control population, based on a threshold score using a validated patient questionnaire. As a secondary endpoint, we evaluated the severity of depression and anxiety symptoms in patients with the respective GI illness relative to healthy controls based on reported validated scoring systems. Scoring methods such as the Hospital Anxiety and Depression Index (HADS) report the sum of patient-reported symptoms as well as symptom severity with a validated cut-off threshold to represent major depressive disorder or anxiety disorder. Study results were arithmetically summed wherever matching criteria were identified which evaluated the presence or severity of depression and anxiety.

Results

We identified seven eligible IBS studies and three eligible studies of UC (Fig. 1). The severity of anxiety and depression symptoms was measured using discrete numerical scales which
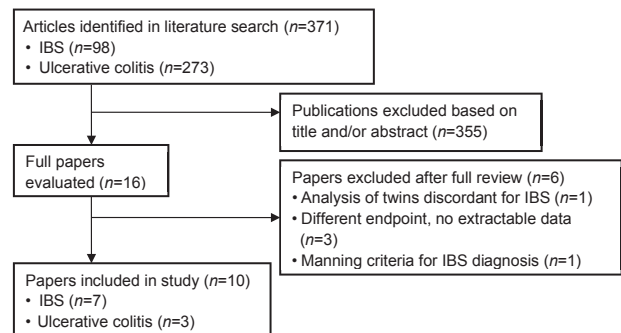

Figure 1 Flowchart of literature search
IBS, irritable bowel syndrome

Table 1 Eligibility criteria

Inclusion criteria
Case-control trial or randomized-controlled trial written in English language
Case/intervention population either has ulcerative colitis or irritable bowel syndrome (evaluated using Rome criteria)
Control/placebo population is described as healthy
The presence and/or severity of co-morbid depression or anxiety is evaluated in case-control studies using a validated scoring system based on patient questionnaire
The presence and/or severity of co-morbid depression or anxiety is evaluated at baseline in randomized-controlled trials using a validated scoring system based on patient questionnaire
Co-morbid depression or anxiety are not included in study eligibility criteria
Exclusion criteria
Twins are purposely enrolled to control/placebo and case/intervention cohorts
Control/placebo patients have ulcerative colitis or irritable bowel syndrome

are well described [23-27]. The percentage of females in either case or control cohorts ranged from 42% to 81%. The full characteristics of eligible studies were variable (Table 2).

Prevalence of anxiety and depression in IBS and UC

Two studies of IBS reported the prevalence of depression and anxiety based on HADS [28] or the Beck Anxiety and Depression Inventories (BAI/BDI)[29]. In Hartono *et al*, the excess prevalence of depression and anxiety was 38.7% and 6.5%, respectively, in IBS patients relative to healthy patients (of which 6.5% and 14.5% reported scores consistent with depression and anxiety), based on diagnostic criteria of a HADS rating greater than eight [28]. In Uz *et al*, the excess prevalence of depression or anxiety relative to healthy controls was 34% and 2%, with 4% and 8% of the healthy population reporting scores consistent with depression and anxiety [29]. Pooled data are reported in Fig. 2 and Table 3.

One study of UC evaluated the prevalence of depression and anxiety relative to healthy controls [30]. The excess prevalence of anxiety in UC patients relative to healthy controls was 41.7%
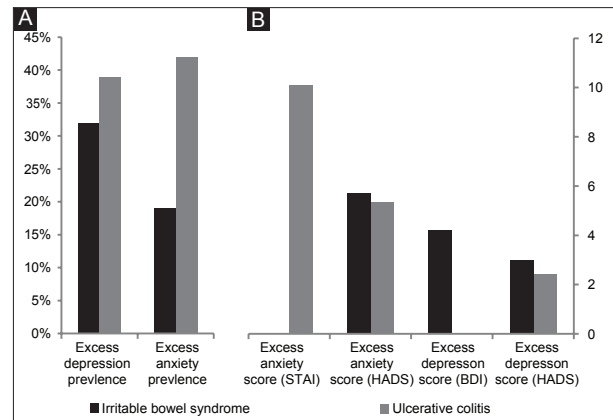

