



Association Between Psychosocial Disorders and Gastroesophageal Reflux Disease: A Systematic Review and Meta-analysis

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Background/Aims

The incidence of gastroesophageal reflux disease (GERD) is increasing annually. Studies have suggested that psychosocial disorders may be linked to the development of GERD. However, studies evaluating the association between psychosocial disorders and GERD have been inconsistent. Thus, we conducted a systematic review and meta-analysis of observational studies that evaluated the association between psychosocial disorders and GERD.

Methods

We systematically searched the PubMed, Embase, Cochrane, and Web of Science databases until October 17, 2020. Pooled OR with 95% CI and subgroup analyses were calculated using a random-effects model. Subgroup analyses were performed to identify the sources of heterogeneity. Sensitivity analysis by one-study removal was used to test the robustness of our results.

Results

This meta-analysis included 1 485 268 participants from 9 studies. Studies using psychosocial disorders as the outcome showed that patients with GERD had a higher incidence of psychosocial disorders compared to that in patients without GERD (OR, 2.57; 95% CI, 1.87-3.54; $I^2 = 93.8\%$; $P < 0.001$). Studies using GERD as an outcome showed an association between psychosocial disorders and an increased risk of GERD (OR, 2.23; 95% CI, 1.42-3.51; $I^2 = 97.1\%$; $P < 0.001$). The results of the subgroup analysis showed that the non-erosive reflux disease group had a higher increased risk of anxiety than erosive reflux disease group (OR, 9.45; 95% CI, 5.54-16.13; $I^2 = 12.6\%$; $P = 0.285$).

Conclusion

Results of our meta-analysis showed that psychosocial disorders are associated with GERD; there is an interaction between the two. (J Neurogastroenterol Motil 2022;28:212-221)

Key Words

Anxiety; Depressive disorder; Gastroesophageal reflux; Meta-analysis; Odds ratio

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Introduction

In recent years, with the rapid development of contemporary societies, people face pressures in all aspects of life. The incidence of gastroesophageal reflux disease (GERD) and psychosocial disorders, especially anxiety, and depression, has increased worldwide annually¹⁻⁵; moreover, GERD and psychosocial disorders often occur together and can affect each other.⁶⁻⁸

GERD is a clinically common gastrointestinal disease in Western countries, affecting up to 20% of the Western population, and is associated with a variety of risk factors such as obesity and smoking.^{9,10} A meta-analysis reported a global incidence of GERD of 13.98%, with an estimated 1.03 billion people worldwide experiencing GERD.¹ GERD mainly refers to the reflux of stomach and duodenum contents to the esophagus, which, in turn, causes acid reflux, heartburn, and other symptoms.¹¹ GERD seriously affects patient quality of life and work efficiency; moreover, long-term burns to the esophagus can also increase the risk of adenocarcinoma of the lower esophagus.¹¹

At present, psychosocial disorders are becoming increasingly common worldwide, especially anxiety and depression.^{4,5} According to the World Health Organization, depression will become the first global burden of disease by 2030.¹² A systematic review collected 87 studies from 44 countries; the final statistics showed that the global prevalence of anxiety disorders was 7.30%.¹³ Psychological disorders in contemporary societies affects many people and are related to many diseases of the digestive tract, among which irritable bowel syndrome, is the most studied.¹⁴⁻¹⁶ Clinical studies have confirmed the association between psychosocial disorders and GERD.¹⁷⁻²⁰ GERD can lead to anxiety and depression, in turn, psychological disorders can also lead to reflux symptoms.^{21,22} People with depression are 1.7 times more likely to develop GERD compared to those without depression.²² In the study of Kessing et al,²³ levels of anxiety can increase the severity of reflux episodes. Treating GERD with antidepressants can improve the symptoms of patients with esophageal visceral allergy.²⁴

