CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/uploads/11080069

https://www.iajps.com/volumes/volume11-april-2024/17-issue-04-april-24/

Available online at: http://www.iajps.com *Review Article*

UPDATES ON THE LINK BETWEEN IRRITABLE BOWEL SYNDROME AND ANXIETY DISORDERS: A SYSTEMATIC REVIEW

Narjes slaman ahmad alkhater [1], Khalil Ibrahim Bograin [2], Fatimah adel alsaad [3], Nura Khalid Alhaider [4], Hawraa Maki Mohammed Alsadiq [5], Bushra Essa Alabbas [6], Fatimah Abdulmonem Bukhamsin [7], Noor Ali Majeed Alqrunawi [8], Anwar Fawzi Alqadeep [9]

[1]Family medicine consultant, Project manger of team based care Qatif sector, Saudi Arabia.
Email: Nalkhater@moh.gov.sa

[2]Family medicine specialist, Alahas PHC center, Saudi Arabia.
Email: dr-khalil2012@hotmail.com

[3]Medical student at king faisal university, Saudi Arabia. Email: Fatimah4alsaad@gmail.com

[4]Medical student at King Faisal university, Saudi Arabia. Email: Xds.sa13@gmail.com

[5]Medical student at Imam Abdulrahman Bin Faisal University, Saudi Arabia.
Email: hawraa1801@gmail.com

[6]Medical student at Imam Abdulrahman Bin Faisal University, Saudi Arabia.
Email: Alabbasbushra@gmail.com

[7]Medical student at Imam Abdulrahman Bin Faisal University, Saudi Arabia.
Email: fatimahbu5050@gmail.com

[8]Medical student at Imam Abdulrahman Bin Faisal University, Saudi Arabia.
Email: Nono.962.g@gmail.com

[9]Medical student at king Faisal University, Saudi Arabia. Email: anwargh463@gmail.com

Article Received: April 2024 **Accepted:** April 2024 **Published:** April 2024

Abstract:

Objectives: *This review aims to systematically review the existing literature to elucidate the relationship between irritable bowel syndrome (IBS) and anxiety disorders, identify gaps in current knowledge, and propose directions for future research.* ***Methods:*** *A comprehensive search of relevant databases was conducted to identify studies that met the inclusion criteria. PubMed, MEDLINE, and Embase were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process.* ***Results:*** *Our results included nine studies with a total of 1,258,591 patients diagnosed with IBS and 407,147 (32.4%) were females. The prevalence of anxiety disorder among IBS patients ranged from 14 (28%) to 88 (83.8%) with a total prevalence of 479,959 (38.1%). All of the included studies stated that IBS patients exhibited a higher rate of anxiety. It is also reported that anxiety worsens the IBS symptoms.* ***Conclusion:*** *This systematic review reported that the prevalence of anxiety disorders is high in IBS patients. It is advised that gastroenterologists and other medical professionals who treat IBS patients observe and evaluate if the patients also have anxiety or depression at the same time and that they take the patient's psychiatric illness into expert care. It is also advised that doctors who treat patients for depression and anxiety should also evaluate them for IBS. Treatment for the co-occurring gastrointestinal condition may expedite the resolution of the co-occurring psychiatric disorders.*

Keywords: Irritable Bowel Syndrome; Anxiety Disorders; Comorbidity; Biopsychosocial; Systematic review.

Corresponding author:
Narjes slaman ahmad alkhater,
Family medicine consultant,
Project manger of team based care Qatif sector,
Saudi Arabia. Email: Nalkhater@moh.gov.sa

Please cite this article in press Narjes slaman ahmad alkhater et al., ***Updates On The Link Between Irritable Bowel Syndrome And Anxiety Disorders: A Systematic Review****., Indo Am. J. P. Sci, 2024; 11 (04).*

BACKGROUND:

IBS and anxiety disorders are two common medical conditions that often coexist in individuals. The link between these two conditions has been the subject of much research and debate in the medical community. While the exact relationship between IBS and anxiety disorders is not fully understood, there is growing evidence to suggest that there is a significant connection between the two [1].

