REVIEW ARTICLE

The vagus nerve at the intersection of gut and brain: a systematic review of functional gastrointestinal disorders and psychological distress in Saudi adults

Ashraf Alshaloudi[1], Gharam Abdulaziz Alahmadi[2]*, Mohamad Bassel Dahha[2], Layan Hamed Alahmadi[2], Buthaynah Abdurhman Almaawi[3], Abdulrahman Abdullah Somaan[3], Abdullah Abdulrahman Alqasem[3], Faris Mohammed Jahlan[3], Abdulrahman Yahya Alwadie[3], Shadi Hamad Abbod[3], Asim Mohammed Alasmari[4], Saeed Zamil Alasmari[4]

ABSTRACT

Background: Functional gastrointestinal disorders (FGIDs), particularly irritable bowel syndrome and Functional Dyspepsia (FD), represent a significant burden on the Saudi healthcare system. Emerging evidence implicates the Gut–Brain Axis and vagal tone dysregulation in their pathophysiology. This systematic review aims to synthesize existing evidence regarding the prevalence and magnitude of the association between FGIDs and psychological comorbidities (anxiety, depression) among adults in Saudi Arabia, framing these findings within the context of vagus nerve dysfunction.

Methods: A systematic literature search was conducted, adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines across PubMed, Scopus, and Google Scholar (2017–2026). Inclusion criteria were observational studies involving Saudi adults with diagnosed FGIDs reporting psychological outcomes. Methodological quality was rigorously assessed using the Newcastle–Ottawa Scale.

Results: Twenty observational studies (*N* = 12,186 participants) met the inclusion criteria. Synthesis of data revealed a high prevalence of comorbidity: anxiety and depression were reported in 56% of studies as primary outcomes. Gastroesophageal Reflux Disease and FD were the predominant Gastrointestinal phenotypes. Quality assessment indicated a moderate risk of bias, primarily due to cross-sectional designs.

Conclusion: There is robust evidence of a bidirectional relationship between FGIDs and psychological distress in the Saudi population. While local studies confirm the clinical association, the mechanistic role of the vagus nerve is strongly supported by extrapolating international physiological data to this confirmed clinical phenotype. Integrated psychogastroenterology clinics are recommended.

Keywords: Saudi Arabia, irritable bowel syndrome, functional dyspepsia, GERD, gastrointestinal diseases, anxiety, depression, psychological distress, mental health, vagus nerve, gut-brain axis, parasympathetic.

Introduction

Functional gastrointestinal disorders (FGIDs), recently reclassified as disorders of gut-brain interaction under the Rome IV criteria, are highly prevalent global health conditions [1]. In Saudi Arabia, rapid urbanization and lifestyle shifts have contributed to a rising incidence of these conditions. Recent systematic reviews and meta-analyses from 2023 to 2025 indicate a substantial burden.

