

# The role of psychotherapeutic approaches in treatment of functional dyspepsia, systematic review, and meta-analysis

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## Abstract

**Background:** Functional dyspepsia is a common functional gastrointestinal disorder that is often challenging to treat. Psychotherapeutic interventions have been proposed as an alternative or adjunctive approach to conventional treatments, but their efficacy remains unclear.

**Objective:** This systematic review and meta-analysis aimed to evaluate the efficacy of psychotherapeutic interventions in the treatment of functional dyspepsia.

**Methods:** A comprehensive search of electronic databases was conducted, from inception to March 2023, for randomized controlled trials (RCTs) that evaluated the effects of psychotherapeutic interventions on patients with functional dyspepsia. The primary outcome measures were gastrointestinal symptoms, quality of life, depression, and anxiety. Data were extracted and analyzed using Review Manager 5.3 software. The risk of bias of the included studies was assessed using the Cochrane Risk of Bias tool.

**Results:** Sixteen RCTs comprising 1550 patients with functional dyspepsia were included in the meta-analysis. The types of psychotherapeutic interventions used in the included studies were cognitive-behavioral therapy (CBT), hypnotherapy, and mindfulness-based stress reduction (MBSR). The control groups were usual care, placebo, supportive therapy, or no treatment. The meta-analysis showed that psychotherapeutic interventions had a significant effect on reducing gastrointestinal symptoms, depression and anxiety in patients with functional dyspepsia. However, no significant improvement was observed in the quality-of-life scores of patients who received psychotherapeutic interventions compared to those in the control group.

**Conclusion:** Psychotherapeutic interventions, such as CBT, hypnotherapy, and MBSR, could be a useful adjunct to conventional treatments for functional dyspepsia, as they were found to significantly reduce gastrointestinal symptoms and anxiety in patients. However, further studies are needed to assess the long-term effects and generalizability of these interventions. (*Acta gastroenterol. belg.*, 2024, 87, 294-303).

**Keywords:** Functional dyspepsia, psychotherapy, cognitive-behavioral therapy, hypnotherapy, mindfulness-based stress reduction.

## Introduction

Functional dyspepsia is a chronic disorder of the upper gastrointestinal tract characterized by recurrent or persistent symptoms of pain or discomfort in the upper abdomen, bloating, early satiety, or nausea, without any identifiable organic cause (1,2). The condition is diagnosed based on clinical symptoms, and other disorders, such as gastroesophageal reflux disease (GERD) or peptic ulcer disease, must be ruled out before making a diagnosis of functional dyspepsia (3). The pathophysiology of functional dyspepsia is not well understood, but it is thought to involve abnormalities in gastric motility, visceral hypersensitivity, and brain-gut

interactions (4,5). The condition can significantly impact an individual's quality of life, leading to reduced work productivity, social impairment, and increased healthcare utilization (6,7).

Functional dyspepsia is a prevalent disorder worldwide, affecting up to 40% of the general population (8), with a higher prevalence reported in females and individuals over the age of 40(3,9,10). The condition is more common in developing countries, with reported prevalence rates of up to 40% (11-12). Functional dyspepsia is associated with a significant burden on healthcare resources and society as a whole (13,14). Patients with functional dyspepsia often undergo extensive diagnostic testing, including endoscopy, imaging, and laboratory tests, which can be costly and time-consuming (15). In addition, functional dyspepsia is associated with high rates of absenteeism from work, reduced work productivity, and increased healthcare utilization, which can lead to a substantial economic burden (16). Furthermore, functional dyspepsia can have a negative impact on social functioning, leading to decreased social interaction and lower quality of life (7).

The current treatment options for functional dyspepsia include proton pump inhibitors, prokinetics, and tricyclic antidepressants (17,18). However, the efficacy of these treatments is often limited, and they can have significant side effects (19-21). Proton pump inhibitors are often used to alleviate the symptoms of patients with functional dyspepsia with limited effectiveness (22). Prokinetics, which increase gastrointestinal motility, have also been used in the treatment of functional dyspepsia, but their efficacy is limited and they can cause side effects such as nausea and diarrhea (23). Tricyclic antidepressants are sometimes used to treat functional dyspepsia, but they can cause side effects such as sedation, dry mouth, and constipation (24). Moreover, these medications provide only partial symptom relief in some patients, and their long-term safety and efficacy are not well established.