Figure 2 Portion of psychological condition attributable to gastrointestinal disease (in excess of control group). (A) Prevalence of concomitant psychological illness (in excess of healthy control) for irritable bowel syndrome (IBS) and ulcerative colitis (UC). (B) Scores for depression and anxiety are reported for both IBS and UC (in excess of scores for healthy controls). There were no studies reporting average STAI scores for IBS and no studies reporting average BDI scores for UC

HADS, hospital anxiety depression scale; STAI, state-trait anxiety index; BDI, beck depression inventory

Table 2 Summary of studies

Study	Case Illness	% female (case/ control)	Enrollment method	Anxiety criteria	Depression criteria	Case group eligibility	IBS subtypes and UC severity	Control group eligibility
Hartono, *et al* [28]	IBS	55/60	Consecutively enrolled (IBS), family of patient (control)	HADS	HADS	Rome III & normal endoscopy	unknown	No GI symptoms
Jerndal, *et al* [31]	IBS	71/77	Referral (IBS), advertisements and previous research studies (control)	HADS	HADS	Rome II	39% D-IBS 22% C-IBS 39% A-IBS	No GI symptoms
Lee, *et al* [32]	IBS	60/42	Consecutively enrolled	HADS	HADS	Rome III	48% D-IBS 31% C-IBS 21% A-IBS	No GI symptoms
Park, *et al* [36]	IBS	44/33	Consecutively enrolled	STAI	BDI	Rome II	100% D-IBS	No GI symptoms
Piche, *et al* [33]	IBS	70/65	Previous research studies	HADS	BDI	Rome III	25% D-IBS 25% C-IBS 50% A-IBS	No GI symptoms
Portincasa, *et al* [37]	IBS	73/70	Unknown	MHQ	MHQ	Rome II	unknown	No GI symptoms
Uz, *et al* [29]	IBS	81/84	Unknown	BAI	BDI	Rome II	19% D-IBS 53% C-IBS 28% A-IBS	No GI symptoms
Addolorato, *et al* [30]	UC	47/44	Consecutively enrolled (IBS), volunteers (control)	STAI	ZDS	Previous diagnosis	No steroid-dependent patients	No organic disease
Goodhand, *et al* [34]	UC	59/43	Advertisements	HADS	HADS	SCCAI>2 and Baron index>1	38% active disease	No organic disease
Tocchi, *et al* [35]	UC	50/50	Consecutively enrolled (UC), mild chronic illness (control)	STAI	-	Endoscopic confirmation	Not reported	Mild chronic disease

IBS, irritable bowel syndrome; UC, ulcerative colitis; HADS, hospital anxiety depression scale; STAI, state-trait anxiety index; BDI/BAI, beck depression/anxiety inventory; MHQ, middlesex hospital questionnaire; ZDS, zung depression scale; SCCAI, simple clinical colitis activity index

Table 3 Pooled results of case-control studies evaluating psychological illness in irritable bowel syndrome or ulcerative colitis

	Irritable bowel syndrome			Ulcerative colitis		
	Pooled study population	Case	Healthy control	Pooled study population	Case	Healthy control
Depression prevalence	249 patients in two studies	38%	6%	72 patients in one study	50%	11%
Anxiety prevalence	249 patients in two studies	32%	13%	72 patients in one study	64%	22%
Average depression score (HADS)	420 patients in two studies	5.4	2.4	227 patients in one study	4.1	1.7
Average depression score (BDI)	60 patients in one study	5.9	1.7	-	-	-
Average anxiety score (HADS)	480 patients in three studies	8.1	2.4	227 in one study	8.5	3.2
Average anxiety score (STAI)	-	-	-	244 in one study	51.9	41.8

HADS, hospital anxiety depression scale; STAI, state-trait anxiety index; BDI, beck depression inventory

(with a 22.2% baseline prevalence in healthy patients) based on a State-Trait Anxiety Inventory (STAI) score greater than 40. Excess depression of 38.9%, with a baseline prevalence of 11.1% in the healthy population, was evaluated with a Zung Depression Scale (ZDS) score greater than 49.

Severity of anxiety and depressive symptoms in IBS and UC

Three studies reported severity of symptoms supportive of anxiety based on an average HADS rating [31-33]. The pooled average anxiety-specific HADS rating derived from these studies was 8.1 among IBS patients and 3.8 among healthy controls. In comparison, the average anxiety-specific HADS rating in one UC study was 8.5 in UC patients and 3.2 in healthy controls [34]. In addition, anxiety ratings based on STAI were higher among UC patients (51.9) than healthy controls (41.8)[35].