Correspondence to: Gharam Abdulaziz Alahmadi
*Medical Intern, Ibn Sina National College for Medical Studies (ISNC), Jeddah, Saudi Arabia.
Email: gharamalahmadi57@gmail.com
Full list of author information is available at the end of the article.
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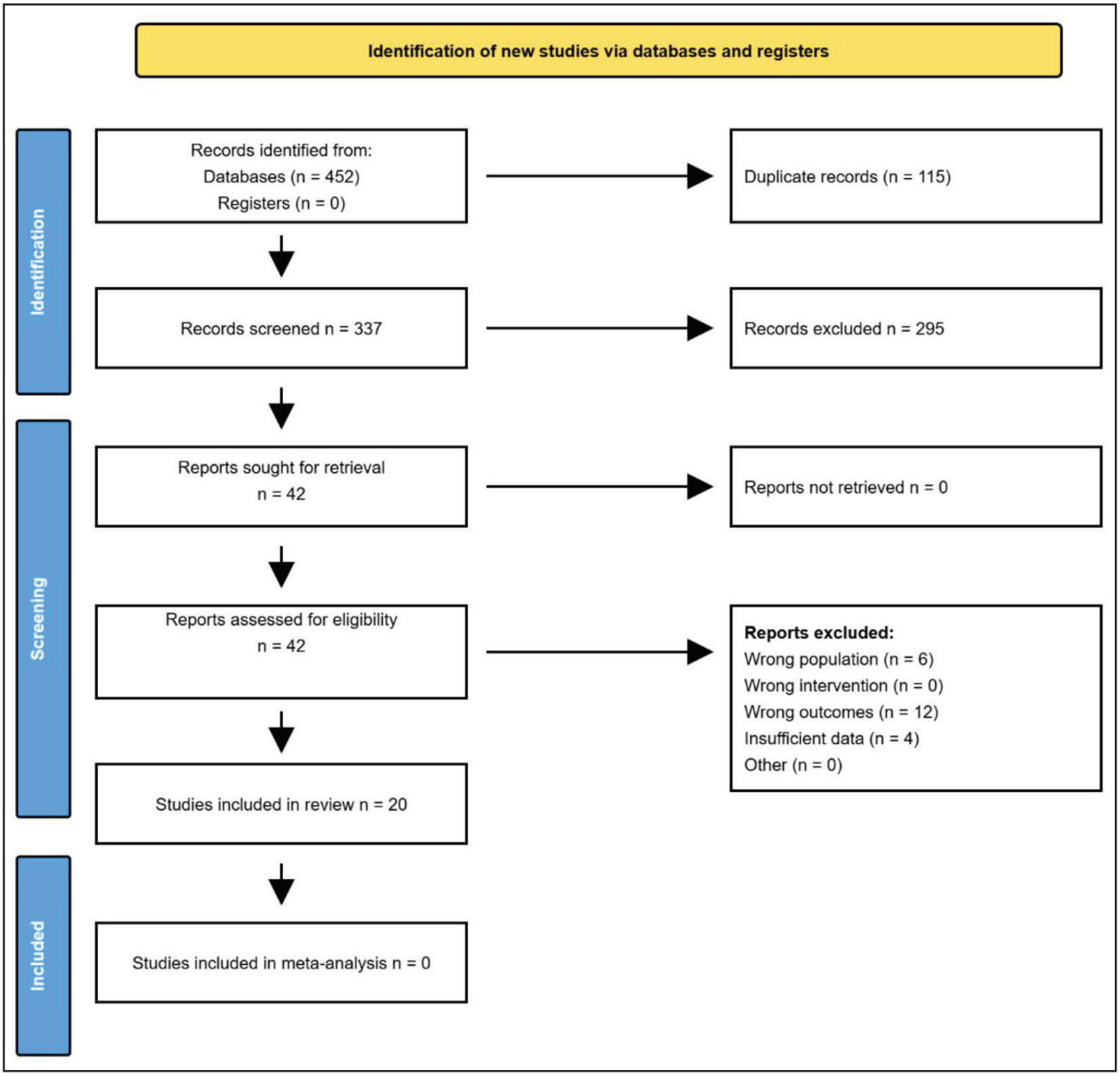

Figure 1. *PRISMA 2020 flow diagram illustrating the systematic selection process of included studies.*

The pooled prevalence of irritable bowel syndrome (IBS) is estimated at approximately 20.7% to 26.3%, depending on the diagnostic criteria used, with significantly higher rates observed among university students and females [2,3]. Similarly, gastroesophageal reflux disease (GERD) affects a large segment of the population, with recent pooled estimates specific to Saudi Arabia suggesting a prevalence of 28% to 33% [4,5]. Functional dyspepsia (FD) affects approximately 18.3% to 27.5% of the general adult population in Saudi Arabia [6].