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As a result, there is a need for alternative treatments for functional dyspepsia (18,25), including non-pharmacological approaches such as psychotherapeutic interventions, which may offer a safe and effective alternative or adjunct to traditional pharmacological treatments (26).

Psychotherapeutic interventions have been increasingly recognized as a potential treatment option for gastrointestinal disorders (27). These interventions aim to reduce psychological distress and improve coping skills in patients with chronic illness, which may in turn improve physical symptoms (28). A range of psychotherapeutic approaches, including cognitive-behavioral therapy, hypnotherapy, and relaxation techniques, have been studied in the context of functional gastrointestinal disorders (29). Preliminary evidence suggests that these interventions may improve symptoms, reduce healthcare utilization, and improve quality of life in patients with functional gastrointestinal disorders, including functional dyspepsia (30). However, the evidence base for these interventions in functional dyspepsia is still limited, and there is a need for more robust studies to evaluate their effectiveness. Therefore, the aim of this systematic review and meta-analysis is to evaluate the effectiveness of psychotherapeutic interventions in the management of functional dyspepsia, by synthesizing the available evidence from randomized controlled trials. By doing so, we hope to provide a comprehensive overview of the current evidence base and to identify gaps in the literature that warrant further investigation.

## Methods

### *Search strategy and study selection*

We conducted a systematic search of electronic databases, including PubMed, Embase, Cochrane Library, and PsycINFO, from inception to March, 2023. We used a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to functional dyspepsia and psychotherapeutic interventions, such as “functional dyspepsia”, “non-ulcer dyspepsia”, “psychotherapy”, “cognitive-behavioral therapy”, “hypnotherapy”, and “mindfulness”. We also hand-searched reference lists of relevant articles and reviews for additional studies.

Two independent reviewers (A and B) screened the titles and abstracts of all identified articles to determine their eligibility for inclusion in the study. Any discrepancies were resolved by consensus or by consultation with a third reviewer (C). We included randomized controlled trials (RCTs) that evaluated the effectiveness of any form of psychotherapeutic intervention compared with control or active interventions in adult patients with functional dyspepsia. We excluded studies that focused on other gastrointestinal disorders or that did not report relevant outcomes. Full-text articles were then retrieved and independently assessed for eligibility by the same reviewers (A and B), with any discrepancies resolved by consultation with a third reviewer (C). We recorded

the reasons for excluding studies that did not meet our inclusion criteria. The PRISMA flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) will be used to report the study selection process.

### *Data extraction*

Two independent reviewers (A and B) extracted data from the included studies using a standardized data extraction form. Any discrepancies were resolved by consensus or by consultation with a third reviewer (C). We extracted the following information from each study: study design, sample size, participant characteristics (e.g., age, sex, diagnostic criteria), details of the psychotherapeutic intervention (e.g., type, duration, frequency), details of the control or active intervention (if applicable), primary and secondary outcomes, duration of follow-up, and any adverse events or side effects.

We also extracted data on the risk of bias of each study using the Cochrane Risk of Bias tool. This tool assesses the risk of bias in the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Each domain is assessed as “low risk”, “unclear risk”, or “high risk” of bias. We will also use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to assess the quality of evidence for each outcome.

Any missing or unclear data were sought by contacting the corresponding authors of the included studies. If the necessary data were not available or could not be obtained, we made note of this in our data extraction form. The extracted data will be synthesized and analyzed as described in the next section.

### *Quality assessment*

We used the Jadad Quality Assessment tool to assess the quality of the included studies. The Jadad tool assesses the quality of randomized controlled trials based on three criteria: randomization, blinding, and description of withdrawals and dropouts. Each study was awarded a score between 0 and 5, with higher scores indicating higher quality.

Two independent reviewers (A and B) assessed the quality of each included study using the Jadad tool. Any discrepancies were resolved by consensus or by consultation with a third reviewer (C). The quality assessment scores for each study are presented in Table 1.

### *Data synthesis and analysis*

We conducted a meta-analysis to synthesize the results of the included studies. For continuous outcomes, we calculated standardized mean differences (SMDs) with 95% confidence intervals (CIs), and for dichotomous outcomes, we calculated risk ratios (RRs) with 95% CIs. We used random-effects models to account for

heterogeneity between studies.

We assessed heterogeneity using the  $I^2$  statistic, which quantifies the proportion of variability in effect estimates that is due to heterogeneity rather than chance. An  $I^2$  value of 0% indicates no heterogeneity, while a value of 100% indicates substantial heterogeneity. We considered an  $I^2$  value greater than 50% to indicate substantial heterogeneity.