Average ratings of depressive symptoms were reported in three IBS trials [31-33]. The pooled average depression-specific HADS rating was 5.4 among IBS patients and 2.4 among healthy controls in two studies [31,32]. Another study reported an average short-form BDI rating of 5.9 in IBS patients and 1.7 in healthy controls [33]. Two additional studies reported significant higher anxiety and depression ratings in IBS patients than controls though mean scores were not reported [36,37]. One UC study reported an average

HADS rating of 4.1 among UC patients and 1.7 among healthy controls [34].

For all utilized depression and anxiety rating scales, higher ratings reflected more prominent and prevalent symptoms suggestive of depression or anxiety. Data are reported in Fig. 2 and Table 3.

Discussion

In this paper, published studies demonstrate that the prevalence of anxiety and depression is higher in both UC and IBS patients as compared to healthy controls. In addition, there is an increase in the severity of anxiety- and depression-related symptoms among UC and IBS patients relative to healthy controls.

The traditional brain-gut axis hypothesis suggests that disordered autonomic and neural gut regulation as well as dysregulated visceral feedback lead to IBS [38,39]. Visceral hyperalgesia is a common finding in IBS subjects [40], and brain imaging [41] suggests altered responses in IBS compared to controls. However, these studies do not explain the exact cause of visceral hypersensitivity or show a causal association of IBS with stress, anxiety, or psychological trauma. It is therefore still unclear if central processing or peripheral signaling to the brain is dysfunctional. Alternatively, conditioning (or hypervigilance) to illness-related symptoms could alter the pathways of pain as a matter of coping [42].

The greatest pitfall in the study of the relationship between IBS and psychological disorders is in the selection of control subjects. Healthy controls are "healthy". By definition, they should have a near-zero illness score for somatic or psychological illness. With this comparison, any disease (from congestive heart failure to eczema) would have some degree of personal anxiety due to physical limitations or appearance. By design, IBS is therefore associated with anxiety and depression. One argument could be that psychological disorders are associated with all illness and are therefore always important. However, one must ask whether the focus is to treat the underlying disease which thus alleviates anxiety and depression, or to treat the depression and anxiety while the medical illness remains [14]. Another argument is that the presence of a psychological disorder might adversely affect subjective patient-reported outcomes as is controversially reported in other disease literature [43]. A number of successful therapies have been derived from this hypothesis. Previous meta-analyses support antidepressants and cognitive behavioral therapy in treating IBS based on subjective endpoints [44]. Cognitive behavioral therapy is based on learning effective strategies of coping with dysfunctional thoughts derived from physical symptoms [45]. The result is an improvement in the same patient-reported outcomes measured in pharmacologic studies without the need for a physical improvement in the objective disease. Similarly, in UC, the recent INSPIRE study found that stress management might improve quality of life though it did not alter the objectively-defined disease course [46].

In this study, we found associations with psychological disorders in both IBS and UC case-control literature. As this

finding was not limited to IBS literature alone, it would be reasonable to consider our results in the context of the severe disability and impaired quality-of-life associated with both illnesses [47,48] as is seen in other chronic illnesses such as HIV, cancer, and ischemic heart disease [49]. This is in contrast to prior conclusions that these associative data might support a psychological mechanism of IBS development [8], as it is clear that case-control studies cannot prove causality on their own. Despite this, the role of psychological health in GI disease is not entirely clear. In one prospective study of 17 patients with active UC, hypnotic therapy was associated with reductions in systemic and mucosal inflammatory response two hours after the therapeutic session ended [50].

Beyond associative studies, the psychosomatic theory in IBS is supported by retrospective cohort studies which revealed preceding psychological illness in clinical interviews of IBS patients [51]. However, a matched case-control study did not reveal a consistent association between war-related stress (such as shooting a gun or killing a person) and development of functional GI disorders among deployed active-duty soldiers except for an association between "any war stressor" and IBS [52]. In that study, only diarrhea and vomiting during the deployment period were significantly associated with functional GI disorder development which may suggest a significant role of post-infectious IBS.