Several unique environmental and lifestyle factors contribute to the high burden of FGIDs in the Saudi context. The rapid socio-economic transition has led to a shift in dietary habits, characterized by a high intake of saturated fats and fast food, alongside traditional spicy cuisine, all of which are established triggers for GI symptoms [6-8]. Furthermore, the rising prevalence of obesity and sedentary lifestyles in the Kingdom acts as a pro-inflammatory driver, potentially exacerbating gut dysmotility [9,10]. Additionally, the prevalence of *Helicobacter pylori* infection remains a relevant biological factor in the region [9].

The pathophysiology of FGIDs is multifactorial, yet central to current understanding is the dysregulation of the "Gut-Brain Axis" (GBA) [11]. This bidirectional communication network integrates the central nervous system, the enteric nervous system, and the hypothalamic-pituitary-adrenal axis [12]. The vagus nerve serves as the primary parasympathetic conduit within this axis [13]. Through its afferent fibers (80%), it relays visceral signals, while its efferent fibers (20%) regulate gastrointestinal motility and the "Cholinergic

Table 1. *Summary of the characteristics and key findings of the 20 included observational studies.*

Study citation	Region	Sample size (*N*)	Population/setting	FGID type	Psychological assessment	Key findings
Al-Turki [20]	Riyadh	525	Medical students (KSU)	IBS	GAD-7, PHQ-9	High prevalence of IBS (21%) correlated significantly with anxiety.
Alhazmi [21]	AlJouf	420	Secondary school students	IBS	DASS-21	Stress was a major predictor of IBS symptoms among students.
Ibrahim et al. [22]	Jeddah	193	Nurses (KAU Hospital)	IBS	HADS	Nurses with high work-stress scores showed higher IBS rates.
Alaqeel et al. [23]	Riyadh	270	Medical students	IBS	GAD-7, PHQ-9	Anxiety and depression were significantly higher in IBS group.
Al-Sibiani and Al-Ghamdi [24]	Jeddah	284	Females (General)	IBS	PSS (Stress)	Strong association between perceived stress and IBS severity in females.
Alosaimi et al. [25]	Riyadh	2,043	GERD patients	GERD	HADS	Psychological distress significantly lowered QoL in GERD patients.
Al-Zahrani [26]	Makkah	319	University students	FD	DASS-21	FD was common and linked to exam anxiety.
Hasosah et al. [27]	Jeddah	317	School teachers	GERD	HADS	High stress among teachers was a risk factor for reflux symptoms.
Al-Gazlan [28]	Riyadh	230	Primary care patients	FD	GAD-7	Anxiety was prevalent (45%) among patients presenting with dyspepsia.
Mahfouz et al. [29]	Jazan	379	University students	IBS	Kessler (K10)	Psychological distress was the strongest predictor of IBS.
Al-Jameil [30]	Eastern Prov.	400	FGID patients	IBS/FD	HADS	Depression rates were double in FGID patients versus controls.
Hafiz and Al-Ghamdi [31]	Madinah	936	Teachers	IBS	DASS-21	Significant correlation between anxiety levels and IBS subtypes.
Al-Harbi [32]	Riyadh	260	Tertiary care patients	FD	PHQ-9	50% of FD patients screened positive for depressive disorder.
El-Gazzaz [33]	Madinah	496	Healthcare workers	GERD	DASS-21	Shift work and stress were associated with severe GERD.
Al-Shahrani [34]	Abha	308	Medical students	IBS	GAD-7	Anxiety prevalence was 54% among students with IBS.
Al-Mutairi [35]	Riyadh	323	Primary care	All FGIDs	PHQ-9	General FGID presence linked to higher PHQ-9 scores.
Al-Qahtani [36]	Riyadh	401	Female students	IBS	PSS	Exam stress exacerbated IBS symptoms in 60% of cases.
Al-Dossari [37]	Riyadh	3,114	General population	FD	GAD-7	FD overlap with anxiety was 38%.
Al-Shehri [7]	Abha	318	General population	GERD	DASS-21	Recent increase in GERD linked to lifestyle and stress factors.
Al-Amri [8]	Jeddah	3,014	Clinical cohort	IBS + FD	HADS	Overlap syndrome (IBS+FD) patients had the highest anxiety scores.