GERD and depression have many similar neurobiological mechanisms, among which the “brain-gut” axis plays an important role in the mechanism of the 2 comorbidities.²⁵ The “brain-gut axis” refers to the 2-way communication between the central and the enteric nervous systems.²⁶ Emotional changes, such as anxiety and depression, in GERD may be related to the hypothalamic-pituitary-adrenal axis. GERD includes reflux esophagitis (RE) with mucosal damage and non-erosive reflux disease (NERD) without

mucosal damage. Compared to patients with erosive reflux disease (ERD), patients with NERD have a higher prevalence of mental illness.²⁷ Recent studies have suggested that the pathogenesis of erosive gastroesophageal reflux disease is mainly due to excessive acid exposure and subsequent mucosal damage caused by reflux. However, for NERD without mucosal damage under gastroscopy, the pathogenesis is mainly due to psychological stress from esophageal hypersensitivity, epithelial permeability, and dilation of intercellular space causing changes in intercellular pH and/or osmotic pressure, leading to pain.²⁸⁻³² Studies have shown that the poor efficacy of proton pump inhibitors in patients with GERD may be caused by psychological factors.³⁰

Although studies have explored their correlation, no meta-analysis has shown a causal relationship between psychosocial disorders and GERD. The present study systematically analyzed the association between psychosocial disorders and GERD to provide a deep understanding of the relationship between these 2 diseases to better manage patients in clinical practice.

Materials and Methods

Search Strategy

We searched the PubMed, Embase, Cochrane, and Web of Science databases for literature published up to October 17, 2020, using terms in the Medical Subject Headings database, including “depression” OR “anxiety” OR “alexithymia” OR “psychological stress” OR “occupational stress” AND “gastroesophageal reflux disease.”

Protocol and Guidance

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Inclusion and Exclusion Criteria

Our inclusion criteria were as follows:

- (1) The included studies reported on the association between psychosocial disorders and GERD
- (2) Definitely diagnosed as GERD
- (3) Diagnosis of psychological disorders based on validated instruments
- (4) Observational studies
- (5) Research that provided ORs and 95% CIs, or that included data from which OR could be calculated

Our exclusion criteria were as follows:

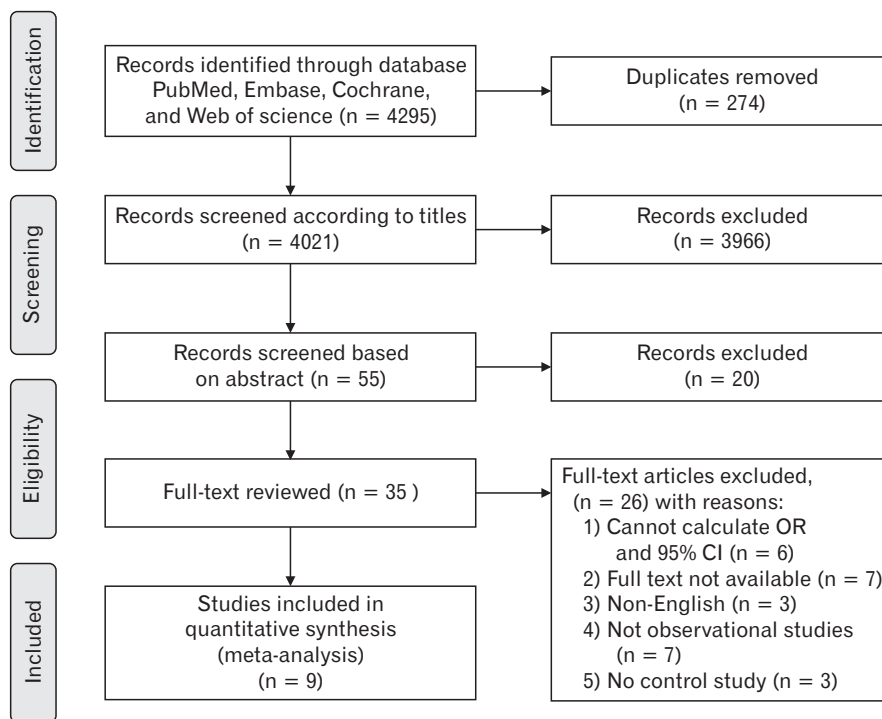


Figure 1. Flow chart of study selection.

- (1) Reviews, case reports, and letters to the editor
- (2) Full text not available
- (3) Non-English articles
- (4) No control group

Study Selection

Two researchers (M.H. and G.B.) screened the article titles and abstracts, as well as the full texts, selected the studies, and extracted general information on the patients in the studies. Disagreements between the researchers on study inclusion were resolved by a third researcher (D.Y.).