Despite the lack of prospective studies to evaluate a direct causal link between life trauma or psychological illness and subsequent IBS, there are emerging data to support interactions between IBS and altered microbiota as well as between behavior and the microbiome. Thus, alterations in gut microbiota may be a confounding factor in the direct evaluation of psychological co-morbidities and functional GI disease, as supported by a study which found differences in the incidence of psychological illness among post-infectious IBS versus non-post-infectious IBS patients [53]. The relationship between psychological derangements (especially through the hypothalamic-pituitary-adrenal axis) and altered gut microbiota have been evaluated in animal studies in which a surgically-induced state intended to mimic depression was associated with elevated corticotropin-releasing hormone leading to subsequently elevated serotonin levels and hyperactive colonic motility [54]. Moreover, stress (and the subsequently increased levels of hormonal mediators) may mediate leaky intestinal epithelia and reduced mucosal protection which may be a mechanism by which patients who experience acute gastroenteritis develop subsequent post-infectious IBS [55].

The opposite effect of an altered microbiome on behavior has been described as well, in which germ-free mice had higher corticosterone levels and a higher stress response which improved with colonization with *Bifidobacterium infantis* [56]. In a more recent study, specific pathogen-free mice were colonized with microbiota and found to have increased exploratory behavior after administration of oral antibiotics [57]. While our understanding of this network of factors is only emerging, the complexity of the relationship between IBS and psychological illness is certainly apparent.

Limitations of this study include the small number of

eligible studies as well as the variety of methods to evaluate the prevalence and severity of anxiety and depression, which together preclude meaningful statistical analysis. Therefore, this study is intended to merely suggest an association between these GI illnesses and both depression and anxiety. More controlled studies appear warranted. Though the included psychological measures have been validated in evaluating anxiety- and depression-related symptoms, they may not have a primary role in diagnosing mood disorders [58]. Similar to ongoing discrepancies in the diagnosis of IBS by the various clinical criteria [59,60], it also remains uncertain whether results from the multiple psychological rating scales are comparable.

Regardless of the cause of these conditions, the impact of these diseases on quality of life should be considered in a multi-disciplinary approach to therapy. In one prospective IBD cohort, psychological health was found to impact health-related quality of life significantly and independently of disease severity [61]. The use of existing tools such as the IBD Questionnaire [46]and IBS Quality of Life [62] scale should be explored in identifying patients who might benefit from support mechanisms to improve the mental health and quality of life of patients suffering from these chronic illnesses.

In this study, we found that both IBS and UC appear to be associated with increased prevalence and severity of psychological disorders. The pathophysiology of UC appears to be related to immune dysfunction, while the etiology of IBS remains unknown. Therefore, it would be reasonable to continue the pursuit of existing organic mechanistic theories of disease while employing a multi-disciplinary approach to therapy for both conditions.

Summary Box

What is already known:

- A psychosomatic theory has been postulated in irritable bowel syndrome in the absence of other objective etiology and biomarkers
- Many chronic conditions are associated with psychological disorders
- Ulcerative colitis was associated with psychosomatic theory until the discovery of immune dysregulation

What the new findings are:

- Both irritable bowel syndrome and ulcerative colitis are associated with psychological disorders versus healthy controls
- The association between irritable bowel syndrome and psychological factors might be attributed to the psychological suffering from chronic and debilitating disease

References

1. Engel GL. Studies of ulcerative colitis. II. The nature of the somatic processes and the adequacy of psychosomatic hypotheses. *Am J Med* 1954;**16**:416-433.

2. McKegney FP, Gordon RO, Levine SM. A psychosomatic comparison of patients with ulcerative colitis and Crohn's disease. *Psychosom Med* 1970;**32**:153-166.

3. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974;**4**:627-630.

4. North CS, Clouse RE, Spitznagel EL, Alpers DH. The relation of ulcerative colitis to psychiatric factors: a review of findings and methods. *Am J Psychiatry* 1990;**147**:974-981.

5. Wood JD, Peck OC, Tefend KS, et al. Evidence that colitis is initiated by environmental stress and sustained by fecal factors in the cotton-top tamarin (Saguinus oedipus). *Dig Dis Sci* 2000;**45**:385-393.

6. White DL, Savas LS, Daci K, et al. Trauma history and risk of the irritable bowel syndrome in women veterans. *Aliment Pharmacol Ther* 2010;**32**:551-561.