IBS is a chronic gastrointestinal disorder that affects the large intestine. It is characterized by symptoms such as abdominal pain, bloating, gas, diarrhea, and constipation. IBS is a functional disorder, meaning that there is no identifiable structural or biochemical cause for the symptoms. Instead, the symptoms are believed to be the result of abnormal functioning of the intestines [2].

Anxiety disorders, on the other hand, are a group of mental health conditions that are characterized by excessive worry, fear, and anxiety. Common anxiety disorders include generalized anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder. Anxiety disorders can have a significant impact on a person's quality of life and can lead to a range of physical and psychological symptoms [3].

Research has shown that there is a strong association between IBS and anxiety disorders. Studies have found that individuals with IBS are more likely to have anxiety disorders than the general population, and vice versa. In fact, some studies have suggested that up to 60% of individuals with IBS also have a coexisting anxiety disorder [4].

There are several theories as to why there is a link between IBS and anxiety disorders. One theory is that the symptoms of IBS, such as abdominal pain and bloating, can trigger anxiety in individuals. The chronic nature of IBS can also lead to increased stress and anxiety, which can exacerbate the symptoms of the condition. Additionally, there is evidence to suggest that there may be a shared underlying biological mechanism that contributes to both IBS and anxiety disorders [2, 5].

The relationship between IBS and anxiety disorders is complex and multidirectional. While anxiety can exacerbate the symptoms of IBS, the symptoms of IBS can also trigger anxiety in individuals. This can create a vicious cycle where anxiety and IBS symptoms feed off each other, leading to a worsening of both conditions [1, 6].

Treatment for individuals with both IBS and anxiety disorders often involves a multidisciplinary approach. This may include a combination of medication, psychotherapy, dietary changes, and stress management techniques. Cognitive-behavioral therapy (CBT) has been shown to be particularly effective in treating both IBS and anxiety disorders. CBT helps individuals to identify and challenge negative thought patterns and develop coping strategies to manage their symptoms [7, 8].

Existing literature suggests a bidirectional relationship between IBS and Anxiety Disorders, with shared risk factors and potential mechanisms contributing to their co-occurrence. However, gaps in knowledge persist regarding the specific factors influencing the link between IBS and Anxiety Disorders, the impact of comorbidity on clinical outcomes, and the implications for treatment strategies. Addressing these gaps through a systematic review is essential to inform evidence-based approaches for the management of individuals with coexisting IBS and Anxiety Disorders.

The significance of this study lies in its potential to enhance our understanding of the complex interplay between gastrointestinal and psychological health, inform the development of more effective treatment strategies for individuals with co-occurring IBS and Anxiety Disorders, and contribute to the growing body of literature on the biopsychosocial model of health and illness.

The aim of this study is to systematically review the existing literature to elucidate the relationship between

IBS and anxiety disorders, identify gaps in current knowledge, and propose directions for future research.

Study Objectives:

1. To conduct a comprehensive literature review to synthesize existing evidence on the association between IBS and Anxiety Disorders.
2. To evaluate the methodological quality of studies investigating the link between IBS and Anxiety Disorders.
3. To identify common risk factors and potential mechanisms underlying the comorbidity between IBS and Anxiety Disorders.
4. To explore the impact of co-occurring anxiety disorders on the clinical presentation and management of IBS.
5. To propose recommendations for future research directions and clinical practice based on the findings of the systematic review.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. A thorough search of electronic databases such as PubMed, MEDLINE, and Embase was undertaken to identify pertinent studies published in English. The search strategy was to incorporate keywords pertaining to IBS association with anxiety disorder. Two reviewers independently screened the search outcomes, chose relevant studies, extracted data, and evaluated the quality of selected studies using suitable assessment tools.

Eligibility Criteria:

Inclusion Criteria:

1. Studies investigating the relationship between IBS and Anxiety Disorders.
2. Studies that include participants diagnosed with IBS and Anxiety Disorders.
3. Studies that report quantitative or qualitative data on the association between IBS and Anxiety Disorders.
4. Recent studies conducted between (2019-2024).
5. Studies available in the English language.
6. Studies conducted on human participants.