Data Extraction and Quality Assessment

Two researchers collected relevant information from each study. The relevant information included the first author and year of publication, country of origin, sample size, study design, age, diagnostic criteria of GERD and psychosocial disorders, and outcome. Two researchers assessed the quality of each study. Cohort and case-control studies were assessed using 3 aspects of the Newcastle-Ottawa quality assessment scale: (1) the selection of study groups, (2) comparability of the groups, and (3) ascertainment of exposure or outcome of interest for case-control studies.³³ The cross-sectional studies were assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality.³⁴

Statistical Methods

Data were analyzed using Stata version 15.1 (StataCorp LLC, College Station, TX, USA). ORs and their associated 95% CIs were used to measure the effect size. We assessed heterogeneity using the I^2 statistic, in which I^2 values greater than 50% indicated substantial statistical heterogeneity.³⁵ We used a random-effects model to calculate the pooled effect size. Subgroup and sensitivity analyses were performed by excluding 1 study at a time.

Results

Included Studies

A total of 4295 articles were identified, 4021 of which were included after deduplication. After checking the titles and abstracts, 35 articles were fully reviewed, and 9 articles were finally included (Fig. 1).

Characteristics and Quality Assessment of the Included Studies

The baseline information for each study is presented in Table. The 9 articles included a total of 1 485 268 participants. Seven studies showed a higher incidence of psychosocial disorders among

Table. Characteristics of the Studies Included in the Meta-analysis

First author (yr)	Study design	Ethnicity	Sample size	Age (yr)	GERD diagnosis	Psychosocial disorders diagnosis	Outcome
Yang et al ³⁶ (2015)	Case-control	Chinese	GERD (n = 279) Healthy controls (n = 100)	RE (41.07 ± 10.61) NERD (39.68 ± 10.80) Controls (40.04 ± 12.22)	Rome III criteria	ZSAS ZSDS	Anxiety/depression
Javadi and Shafikhani ³⁷ (2017)	Case-control	Iranian	GERD (n = 100) Healthy controls (n = 100)	NR	Los Angeles classification	HADS	Anxiety/depression
Denver et al ³⁸ (2013)	Case-control	Irish	RO (n = 230) Controls (n = 260)	Controls (63.0) RO (61.7) BO (62.4)	Savary-Miller classification Hetzel-Dent classification Los Angeles classification	4-item Reed Stress Inventory	Anxiety/depression
Kim et al ³⁹ (2018)	Case-control	Korean	Study 1: Depression (n = 60 957) Control (n = 243 828) Study 2 GERD (n = 133 089) Control (n = 266 178)	> 20	ICD-10 codes	ICD-10 codes	Study 1: GERD Study 2: Depression
Lee et al ⁴⁰ (2018)	Cohort study	Korean	GERD (n = 9503) Healthy controls (n = 9503)	> 19	KCD-6 codes 24-hr pH monitoring	KCD-6 codes	Psychological disorders
On et al ⁴¹ (2017)	Cohort study	Australian	GERD (n = 221) Healthy controls (n = 1391)	35-80	GERDQ	Beck Depression Inventory Centre for Epidemiological Studies Depression Scale Generalized Anxiety Disorder-7 scale	Anxiety/depression
You et al ⁴² (2015)	Cohort study	Chinese	GERD (n = 3813) Healthy controls (n = 15 252)	GERD (45.9) Control (45.9)	ICD-9-CM codes	ICD-9-CM codes	Psychological disorders
Song et al ⁴³ (2013)	Cross-sectional	Korean	Stress group (n = 902) Reference group (n = 6023)	Stress (42.3 ± 10.5) Control (44.1 ± 9.7)	Los Angeles classification	BEPSI-K	GERD
Chou et al ⁴⁴ (2014)	Cross-sectional	Chinese	General population (n = 728 749) Patients with MDD (n = 4790)	> 20	ICD-9-CM codes	ICD-9-CM codes	GERD