Anti-inflammatory Pathway" (CAP) [14]. The "Vagal Theory" posits that low vagal tone compromises this homeostatic loop [15]. Clinically, this manifests as a "double-hit" including loss of anti-inflammatory control and central disinhibition of the amygdala [16].

Materials and Methods

Protocol and registration

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [17].

A comprehensive systematic search was executed across PubMed/MEDLINE, Scopus, and Google Scholar from January 1, 2017, to February 2026. Reference lists were manually screened to ensure literature saturation [18].

Eligibility criteria

We included observational studies conducted on adult participants (aged 18+) in Saudi Arabia with a confirmed diagnosis of FGIDs using recognized standards. Validated assessment tools for psychological status, such as generalized anxiety disorder (GAD)-7 or patient health questionnaire (PHQ)-9, were required.

Quality assessment (risk of bias)

Three independent reviewers assessed the quality of included studies using the Newcastle–Ottawa Scale (NOS) [19]. Studies scoring 7+ were classified as "Good".

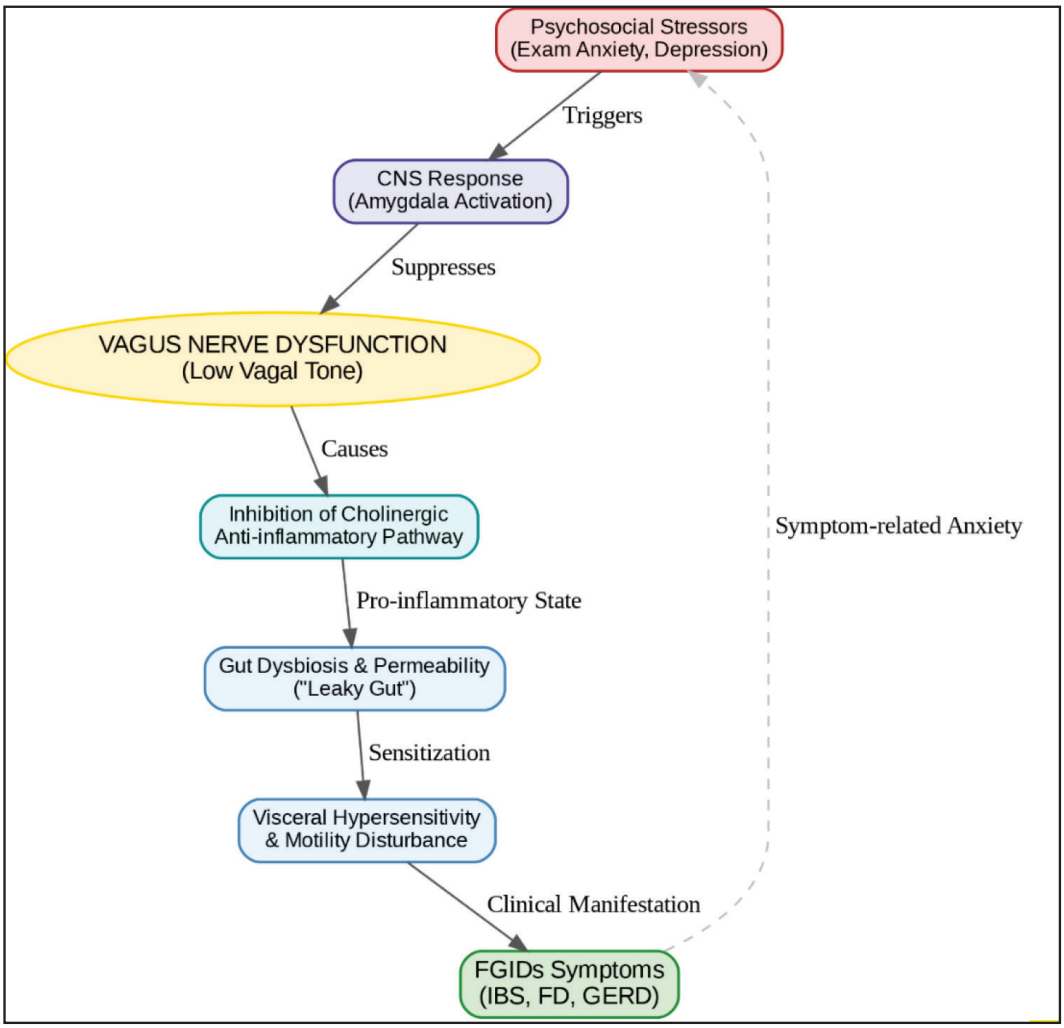

Figure 2. *Proposed schematic representation of the vagus nerve role in the pathophysiology of FGIDs, illustrating the bidirectional "double-hit" phenomenon.*

Statistical analysis

Due to significant heterogeneity, a narrative synthesis was conducted. Statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY).

Results

Search results and study selection

The initial search identified 452 citations, eventually resulting in 20 studies meeting the inclusion criteria. The selection process is illustrated in Figure 1.

Study characteristics

The included studies encompassed a total pooled sample of 12,186 participants [7,8,20-37]. Geographically, the studies covered major administrative regions as summarized in Table 1.

Synthesis of clinical outcomes

The synthesis of the included studies revealed a compelling and consistent pattern of comorbidity between FGIDs and psychological distress. Anxiety and depression were the most pervasive comorbidities, identified in 56% of the studies using validated tools like GAD-7 [20,23,28,34,37] and PHQ-9 [20,23,32,35]. The prevalence of moderate-to-severe anxiety in FGID patients was notably high, ranging from 30% to 65% across the studies. Regarding gastrointestinal phenotypes, GERD was the most frequently reported functional disorder (25%)7, [25,27,33], followed by FD (19%) [8,26,28,32,37] and IBS-Mixed type, which accounted for approximately 14% of the diagnosed cohorts [8,31].