Exclusion Criteria:

1. Studies that do not focus on the relationship between IBS and Anxiety Disorders.
2. Studies that do not report relevant data on the association between IBS and Anxiety Disorders.
3. Studies including patients with IBS and associated comorbidities such as COVID-19 or other autoimmune diseases.
4. Studies with insufficient methodological rigor or quality.
5. Studies not available in the English language.

Data Extraction

The search results were validated using Rayyan (QCRI) [10] to confirm precision. Inclusion and exclusion criteria were employed to evaluate the pertinence of titles and abstracts within the search results. Papers that align with the inclusion criteria will be subjected to thorough examination by reviewers. Any discrepancies were resolved through deliberation. A predefined data extraction template was employed to record pertinent study information, including titles, authors, study year, location, participants, gender, population type, prevalence of anxiety among IBS patients, IBS diagnostic tool, anxiety diagnostic tool, and primary outcomes. A distinct document was generated for assessing the risk of bias.

Data Synthesis Strategy

Summary tables were generated based on information extracted from relevant studies to provide a qualitative evaluation of the research findings and components. Once data for the systematic review is collected, the most effective approach for utilizing the information from the included studies was determined.

Risk of Bias Assessment

The Joanna Briggs Institute (JBI) [11] critical assessment criteria for studies reporting prevalence data were employed to evaluate research quality. This tool comprises nine questions, with a score of 1 assigned to affirmative responses and 0 to negative, ambiguous, or not applicable responses. Overall quality ratings of < 4, 5 to 7, and ≥ 8 were considered as low, moderate, and excellent quality, respectively. Researchers independently assessed study quality, with any discrepancies resolved through discussion.

RESULTS:

Search results

The systematic search yielded 1016 study articles in total, of which 502 duplicates were eliminated. 448 studies were eliminated after 514 studies had their titles and abstracts screened. Of the 66 reports that were requested to be retrieved, only 3 items were

found. After screening 63 papers for full-text assessment, 36 were rejected due to incorrect study results, 16 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review had nine study papers that met the eligibility criteria. **Figure 1** presents an overview of the process used to select the studies.