GERD, gastroesophageal reflux disease; RE, reflux esophagitis; NERD, non-erosive reflux disease; ZSAS, Zung Self-Rating Anxiety Scale; ZSDS, Zung Self-Rating Depression Scale; NR, not reported; HADS, Hospital Anxiety and Depression Scale; RO, reflux oesophagitis; BO, Barrett's esophagus; ICD-10, International Classification of Disease-10; KCD-6, Korean Classification of Diseases, sixth revision; GERDQ, gastroesophageal reflux disease; ICD-9-CM, International Classification of Diseases, ninth revision, clinical modification; BEPSI-K, Brief Encounter Psychosocial Instrument; MDD, major depressive disorder.

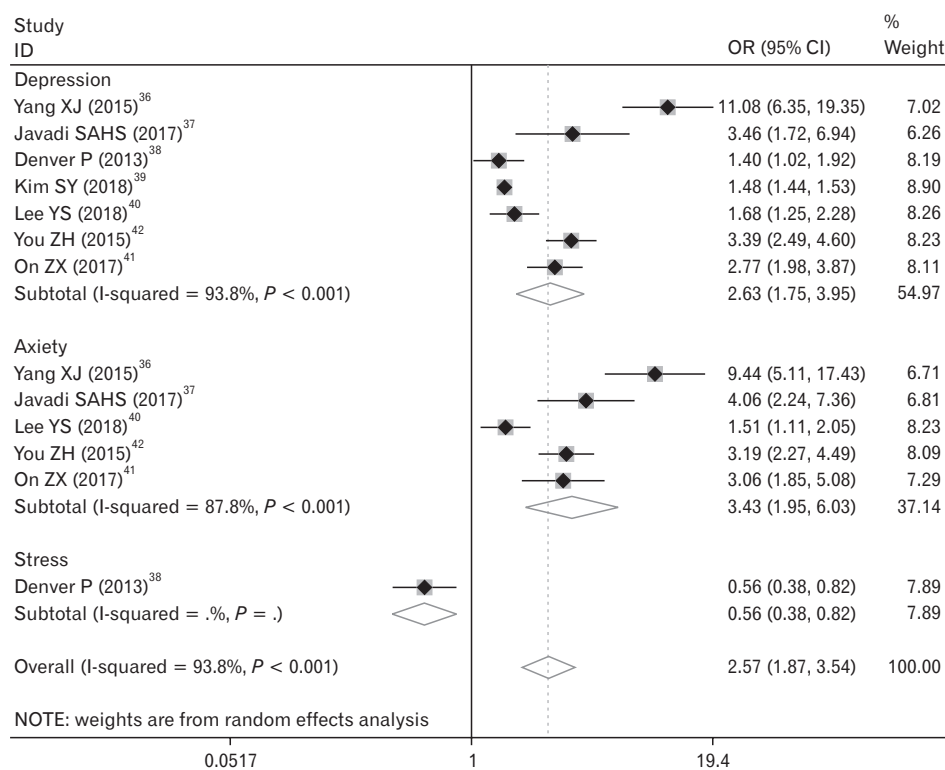


Figure 2. Forest plot of the associations between gastroesophageal reflux disease and psychosocial disorders.

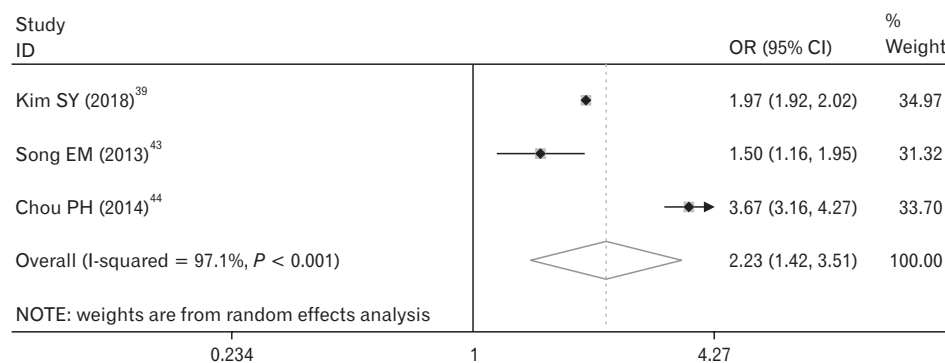


Figure 3. Forest plot of the associations between psychosocial disorders and gastroesophageal reflux disease.