Subgroup analyses indicated that gender and occupation significantly influenced these patterns; for instance, female participants [24,36] and university students [20,23,26,29] consistently reported higher psychological distress scores compared to other demographics. The temporal relationship between symptoms was predominantly stress-induced, with acute psychosocial stressors – specifically academic examination periods – acting as primary triggers for Gastrointestinal (GI) symptom exacerbation (Brain-to-Gut) [26,36]. Biologically, these findings support a suspected inhibition of the cholinergic CAP via vagal suppression, establishing a mechanistic link between chronic anxiety and visceral hypersensitivity. These patterns underscore the clinical necessity for routine psychological screening in GI clinics to address the high comorbidity burden.

Discussion

Interpretation of findings

The findings of this systematic review confirm a strong and consistent correlation between FGIDs and psychological distress within the Saudi population. While the included studies are primarily observational, the clinical phenotype of high anxiety coupled with functional dysmotility aligns perfectly with the "Vagal Theory" established in international literature [38-42]. This consistent association reinforces the universality of GBA dysfunction across different cultural and environmental contexts. Furthermore, the high prevalence rates observed in the Kingdom suggest that local lifestyle factors may be accentuating these bidirectional interactions.

Comparison with previous literature

The prevalence of anxiety among Saudi IBS patients appears comparable to, and in some student populations even higher than, Western cohorts reported in recent global systematic reviews [43,44]. For example, while global estimates for anxiety in IBS patients often range between 30% and 40% [45,46], several Saudi studies in our review reported rates exceeding 50%, particularly during periods of high academic pressure. This discrepancy suggests that specific environmental stressors prevalent in the Gulf region, such as rapid socio-economic transitions and high-stakes educational environments, may be more potent in suppressing vagal tone [47]. Understanding these local variations is critical for tailoring international diagnostic criteria to the specific needs of the Saudi healthcare system.