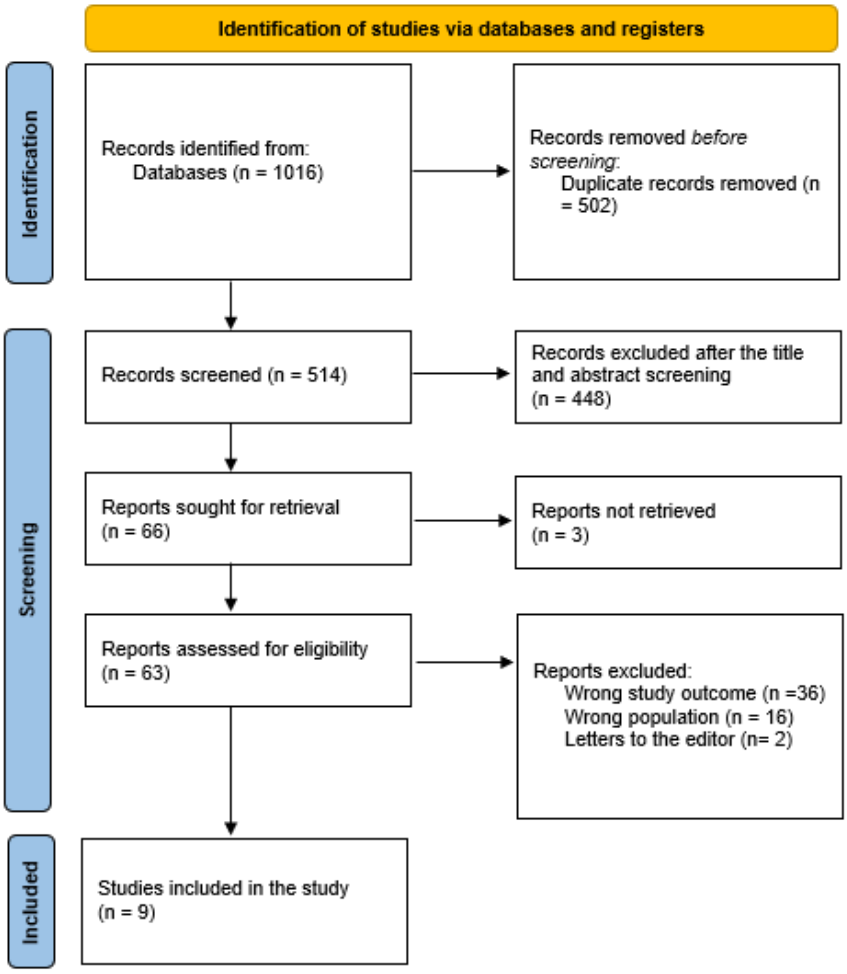

Figure (1): Study decision is summed up in a PRISMA diagram.

Characteristics of the included studies

The sociodemographic details of the research articles that are included are shown in **Table 1.** Our results included nine studies with a total of 1,258,591 patients diagnosed with IBS and 407,147 (32.4%) were females. Six studies were cross-sectional [13, 14, 16, 17, 19, 20], two were retrospective in nature [12, 15], and one was a case-control study [18]. Two studies were conducted in Iraq [13, 18], two in Egypt [14, 19], two in Pakistan [17, 20], one in the USA [12], one in Sweden [15], and one in the UK [16].

Clinical outcomes

The clinical features are displayed in **Table (2)**. There was variability in the diagnostic tools used for IBS including The International Classification of Diseases (ICD) [12], Rome III [13, 15, 17, 19], Rome IV [14, 16], Rome II [18], and self-administrated questionnaire [20]. The included studies did not use the same tool for anxiety diagnosis. They used ICD [12], self-administrated questionnaire [13], Beck Anxiety Inventory (BAI) [14], Hospital Anxiety and Depression Scale (HADS) [15, 16, 17], ICD-10 [18], and the Generalized Anxiety Disorder 7-item (GAD-7) [20].

The prevalence of anxiety disorder among IBS patients ranged from 14 (28%) [19] to 88 (83.8%) [13] and with a total prevalence of 479,959 (38.1%). All of the included studies stated that IBS patients exhibited a higher rate of anxiety [12-20]. It is also reported that anxiety worsens the IBS symptoms [14].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age	Females (%)
Tarar et al., 2023 [12]	Retrospective cohort	USA	1,256,325	58.8	406,355 (84.92%)
Abd AL-Khaliq et al., 2023 [13]	Cross-sectional	Iraq	105	18-23	83 (79%)
Abdelaziz et al., 2023 [14]	Cross-sectional	Egypt	145	40.26 ± 8.8	145 (100%)
Midenfjord et al., 2019 [15]	Retrospective cohort	Sweden	769	36	558 (73%)
Black et al., 2020 [16]	Cross-sectional	UK	811	47.4 ± 15.2	697 (85.9%)
Shafique et al., 2021 [17]	Cross-sectional	Pakistan	152	18-25	112 (73.7)
Ali et al., 2019 [18]	Case-control	Iraq	150	40.9 ± 11.1	98 (65.3%)
El Sharawy et al., 2022 [19]	Cross-sectional	Egypt	50	22.6 ± 1.4	34 (68%)
Hisam et al., 2022 [20]	Cross-sectional	Pakistan	84	18-30	65 (77.4%)