patients with GERD, as compared to the healthy control group³⁶⁻⁴²; 3 studies reported that patients with psychosocial disorders were associated with an increased risk for GERD.^{39,43,44} Application of the modified Newcastle-Ottawa Scale method for evaluating article quality showed that the 7 studies had 5 or more stars (Supplementary Tables 1 and 2). The included cross-sectional studies were assessed using an 11-item checklist (Supplementary Table 3).

Psychosocial Disorders and Gastroesophageal Reflux Disease

The 7 studies using psychosocial disorders as the outcome showed a higher incidence of psychosocial disorders in patients with

GERD than that in patients without GERD (OR, 2.57; 95% CI, 1.87-3.54; *I*² = 93.8%; *P* < 0.001) (Fig. 2). The other 3 studies using GERD as an outcome showed that psychosocial disorders were associated with an increased risk of GERD (OR, 2.23; 95% CI, 1.42-3.51; *I*² = 97.1%; *P* < 0.001) (Fig. 3).

Subgroup Analysis

First, a subgroup analysis was conducted according to the types of study. In the subgroup analysis exploring the association between GERD and depression (Fig. 4), the results showed OR, 2.83 (95% CI, 1.41-5.69; *I*² = 94.6%; *P* < 0.001) for case-control studies and OR, 2.50 (95% CI, 1.64-3.82; *I*² = 81.6%; *P* = 0.004) for cohort

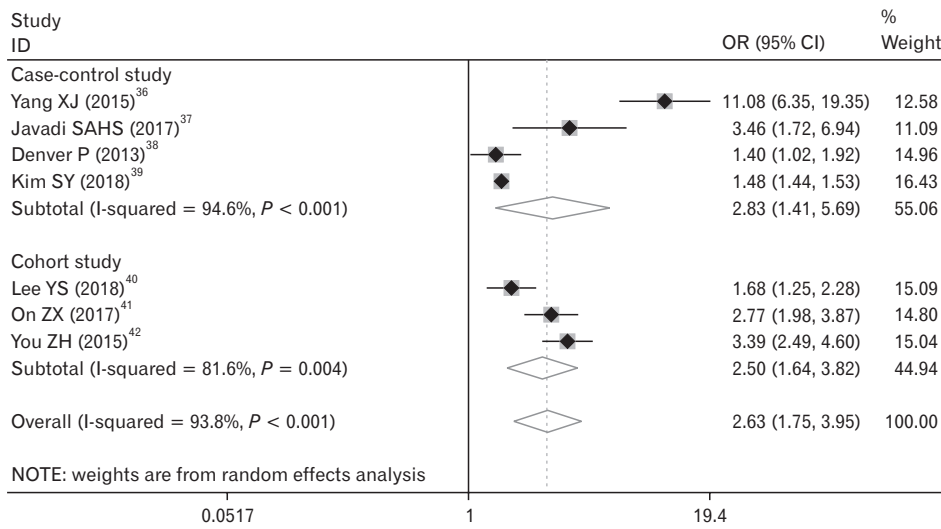


Figure 4. Subgroup analysis of the associations between gastroesophageal reflux disease and depression according to the study type.