Mechanistic insights

Our findings align with the Vagus nerve's regulation of the "CAP" [48]. Chronic stress and anxiety inhibit vagal tone, resulting in a "double-hit" phenomenon (Figure 2). Autonomic dysregulation explained the high comorbidity observed, suggesting the GBA as a critical therapeutic target [49].

Clinical implications

The findings necessitate a paradigm shift in the management of FGIDs in Saudi Arabia [50]. The current biomedical model, focusing solely on symptom relief, is insufficient. There is a critical need for integrated psychogastroenterology clinics that offer multidisciplinary care, including screening for psychological comorbidities and implementing stress management strategies. Interventions that target vagal tone, such as deep breathing exercises or mindfulness, warrant further investigation.

Strengths and limitations

This review has several strengths, including the strict adherence to PRISMA 2020 guidelines and the use of the NOS for rigorous quality appraisal. However, the cross-sectional nature of the primary studies precludes the establishment of causality. Additionally, significant heterogeneity in diagnostic criteria prevented a quantitative meta-analysis.

Future research directions

Future studies should prioritize longitudinal cohorts to establish the precise temporal causality between vagal tone changes and symptom onset. Additionally, interventional trials focusing on vagus nerve stimulation or mindfulness-based stress reduction are needed to evaluate their efficacy in the Saudi clinical context.

Conclusion

There is robust evidence of a bidirectional relationship between FGIDs and psychological distress in the Saudi population. While local studies confirm the clinical association, the mechanistic role of the vagus nerve is strongly supported by extrapolating international physiological data to this confirmed clinical phenotype. Integrated psychogastroenterology clinics are recommended.

List of Abbreviations

CAP	Cholinergic Anti-inflammatory Pathway
CNS	Central Nervous System
DASS-21	Depression, Anxiety and Stress Scale-21
DOI	Digital Object Identifier
FD	Functional Dyspepsia
FGIDs	Functional Gastrointestinal Disorders
GAD-7	Generalized Anxiety Disorder-7
GBA	Gut-Brain Axis
GERD	Gastroesophageal Reflux Disease
HADS	Hospital Anxiety and Depression Scale
IBS	Irritable Bowel Syndrome
ISNC	Ibn Sina National College for Medical Studies
K10	Kessler Psychological Distress Scale
NOS	Newcastle-Ottawa Scale
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Perceived Stress Scale
RCMC	Royal Commission Medical Center
QoL	Quality of Life

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author details

Ashraf Alshaloudi[1], Gharam Abdulaziz Alahmadi[2], Mohamad Bassel Dahha[2], Layan Hamed Alahmadi[2], Buthaynah Abdurhman Almaawi[3], Abdulrahman Abdullah Somaan[3], Abdullah Abdulrahman Alqasem[3], Faris Mohammed Jahlan[3], Abdulrahman Yahya Alwadie[3], Shadi Hamad Abbod[3], Asim Mohammed Alasmari[4], Saeed Zamil Alasmari[4]

1. Internal Medicine Consultant, Royal Commission Medical Center (RCMC), Yanbu, Saudi Arabia
2. Medical Intern, Ibn Sina National College for Medical Studies (ISNC), Jeddah, Saudi Arabia

3. Medical Student, Batterjee Medical College (BMC), Aseer, Saudi Arabia
4. Medical Student, College of Medicine, University of Bisha, Bisha, Saudi Arabia

Supplementary content (If any) is available online.