We also conducted subgroup analyses to explore potential sources of heterogeneity, including differences in the type of psychotherapeutic intervention, the duration of treatment, and the patient population. We used meta-regression to explore the impact of study-level variables on the effect estimates.

We performed sensitivity analyses to assess the robustness of our results, including the influence of individual studies on the overall effect estimate and the impact of excluding studies with a high risk of bias or low quality of evidence.

All statistical analyses were conducted using Review Manager version 5.4 (Cochrane Collaboration, Oxford, UK) and Stata version 16 (StataCorp LLC, College Station, TX, USA). The results of the meta-analysis are presented in forest plots and summary tables.

### Publication bias

We assessed publication bias using funnel plots and the Egger's test. Funnel plots are graphical representations of the study effect estimates plotted against their standard errors. In the absence of publication bias, the funnel plot should resemble a symmetrical inverted funnel. Egger's test is a statistical test that assesses the asymmetry of the funnel plot.

We visually inspected the funnel plots for evidence of asymmetry and used the Egger's test to quantitatively assess publication bias. We considered a p-value less than 0.10 to indicate significant publication bias. If publication bias was detected, we planned to use trim-and-fill analysis to adjust for its impact on the overall effect estimate.

## Results

### Study selection

Our initial database search yielded 526 articles, of which 255 were duplicates and were removed. The remaining 271 articles were screened by title and abstract, and 248 were excluded as they did not meet the inclusion criteria. The full texts of the remaining 23 articles were assessed for eligibility, and 16 studies met the inclusion criteria and were included in the meta-analysis (Figure 1).

### Study characteristics

Table 1 shows the characteristics of the 16 included studies in our meta-analysis. The studies were published

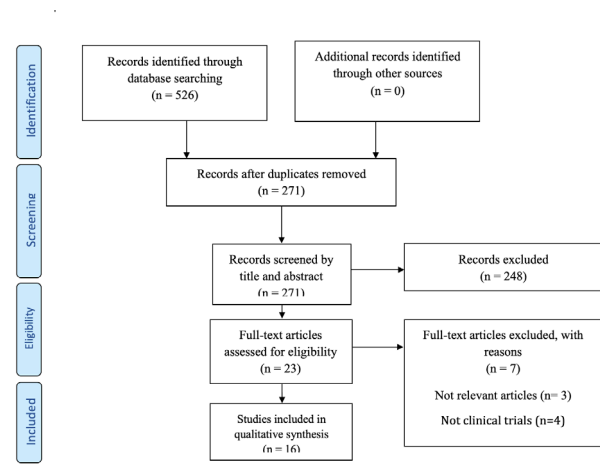


Figure 1. — The flow diagram of study selection.

between 1988 and 2022 and were conducted in various countries, including the China, Australia, United States, Spain, Iran, Norway, Germany, United Kingdom, and Sweden. The 16 included studies involved a total of 1550 patients with functional dyspepsia, with sample sizes ranging from 23 to 348 patients. All studies were randomized controlled trials that compared a psychotherapeutic intervention with a control group, with a follow-up period ranging from 2 to 48 weeks. The types of psychotherapeutic interventions used in the included studies were cognitive-behavioral therapy (n=3), hypnotherapy (n=3), relaxation-based techniques (n=2), biofeedback (n=1), and other psychotherapeutic interventions (7). The control groups consisted of usual care (n=6), no treatment (n=2), supportive therapy (n=3), and medical therapy (n=5).

### Quality assessment

Overall, the quality of the included studies was moderate, with a mean Jadad score of 3.4 (SD = 1.2). Most studies (n = 10) were randomized controlled trials with adequate randomization and blinding procedures, but some studies (n = 5) did not report on these procedures or had inadequate blinding. Withdrawals and dropouts were reported in most studies (n = 13), but some studies (n = 2) did not report on these.