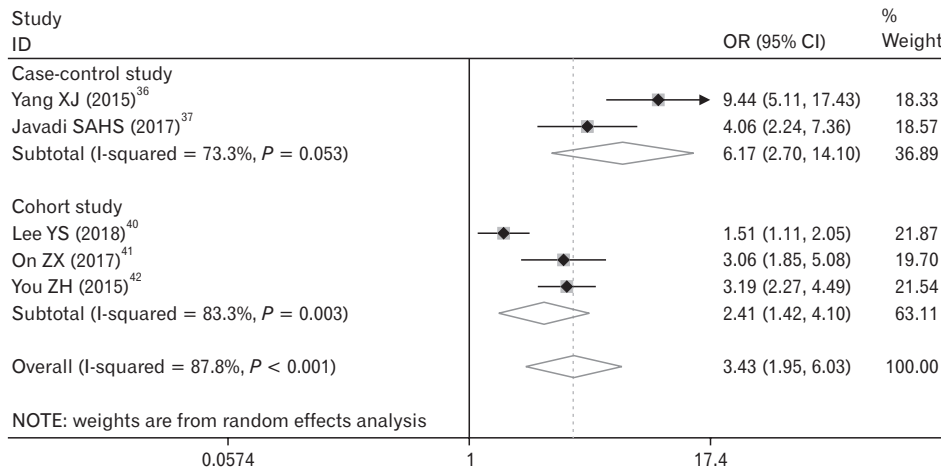


Figure 5. Subgroup analysis of the associations between gastroesophageal reflux disease and anxiety according to study type.

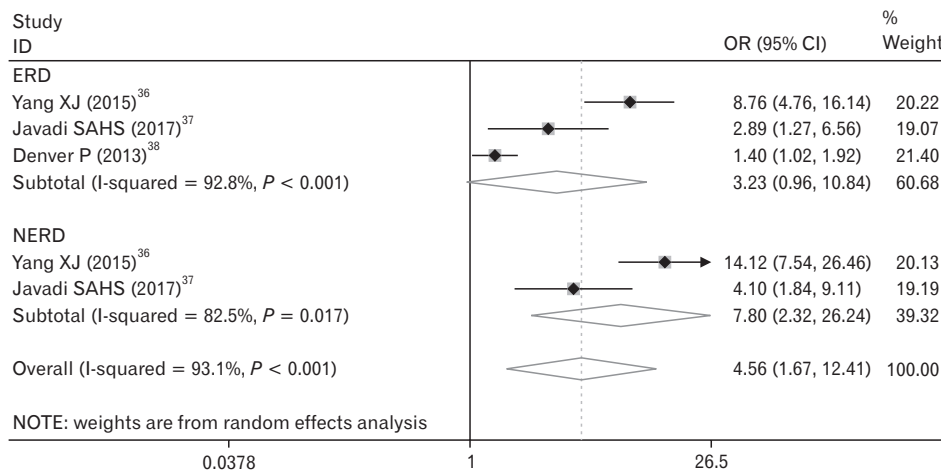


Figure 6. Subgroup analysis of the associations between gastroesophageal reflux disease (GERD) and depression according to the GERD type. ERD, erosive reflux disease; NERD, non-erosive reflux disease.

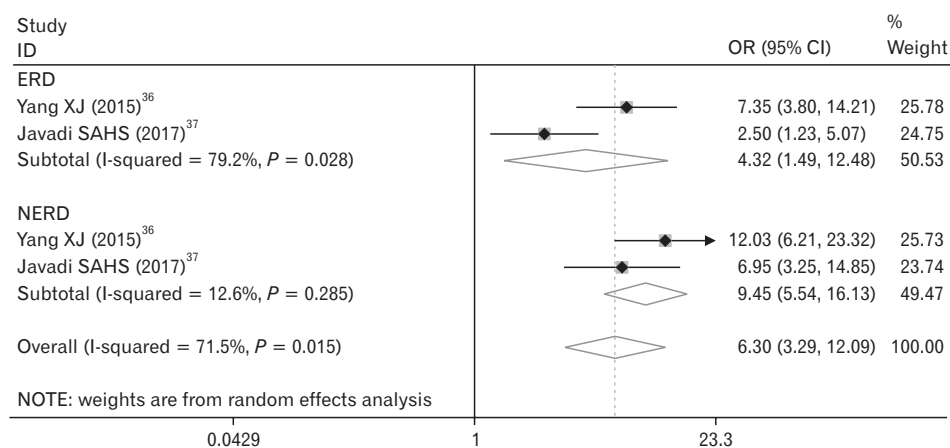


Figure 7. Subgroup analysis of the associations between gastroesophageal reflux disease (GERD) and anxiety according to GERD type. ERD, erosive reflux disease; NERD, non-erosive reflux disease.

studies. In the subgroup analysis exploring the association between GERD and anxiety (Fig. 5), the results showed OR, 6.17 (95% CI, 2.70-14.10; $I^2 = 73.3\%$; $P = 0.053$) for case-control studies, and OR, 2.41 (95% CI, 1.42-4.10; $I^2 = 83.3\%$; $P = 0.003$) for cohort studies. The results indicated that the heterogeneity was not attributed to the types of study.