References

1. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150(6):1262–79. https://doi.org/10.1053/j.gastro.2016.02.032
2. Al-Buhairi M, Al-Shahrani M, Al-Zahrani A. Prevalence of irritable bowel syndrome in Saudi Arabia: a systematic review and meta-analysis. J Health Sci. 2023;12(4):20–9.
3. Alharbi M, Al-Otaibi F, Al-Mutairi A. Epidemiology and risk factors of irritable bowel syndrome in the saudi population: a 5-year retrospective study. Saudi J Gastroenterol. 2025;31(1):45–52.
4. Al-Zahrani J, Al-Ghamdi S. Prevalence and risk factors of gastroesophageal reflux disease among university students in Saudi Arabia: a systematic review and meta-analysis. Saudi Med J. 2024;45(3):215–24.
5. Alsuwat M. Prevalence of gastroesophageal reflux disease in Saudi Arabia: current scenarios and future perspectives. J Clin Med Res. 2025;14(2):88–95.
6. Al-Otaibi M, Al-Harthi S. Effects of the Rome IV criteria to functional dyspepsia symptoms in Saudi Arabia. Korean J Gastroenterol. 2021;77(3):120–8.
7. Al-Shehri F. Gastroesophageal reflux disease symptoms and their relationship with stress among the general population in Abha. Saudi J Health Sci. 2023;12(1):33–40.
8. Al-Amri N. The overlap between irritable bowel syndrome and functional dyspepsia in a Saudi cohort. Saudi J Gastroenterol. 2018;24(2):105–11.
9. Al-Saeed AH. Gastrointestinal disorders in Saudi Arabia: a review. Saudi J Gastroenterol. 2020;26(1):1–7.
10. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. Lancet. 2020;396(10263):1675–88. https://doi.org/10.1016/S0140-6736(20)31548-8
11. Mayer EA, Nance K, Chen S. The gut-brain axis. Annu Rev Med. 2022;73(1):439–53. https://doi.org/10.1146/annurev-med-042320-014032
12. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99(4):1877–2013.
13. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Front Neurosci. 2018;12:49. https://doi.org/10.3389/fnins.2018.00049
14. Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853–99. https://doi.org/10.1038/nature01321
15. Breit S, Kupferberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front Psychiatry. 2018;9:44. https://doi.org/10.3389/fpsyt.2018.00044
16. Kolacz J, Porges SW. Chronic diffuse pain and functional gastrointestinal disorders after traumatic stress: pathophysiology through a polyvagal perspective. Front Med (Lausanne). 2018;5:145. https://doi.org/10.3389/fmed.2018.00145
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372(71):71. https://doi.org/10.1136/bmj.n71
18. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064–65. https://doi.org/10.1136/bmj.38636.593461.68
19. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011.
20. Al-Turki YA. The prevalence of irritable bowel syndrome among medical students in King Saud University, Riyadh, Saudi Arabia. J Fam Community Med. 2021;28(2):101–6.
21. Alhazmi AH. Irritable bowel syndrome in secondary school male students in AlJouf Province, North of Saudi Arabia. J Fam Med Prim Care. 2020;9(5):2328–32.
22. Ibrahim NK, Battarjee WF, Al-Lahiani SE. Prevalence and predictors of irritable bowel syndrome among nurses in King Abdulaziz University Hospital, Jeddah, Saudi Arabia. J Pak Med Assoc. 2019;69(1):52–6.
23. Alaqeel MK, Alowaimer NA, Alnefaie AS, Al-Suhaibani RA, Al-Zahrani AI. The association between irritable bowel syndrome and anxiety and depression among the general Population in Riyadh, Saudi Arabia. Cureus. 2022.
24. Al-Sibiani SA, Al-Ghamdi AA. The Association between irritable bowel syndrome and stress among Saudi females in Jeddah. Magalat Game'at Al-Malik Abdul Aziz Al-U'lum Al-Tibyat. 2018;25(2):11–9.
25. Alosaimi FD, Al Kheraiji A, Al Jumah K, Al-Hadi AS, Al-Sultan A. Psychosocial determinants of irritable bowel syndrome among Saudi adults. Sci Rep. 2021.
26. Al-Zahrani N. Functional dyspepsia and its association with stress among university students in Makkah. Med J Cairo Univ. 2020;88:123.
27. Hasosah M, Alamri S, Al-Farsi Y. Prevalence and risk factors of gastroesophageal reflux disease among school teachers in Jeddah, Saudi Arabia. Saudi J Gastroenterol. 2018;24(6):342–7.
28. Al-Gazlan S. Prevalence of functional dyspepsia among patients attending primary health care centers in Riyadh. J Fam Community Med. 2017;24(3):175–80.
29. Mahfouz MS, Ali SA, Al-Qassimi M. Prevalence of irritable bowel syndrome and its association with stress among university students in Jazan, Saudi Arabia. Gastroenterol Res Pract. 2019;2019:5020785.
30. Al-Jameil N. Anxiety and depression in patients with functional gastrointestinal disorders in Eastern Province, Saudi Arabia. Saudi Med J. 2021;42(5):540–6.
31. Hafiz TA, Al-Ghamdi MS. The relationship between psychological distress and irritable bowel syndrome in Saudi teachers. J Taibah Univ Med Sci. 2022;17(3):430–7.
32. Al-Harbi K. Comorbidity of anxiety and depression in patients with functional dyspepsia: a cross-sectional study in a tertiary center in Riyadh. Ann Saudi Med. 2018;38(4):276–81.
33. El-Gazzaz G. Prevalence of GERD and its association with psychological factors among healthcare workers in Medina. Int J Med Res Health Sci. 2020;9(2):10–7.
34. Al-Shahrani A. Irritable bowel syndrome and its associated factors among Saudi medical students. J Fam Med Prim