7. Maguen S, Madden E, Cohen B, et al. Association of mental health problems with gastrointestinal disorders in Iraq and Afghanistan veterans. *Depress Anxiety* 2014;**31**:160-165.

8. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002;**122**:1140-1156.

9. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome -a meta-analysis. *Am J Gastroenterol* 2006;**101**:1894-1899; quiz 1942.

10. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007;**26**:535-544.

11. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2012;**107**:1474-1482.

12. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br J Psychiatry* 2013;**202**:14-21.

13. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;**24**:1069-1078.

14. Nair N, Farmer C, Gongora E, Dehmer GJ. Commonality between depression and heart failure. *Am J Cardiol* 2012;**109**:768-772.

15. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J* 2014;**35**:1365-1372.

16. Corotto PS, McCarey MM, Adams S, et al. Heart failure patient adherence: epidemiology, cause, and treatment. *Heart Fail Clin* 2013;**9**:49-58.

17. Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med* 2012;**157**:785-795.

18. Kop WJ, Synowski SJ, Gottlieb SS. Depression in heart failure: biobehavioral mechanisms. *Heart Fail Clin* 2011;**7**:23-38.

19. Chai-Coetzer CL, Luo YM, Antic NA, et al. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep* 2013;**36**:1929-1937.

20. Yeager KR, Binkley PF, Saveanu RV, et al. Screening and identification of depression among patients with coronary heart disease and congestive heart failure. *Heart Fail Clin* 2011;**7**:69-74.

21. Rumsfeld JS, Havranek E, Masoudi FA, et al. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol* 2003;**42**:1811-1817.

22. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care* 2000;**23**:1556-1562.

23. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;**52**:69-77.

24. Crisp AH, Jones MG, Slater P. The Middlesex Hospital questionnaire: a validity study. *Br J Med Psychol* 1978;**51**:269-280.

25. Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the state--trait anxiety inventory and the Zung Self-Rating depression scale. *Br J Clin Psychol* 1983;**22**(Pt 4):245-249.

26. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Rev Bras Psiquiatr* 2013;**35**:416-431.

27. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;**56**:893-897.

28. Hartono JL, Mahadeva S, Goh KL. Anxiety and depression in various functional gastrointestinal disorders: do differences exist? *J Dig Dis* 2012;**13**:252-257.

29. Uz E, Türkay C, Aytac S, Bavbek N. Risk factors for irritable bowel syndrome in Turkish population: role of food allergy. *J Clin Gastroenterol* 2007;**41**:380-383.

30. Addolorato G, Capristo E, Stefanini GF, Gasbarrini G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand J Gastroenterol* 1997;**32**:1013-1021.

31. Jerndal P, Ringström G, Agerforz P, et al. Gastrointestinal-specific anxiety: an important factor for severity of GI symptoms and quality of life in IBS. *Neurogastroenterol Motil* 2010;**22**:646-e179.

32. Lee KJ, Kim YB, Kim JH, et al. The alteration of enterochromaffin cell, mast cell, and lamina propria T lymphocyte numbers in irritable bowel syndrome and its relationship with psychological factors. *J Gastroenterol Hepatol* 2008;**23**:1689-1694.

33. Piche T, Ducrotté P, Sabate JM, et al. Impact of functional bowel symptoms on quality of life and fatigue in quiescent Crohn disease and irritable bowel syndrome. *Neurogastroenterol Motil* 2010;**22**:626-e174.

34. Goodhand JR, Wahed M, Mawdsley JE, et al. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. *Inflamm Bowel Dis* 2012;**18**:2301-2309.

35. Tocchi A, Lepre L, Liotta G, et al. Familial and psychological risk factors of ulcerative colitis. *Ital J Gastroenterol Hepatol* 1997;**29**:395-398.

36. Park JH, Rhee PL, Kim HS, et al. Mucosal mast cell counts correlate with visceral hypersensitivity in patients with diarrhea predominant irritable bowel syndrome. *J Gastroenterol Hepatol* 2006;**21**:71-78.

37. Portincasa P, Moschetta A, Baldassarre G, et al. Pan-enteric dysmotility, impaired quality of life and alexithymia in a large group of patients meeting ROME II criteria for irritable bowel syndrome. *World J Gastroenterol* 2003;**9**:2293-2299.