Next, we conducted a subgroup analysis according to the different types of GERD. Although individual studies showed an increased risk for depression in those with depression outcomes (Fig. 6), the combined study did not have any statistical significance (OR, 3.23; 95% CI, 0.96-10.84; $I^2 = 92.8\%$; $P < 0.001$). Compared to the health control group, the NERD group had a higher risk for depression (OR, 7.80; 95% CI, 2.32-26.24; $I^2 = 82.5\%$; $P = 0.017$). In studies with anxiety outcomes (Fig. 7), ERD increased the risk for anxiety, as compared with healthy controls (OR, 4.32; 95% CI, 1.49-12.48; $I^2 = 79.2\%$; $P = 0.028$). The NERD group had a higher increased risk for anxiety (OR, 9.45; 95% CI, 5.54-16.13; $I^2 = 12.6\%$; $P = 0.285$); the NERD group was more homogeneous.

Sensitivity Analysis

A sensitivity analysis was carried out in which 1 study was sequentially omitted to assess the robustness of the pooled effects. After item-by-item elimination, the sensitivity analysis results show that the stability is good. The pooled ORs of the association between GERD and depression ranged from 2.10 (95% CI, 1.52-2.90) to 2.97 (95% CI, 1.81-4.87) (Supplementary Fig. 1). The pooled OR of the association between GERD and anxiety ranged from 2.69 (95% CI, 1.68-4.31) to 4.23 (95% CI, 2.67-6.72) (Supplementary Fig. 2).

Discussion

This study aimed to explore the association between psychosocial disorders and GERD. Overall, this meta-analysis based on 9 studies and 1 485 268 subjects found a significant positive association between psychosocial disorders and GERD. To our knowledge, this is the first systematic review and meta-analysis to assess the association between psychosocial disorders and GERD.

Previous studies have reported the relationships between psychosocial disorders and GERD. According to a cross-sectional study, the levels of depression and anxiety were significantly higher in the subjects with GERD, especially NERD, than in controls.⁴⁵ Lee et al⁴⁰ reported that patients with GERD had higher risks of psychological disorders than those without GERD (hazard ratio = 1.25; 95% CI, 1.07-1.47; $P = 0.006$).⁴⁰ Jansson et al²² indicated that anxiety increased risk of reflux symptoms compared to the subjects without reflux symptoms (OR, 3.2; 95% CI, 2.7-3.8; $P < 0.0001$), and that depression led to a 1.7-fold increase of risk (OR, 1.7; 95% CI, 1.4-2.1; $P < 0.0001$).²² Despite many clinical studies demonstrating the association between GERD and mental illness, the sample size of individual studies was small, which can lead to the biased results. In this regard, meta-analysis methods can be used to increase sample size, reduce bias, and improve the level of evidence.

This meta-analysis of 9 observational studies provided evidence of an increased OR for GERD of 2.57 with the occurrence of psychosocial disorders (95% CI, 1.87-3.54). Individuals with GERD had a 2.63-fold higher risk of depression (OR, 2.63; 95% CI, 1.75-3.95) and a 3.43-fold higher risk of anxiety (OR, 3.43; 95% CI, 1.95-6.03). This result proved that patients with GERD are more likely to experience anxiety than depression. In addition, individuals

with psychosocial disorders had a 2.23-fold increased occurrence of GERD (95% CI, 1.42-3.51).

Due to the high heterogeneity of mergers, we further performed subgroup analysis and sensitivity analyses. The subgroup analysis showed that the risk for anxiety in NERD patients was significantly higher than that in ERD patients. In the sensitivity analysis, we found that the removal of Yang et al³⁶ had a greater impact on the results. In this study, patients with NERD had significantly higher anxiety and depression scores than patients with ERD. These results indicated that NERD and ERD may have different pathogeneses.