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Population type	IBS diagnostic tool	Anxiety diagnostic tool	Prevalence of anxiety	Main outcomes	JBI
Tarar et al., 2023 [12]	General population	ICD	ICD	478,515 (38.1%)	IBS patients exhibited a higher rate of anxiety, depression, and suicidal ideation than the general population. IBS subtypes are independently related to an elevated risk of mental illnesses.	Moderate
Abd AL-Khaliq et al., 2023 [13]	University students	Rome III	Self-administered questionnaire	88 (83.8%)	IBS patients appeared to have a substantial association with psychological aspects (anxiety and stress), with more than 60% of students in this study experiencing mild to moderate or severe anxiety, food hypersensitivity, and persistent difficulties.	Moderate
Abdelaziz et al., 2023 [14]	Female population	Rome IV	BAI	127 (87.6%)	Anxiety worsens the IBS symptoms. Female IBS sufferers are experiencing increased anxiety as a result of the COVID-19 epidemic.	Low
Midenfjord et al., 2019 [15]	General population	Rome III	HADS	345 (45%)	Anxiety and depression symptoms, often known as psychological distress, are linked to IBS's complicated pathophysiology and clinical presentation.	Moderate
Black et al., 2020 [16]	General population	Rome IV	HADS	609 (75.1%)	The findings call into question the key role of gastrointestinal symptom-specific anxiety in determining symptom intensity in IBS.	High
Shafique et al., 2021 [17]	Medical students	Rome III	HADS	100 (65.8%)	Medical students are more likely to have IBS, which is exacerbated by stress-related anxiety due to the vast curriculum and pressure from peers to perform well on exams among the intellectual portion of society, which is difficult to cope with.	Moderate
Ali et al., 2019 [18]	General population	Rome II	ICD-10	91 (60.7%)	IBS patients appeared to have a substantial connection with anxiety and depression, which may have had a causal role in the development of IBS.	Moderate
El Sharawy et al., 2022 [19]	Medical students	Rome III	NM	14 (28%)	Anxiety, depression, coffee consumption, a lack of fruits and vegetables, and chronic medication use were all identified as risk factors for IBS.	Moderate
Hisam et al., 2022 [20]	Medical students	Self-administered questionnaire	GAD-7	70 (83.3%)	There was a substantial correlation between IBS and gender, as well as IBS and anxiety levels.	Moderate

*NM=Not-mentioned

DISCUSSION:

After conducting a thorough search of several databases, we identified 9 studies with an overall sample size of 1,258,591 IBS patients for our review. The first substantial finding of our study is that IBS patients exhibited a higher rate of anxiety [12-20]. It is also reported that anxiety worsens the IBS symptoms [14]. This is similar to **Fond *et al.*** [21] This finding is not surprising given the scientific literature as a whole, but it does provide additional support for the biopsychological hypothesis of IBS and brain-gut system dysfunction. Dysfunctional brain-gut interactions have been observed in maternally separated rats, an extensively researched model of early-life stress in IBS, but not in humans. It is then expected that monitoring and treating IBS symptoms in people with anxiety and depression disorders will enhance their mental symptomatology. Therapies targeting the microbiome may thus represent a new area of research and development in anxiety and depressive disorders [22].

However, it is still unclear whether gastrointestinal disorders are caused by anxiety and depressive disorders, or whether microbiota dysbiosis causes these symptoms (through increased gut permeability, secretion of endotoxins and/or neuropeptides, mucosal and general inflammation, modifications to the absorption of nutrients, and modulation of the autonomic nervous system). The former occurs primarily through the autonomic nervous system, which has been well-described in depressive disorders, but also through the secretion of stress hormones and immune dysfunction that have been linked to these disorders [23, 24].

These findings might have significant therapeutic ramifications. Anxiety symptomatology is quite likely in IBS patients. It is important to systematically assess and manage these comorbidities. When it comes to moderating symptom severity, symptom persistence, treatment decisions, and treatment response, psychological aspects seem to be especially significant [25].

We also found that the prevalence of anxiety disorder among IBS patients ranged from 14 (28%) [19] to 88 (83.8%) [13] with a total prevalence of 479,959 (38.1%). This was higher than the prevalence reported by **Zamani *et al.*** 23% [26]. The prevalence of anxiety and depression can change depending on the cultural area, which can be caused by real variations in prevalence as well as measurement errors (caused by poor translation and questionnaire validation) [27]. Another possible cause of variability was differences in the cut-offs of heightened symptoms for the same instruments. Overall, it is not surprising that prevalence meta-analyses show such a significant level of variability [28].

According to the top-down hypothesis, some studies have indicated that psychological intervention may enhance the management of the evolution of gastrointestinal disorders as well as the patient's quality of life, even in cases where patients are in remission but still experience residual symptoms like fatigue [29, 30]. **Van Tilburg *et al.*** examined which psychological factors had the greatest influence on the severity of IBS symptoms and discovered that anxiety had an indirect effect on IBS symptoms through somatization and catastrophizing. Stressful life events and neuroticism were found to be predictive of anxiety [31]. Prospective cohort studies might also be beneficial in investigating the issues brought up, such as which way the found correlation is causally related [32, 33].