38. Jones MP, Dilley JB, Drossman D, Crowell MD. Brain-gut connections in functional GI disorders: anatomic and physiologic relationships. *Neurogastroenterol Motil* 2006;**18**:91-103.

39. Delvaux M. Role of visceral sensitivity in the pathophysiology of irritable bowel syndrome. *Gut* 2002;**51**(Suppl 1):i67-i71.

40. Larauche M, Mulak A, Taché Y. Stress and visceral pain: from animal models to clinical therapies. *Exp Neurol* 2012;**233**:49-67.

41. Price DD, Craggs JG, Zhou Q, et al. Widespread hyperalgesia in irritable bowel syndrome is dynamically maintained by tonic

visceral impulse input and placebo/nocebo factors: evidence from human psychophysics, animal models, and neuroimaging. *Neuroimage* 2009;**47**:995-1001.

42. Lembo T, Naliboff B, Munakata J, et al. Symptoms and visceral perception in patients with pain-predominant irritable bowel syndrome. *Am J Gastroenterol* 1999;**94**:1320-1326.

43. Macleod J, Davey Smith G, Heslop P, et al. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. *BMJ* 2002;**324**:1247-1251.

44. Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut* 2009;**58**:367-378.

45. Chilcot J, Moss-Morris R. Changes in illness-related cognitions rather than distress mediate improvements in irritable bowel syndrome (IBS) symptoms and disability following a brief cognitive behavioural therapy intervention. *Behav Res Ther* 2013;**51**:690-695.

46. Boye B, Lundin KE, Jantschek G, et al. INSPIRE study: does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflamm Bowel Dis* 2011;**17**:1863-1873.

47. Graham DP, Savas L, White D, et al. Irritable bowel syndrome symptoms and health related quality of life in female veterans. *Aliment Pharmacol Ther* 2010;**31**:261-273.

48. Zhang CK, Hewett J, Hemming J, et al. The influence of depression on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:1732-1739.

49. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA* 2007;**298**:1685-1687.

50. Mawdsley JE, Jenkins DG, Macey MG, et al. The effect of hypnosis on systemic and rectal mucosal measures of inflammation in ulcerative colitis. *Am J Gastroenterol* 2008;**103**:1460-1469.

51. Sykes MA, Blanchard EB, Lackner J, et al. Psychopathology in irritable bowel syndrome: support for a psychophysiological model. *J Behav Med* 2003;**26**:361-372.

52. Porter CK, Gloor K, Cash BD, Riddle MS. Risk of functional gastrointestinal disorders in U.S. military following self-reported diarrhea and vomiting during deployment. *Dig Dis Sci* 2011;**56**:3262-3269.

53. Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. *Am J Gastroenterol* 2003;**98**:1578-1583.

54. Park AJ, Collins J, Blennerhassett PA, et al. Altered colonic function and microbiota profile in a mouse model of chronic depression. *Neurogastroenterol Motil* 2013;**25**:733-e575.

55. Vanuytsel T, van Wanrooy S, Vanheel H, et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut* 2013. Epub ahead of print. doi:10.1136/gutjnl-2013-305690.

56. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol* 2004;**558**:263-275.

57. Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology* 2011;**141**:599-609.

58. Julian LJ. Measures of anxiety: state-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res* (Hoboken) 2011;**63**(Suppl 11):S467-S472.

59. Ford AC, Bercik P, Morgan DG, et al. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gastroenterology* 2013;**145**:1262-1270.

60. Ghoshal UC, Abraham P, Bhatia SJ, et al. Comparison of Manning, Rome I, II, and III, and Asian diagnostic criteria: report of the Multicentric Indian Irritable Bowel Syndrome (MIIBS) study. *Indian J Gastroenterol* 2013;**32**:369-375.

61. Guthrie E, Jackson J, Shaffer J, et al. Psychological disorder and severity of inflammatory bowel disease predict health-related quality of life in ulcerative colitis and Crohn's disease. *Am J Gastroenterol* 2002;**97**:1994-1999.

62. Andrae DA, Patrick DL, Drossman DA, Covington PS. Evaluation of the Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire in diarrheal-predominant irritable bowel syndrome patients. *Health Qual Life Outcomes* 2013;**11**:208.