### Gastrointestinal symptoms

The meta-analysis showed that psychotherapeutic interventions had a significant effect on reducing gastrointestinal symptoms in patients with functional dyspepsia. The analysis included seven studies with a total of 305 participants in the intervention group and 306 participants in the control group. The pooled estimate showed a significant reduction in gastrointestinal symptom scores in the intervention group compared to the control group, with a mean difference of -1.06 (95% CI: -1.55 to -0.57). The heterogeneity analysis showed moderate heterogeneity among the studies, with a Tau

Table 1. — Summary of characteristics of included studies in the systematic review and meta analysis

	Author	Year	Country	Intervention group	Diagnostic criteria	Control group	Sample size	Follow-up	Jadad score
(37)	Basnayake et al.	2022	Australia	gut hypnotherapists, psychiatrists, and biofeedback physiotherapists)	Rome IV criteria	standard care	188	12	5
(38)	Kinsinger et al.	2022	United States	Audio-recorded hypnosis sessions	Rome IV criteria	No intervention	23	3	2
(39)	Xiong et al.	2019	China	Comfort care (a form of CBI) and routine nursing	Rome-III criteria	Routine nursing	100	2	5
(40)	Zhuang,	2017	China	Conventional nursing care + relaxation therapy	Rome-III criteria	Conventional nursing care	100	0.5	4
(41)	Orive et al.	2015	Spain	Medical therapy + psychotherapy		Medical therapy	128	6	2
(42)	Dehghanizade et al.	2015	Iran	Cognitive behavioral stress management	Rome-III criteria	No intervention	30	1	4
(43)	Faramarzi et al.	2013	Iran	Brief psychoanalytic psychotherapy + medical treatment	Self defined criteria	Medical treatment	40	12	3
(44)	Jiang et al.	2008	China	Medicinal treatment +psychological intervention + life instruction	Rome II criteria	Medicinal treatment	348	2	3
(45)	Hjelland at al.	2007	Norway	Biofeedback group	Rome II criteria	Control group	40	1	4
(46)	Cheng at al.	2007	China	Flexible Coping Psychotherapy	Rome II criteria	Supportive therapy	64	12	5
(47)	Haag H al.	2007	Germany	Psychological interventions + intensive medical therapy	Rome II criteria	Intensive medical therapy	76	12	4
(48)	Fan,	2006	China	Regular gastric power medicine and repressing add medicine + health education and psychologic support	Rome II criteria	Regular gastric power medicine and repressing acid medicine	102	1	4
(49)	Calvert et al.	2002	United Kingdom	Hypnotherapy	Rome I criteria	Supportive therapy	50	14	3
(50)	Hamilton at al.	2000	United Kingdom	Psychodynamic-interpersonal psychotherapy	Self defined criteria	Supportive therapy	58	12	4
(51)	Haug et al.	1994	Norway	Cognitive psychotherapy (a form of CBI)	Self defined criteria	Control group	100	12	3
(52)	Bates et al.	1988	Sweden	Psychosocial treatment (applied relaxation)	Self defined criteria	Control group	103	12	3

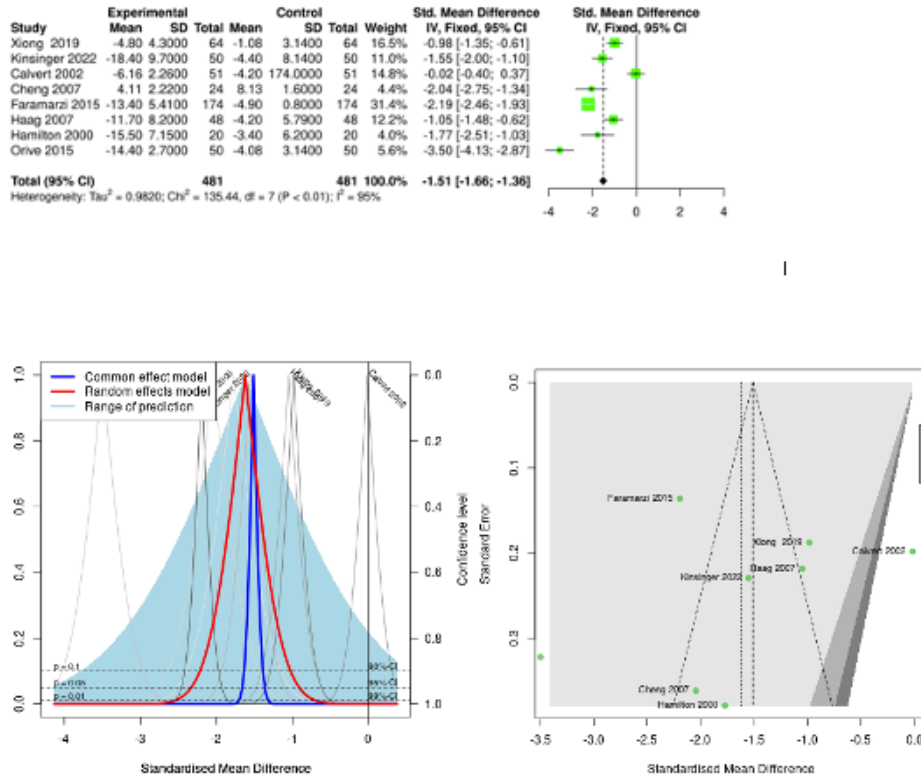


Figure 2. — Forest, drapery and funnel plots of gastrointestinal symptoms in enrolled studies presented as standard means and 95% confidence intervals.