This study's primary strength is the vast array of reports it examines, as well as the sheer number of patients it examines. However, our study has some limitations and possible sources of bias due to the different diagnostic tools used for IBS and anxiety with different cut-offs and including variable populations such as medical students, university students, and the general population.

CONCLUSION:

This systematic review reported that the prevalence of anxiety disorder is high in IBS patients. It is advised that gastroenterologists and other medical professionals who treat IBS patients observe and evaluate if the patients also have anxiety or depression at the same time and that they take the patient's psychiatric illness into expert care. It is also advised that doctors who treat patients for depression and anxiety should also evaluate them for IBS. Treatment for the co-occurring gastrointestinal condition may expedite the resolution of the co-occurring psychiatric disorders.

REFERENCES:

1. Abdelaziz HA, Ellakany WI, Ellakany A, et al. The relationship between anxiety and irritable bowel syndrome symptoms among females: A cross-sectional study in Egypt. Medicine

(Baltimore). 2023;102(32):e34777. doi:10.1097/MD.0000000000034777
2. Banerjee A, Sarkhel S, Sarkar R, Dhali GK. Anxiety and Depression in Irritable Bowel Syndrome. Indian J Psychol Med. 2017;39(6):741-745. doi:10.4103/IJPSYM.IJPSYM_46_17
3. Hausteiner-Wiehle C, Henningsen P. Irritable bowel syndrome: relations with functional, mental, and somatoform disorders. World J Gastroenterol. 2014;20:6024–30.
4. Lee C, Doo E, Choi JM, et al.. The increased level of depression and anxiety in irritable bowel syndrome patients compared with healthy controls: systematic review and meta-analysis. J Neurogastroenterol Motil. 2017;23:349–62
5. Umrani S, Jamshed W, Rizwan A. Association Between Psychological Disorders and Irritable Bowel Syndrome. Cureus. 2021;13(4):e14513. Published 2021 Apr 16. doi:10.7759/cureus.14513
6. Staudacher HM, Black CJ, Teasdale SB, Mikocka-Walus A, Keefer L. Irritable bowel syndrome and mental health comorbidity - approach to multidisciplinary management. Nat Rev Gastroenterol Hepatol. 2023;20(9):582-596. doi:10.1038/s41575-023-00794-z
7. Chen Y, Lian B, Li P, Yao S, Hou Z. Studies on irritable bowel syndrome associated with anxiety or depression in the last 20 years: A bibliometric analysis. Front Public Health. 2022;10:947097. Published 2022 Aug 15. doi:10.3389/fpubh.2022.947097
8. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2019;50(2):132-143. doi:10.1111/apt.15325
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. International journal of surgery. 2021 Apr 1;88:105906.
10. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic reviews. 2016 Dec;5:1-0.
11. Munn Z, Aromataris E, Tufanaru C, Stern C, Porritt K, Farrow J, Lockwood C, Stephenson M, Moola S, Lizarondo L, McArthur A. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). JBI evidence implementation. 2019 Mar 1;17(1):36-43.
12. Tarar ZI, Farooq U, Zafar Y, Gandhi M, Raza S, Kamal F, Tarar MF, Ghouri YA. Burden of anxiety and depression among hospitalized patients with irritable bowel syndrome: a nationwide analysis. Irish Journal of Medical Science (1971-). 2023 Oct;192(5):2159-66.
13. Abd AL-Khaliq IM. Prevalence of Irritable Bowel Syndrome and its Association with Anxiety among Students of AL-Kindy College of Medicine. South Asian Res J Bio Appl Biosci. 2023;5(4):60-7.
14. Abdelaziz HA, Ellakany WI, Ellakany A, Dean YE, Rouzan SS, Bamousa BA, Shebl MA, Elawady SS, Verma S, Gir D, Sbitli T. The relationship between anxiety and irritable bowel syndrome symptoms among females: A cross-sectional study in Egypt. Medicine. 2023 Aug 11;102(32):e34777.
15. Midenfjord I, Polster A, Sjövall H, Törnblom H, Simrén M. Anxiety and depression in irritable bowel syndrome: Exploring the interaction with other symptoms and pathophysiology using multivariate analyses. Neurogastroenterology & Motility. 2019 Aug;31(8):e13619.
16. Black CJ, Yiannakou Y, Houghton LA, Shuweihdi F, West R, Guthrie E, Ford AC. Anxiety-related factors associated with symptom severity in irritable bowel syndrome. Neurogastroenterology & Motility. 2020 Aug;32(8):e13872.
17. Shafique S, Faraz N, Wasti H, Surti A. Irritable bowel syndrome among medical students and its association with anxiety. The Professional Medical Journal. 2021 Oct 31;28(11):1561-5.
18. Ali FH, Al–Dabbagh SA. Association between anxiety and depression with irritable bowel syndrome in Mosul. Annals of the College of Medicine, Mosul. 2019 Jun 30;41(1):63-8.
19. El Sharawy SM, Amer IF, Elkadeem MZ. Irritable bowel syndrome in Egyptian medical students, prevalence and associated factors: a cross-sectional study. Pan African Medical Journal. 2022 Apr 18;41(1).
20. Hisam A, Mashhadi SF, Ashfaq M, Javed H, Ahmed H, Waqas M, Amtal T. Prevalence of Anxiety Related Irritable Bowel Syndrome Symptoms Among Medical Students of