We identified several possible explanations for the increased risk of psychosocial disorders caused by GERD. First, acid reflux events disrupts sleep architecture. More than half of patients with chronic GERD report nocturnal symptoms, which seriously affect rest and increase anxiety and tension.^{46,47} Second, the abnormal expression of inflammatory cytokines in the esophageal mucosa, such as interleukin IL-6, IL-8, IL-1beta, interferon-gamma, and tumor necrosis factor-alpha (TNF- α) may also play a role.⁴⁸ The mucosal barrier is damaged by the mediation of inflammatory chemokines, which, in turn, sensitizes nerve endings in the submucosa of the esophagus. Abnormal expression of inflammatory factors in the body is an important factor in the progression of RE. The more severe the illness, the stronger the inflammatory response.⁴⁹ The occurrence of peripheral inflammation affects inflammation of the central nervous system (CNS)⁵⁰; moreover, central inflammation can lead to mental illness.⁵¹

Psychosocial disorders may also increase the risk of developing GERD. Psychological disorders can regulate the sensation of esophageal pain. These factors often cause patients to feel hypersensitivity to internal organs; that is, pain sensation in response to stimulation below the threshold.¹⁷ The specific mechanisms are as follows. First, the tight junctions of the esophageal epithelium of psychologically stressed rats are destroyed, thereby weakening or reducing the barrier function of the esophageal mucosa.⁵² Second, mental states such as anxiety may impair esophageal motor function and cause esophageal motility disorders by reducing the pressure of the lower esophageal sphincter.⁵³ Third, psychological disorders can affect esophageal sensitivity through peripheral and central mechanisms; that is, peripheral sensitization and central sensitization. Central sensitization also plays a vital role in esophageal visceral hypersensitivity. Mechanical and chemical stimulation are converted into action potentials through the nociceptive receptors on the esophageal nerve and then transmitted to the CNS through the spinal or vagus nerves, causing excitatory synaptic responses

that, in turn, amplify the patient's sensitivity to physiological stimuli. When injured, central overexcitation persists when the stimulation is removed. This is because the nerve center has a high degree of plasticity during visceral pain, leading to continuous pain.⁵⁴ Acid exposure in patients with GERD causes faster and greater brain activity compared to that in healthy controls.⁵⁵ Fourth, psychological disorders increase the esophageal mucosal perception of stimuli in the esophagus through the interaction of the brain-gut axis, leading to small stimuli that can also cause pain and heartburn.^{52,56} In addition, stress can promote inflammation and increase the occurrence of reflux symptoms. Animal experiments have shown that 2 weeks of binding stress significantly increased the levels of inflammatory cytokines in the esophagus and plasma, including IL-6, IL-8, interferon, and TNF- α , indicating that stress can induce inflammation of the esophagus.⁵⁷

This study had several limitations. First, it was difficult to address heterogeneity. Although subgroup analysis reduced this heterogeneity, it remained high. This may be due to the region or the number of people studied. Second, because of the small number of included studies, publication bias was not tested. Third, the included studies have different diagnostic criteria for GERD and psychosocial disorders, which can lead to bias. Fourth, the present study focused on GERD and psychosocial disorders. Additional studies are needed to analyze the relationships between RE, NERD, and psychosocial stress based on the classification of GERD.

In conclusion, the results of our meta-analysis showed a significant positive association between psychosocial disorders and GERD. GERD patients are more likely to develop psychosocial disorders than healthy people; at the same time, psychosocial disorders can also increase the risk of GERD. There was a positive interaction between the 2 variables. Therefore, we suggest that gastroenterologists and psychologists should pay attention to assess whether patients have both GERD and psychosocial disorders. If the 2 coexist, treatment should be considered at the same time in order to achieve a better outcome.

Supplementary Materials

Note: To access the supplementary tables and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at <http://www.jnmjournal.org/>, and at <https://doi.org/10.5056/jnm21044>.

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Conflicts of interest: None.

Author contributions: Guang Bai conceived the research design and obtained the funding; Meijun He and Qun Wang collected the data; Meijun He drafted the manuscript; Da Yao, Qun Wang, and Jing Li analyzed and interpreted the data; and Jing Li revised the paper for important content. All authors approved the final paper.

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