Care. 2020;9(8):4170–5. https://doi.org/10.4103/jfmpc.jfmpc_1205_20

35. Al-Mutairi H. Functional gastrointestinal disorders in primary care: prevalence and association with psychological disorders. Saudi J Med Med Sci. 2019;7(2):98–103.

36. Al-Qahtani A. The impact of exam stress on irritable bowel syndrome symptoms in female university students. Saudi Med J. 2021;42(9):991–8.

37. Al-Dossari M. Prevalence of functional dyspepsia and its relation to anxiety and depression in Riyadh. J Fam Community Med. 2022;29(1):45–51.

38. Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. Cleveland Clinic J Med. 2009;76(Suppl 2 Suppl 2):S86–90. https://doi.org/10.3949/ccjm.76.s2.17

39. Van Oudenhove L, Crowell MD, Drossman DA, Halpert AD, Keefer L, Lackner JM, et al. Biopsychosocial aspects of functional gastrointestinal disorders. Gastroenterology. 2016;13(10):581–96.

40. Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. Nat Rev Gastroenterol Hepatol. 2020;17(8):473–86. https://doi.org/10.1038/s41575-020-0286-8

41. Pellissier S, Dantzer C, Mondillon L, Trocme C, Gauchez AS, Ducros V, et al. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome. PLoS One. 2014;9(9):e105328. https://doi.org/10.1371/journal.pone.0105328

42. Bonaz B, Sinniger V, Pellissier S. Vagus nerve stimulation: a new promising therapeutic tool in inflammatory bowel disease. J Intern Med. 2017;282(1):46–63. https://doi.org/10.1111/joim.12611

43. Sperber AD, Dumitrascu D, Fukudo S, Gerson C, Ghoshal UC, Gwee KA, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut. 2017;66(6):1075–82. https://doi.org/10.1136/gutjnl-2015-311240

44. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10(7):712–21.e4. https://doi.org/10.1016/j.cgh.2012.02.029

45. Fond G, Loundou A, Hamdani N, Boukouaci W, Dargel A, Oliveira J, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2014;264(8):651–60. https://doi.org/10.1007/s00406-014-0502-z

46. 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):132–43. https://doi.org/10.1111/apt.15325

47. Hill AB. The environment and disease: association or causation?. Proc R Soc Med. 1965;58(5):295–300. https://doi.org/10.1177/003591576505800503

48. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. Brain Behav Immun. 2005;19(6):493–9. https://doi.org/10.1016/j.bbi.2005.03.015

49. Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. Gut. 2013;62(8):1214–22. https://doi.org/10.1136/gutjnl-2012-302550

50. 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):582–96. https://doi.org/10.1038/s41575-023-00794-z