Rawalpindi. Pakistan Armed Forces Medical Journal. 2022;72(SUPPL-4):S914-18.
21. Fond G, Loundou A, Hamdani N, Boukouaci W, Dargel A, Oliveira J, Roger M, Tamouza R, Leboyer M, Boyer L. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. European archives of psychiatry and clinical neuroscience. 2014 Dec;264:651-60.
22. Fond G, Boukouaci W, Leboyer M, Tamouza R. Targeting microbiota in major psychiatric disorders: mechanisms, preclinical data, gastro-intestinal comorbidities and therapeutic options.
23. Cheng J, Zhang J, Lu C, Wang L. Using optogenetics to translate the "inflammatory dialogue" between heart and brain in the context of stress. Neuroscience bulletin. 2012 Aug;28:435-48.
24. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013 Aug 29;246:199-229.
25. Drossman DA, Chang L, Bellamy N, Gallo-Torres HE, Lembo A, Mearin F, Norton NJ, Whorwell P. Severity in irritable bowel syndrome: a Rome Foundation Working Team report. Official journal of the American College of Gastroenterology| ACG. 2011 Oct 1;106(10):1749-59.
26. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. Alimentary pharmacology & therapeutics. 2019 Jul;50(2):132-43.
27. Lee C, Doo E, Choi JM, et al. The increased level of depression and anxiety in irritable bowel syndrome patients compared with healthy controls: systematic review and meta-analysis. J Neurogastroenterol Motil. 2017; 23: 349-362.
28. Zamani M, Derakhshan M, Zamani V, Shokri-Shirvani J. Editorial: the prevalence of Helicobacter pylori infection worldwide-knowns and unknowns. Authors' reply. Aliment Pharmacol Ther. 2018; 47: 1331–1332.
29. Graff LA, Clara I, Walker JR, Lix L, Carr R, Miller N, Rogala L, Bernstein CN. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. Clinical Gastroenterology and Hepatology. 2013 Sep 1;11(9):1140-6.
30. Solmaz M, Kavuk I, Sayar K. Psychological factors in the irritable bowel syndrome. European journal of medical research. 2003 Dec 1;8(12):549-56.
31. van Tilburg MA, Palsson OS, Whitehead WE. Which psychological factors exacerbate irritable bowel syndrome? Development of a comprehensive model. Journal of psychosomatic research. 2013 Jun 1;74(6):486-92.
32. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. Archives of Internal Medicine. 2003 Feb 10;163(3):265-74.
33. Occhipinti K, Smith JW. Irritable bowel syndrome: a review and update. Clinics in colon and rectal surgery. 2012 Mar;25(01):046-52.