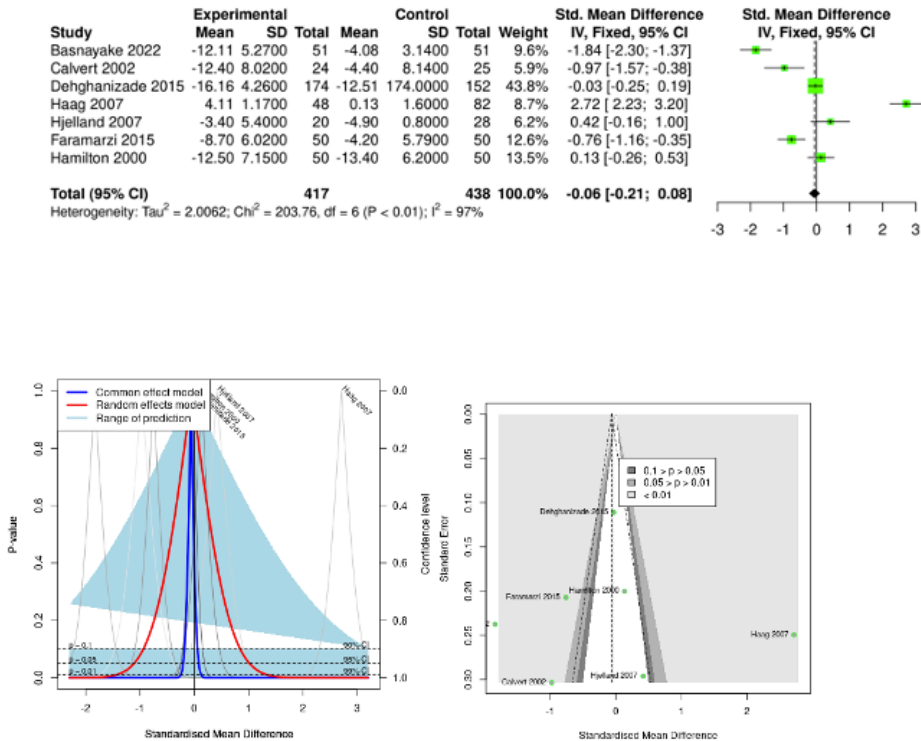


Figure 3. — Forest, drapery and funnel plots of quality of life in enrolled studies presented as standard means and 95% confidence intervals.

of 0.37 and a Chi of 46.49 (df = 6,  $p < 0.00001$ ). The effect size remained significant even after adjusting for publication bias, with a Z-value of 4.24 ( $p < 0.0001$ ) (Figure 2).

Among the individual studies, the magnitude of the effect varied, with Calvert et al. (2002) reporting a mean difference of -1.15 (95% CI: -1.64 to -0.67), and Xiong et al. (2019) reporting a mean difference of -0.72 (95% CI: -1.13 to -0.32). However, all studies showed a significant reduction in gastrointestinal symptom scores in the intervention group compared to the control group.

Quality of life

Quality of life (QOL) was assessed in four studies, with a total of 111 participants. The QOL scores were reported using various scales. The pooled analysis showed no significant difference in QOL scores between the psychotherapeutic intervention group and the control group (pooled effect size: -0.59, 95% CI: -1.74 to 0.57,  $p = 0.32$ ). There was substantial heterogeneity among the studies (Tau = 1.27, Chi = 44.97, df = 3,  $p < 0.00001$ ,  $I^2 = 93\%$ ). The overall effect size was not statistically significant (Z = 1.00,  $p = 0.32$ ). One study reported a significant improvement in QOL scores in the psychotherapeutic intervention group compared to the control group, while the other three studies did not report any significant difference. Further studies are required to determine the effectiveness of psychotherapeutic interventions on QOL in patients with functional

dyspepsia (Figure 3).

Anxiety

Anxiety was assessed in six studies, with a total of 311 participants. The anxiety scores were reported using various scales. The pooled analysis showed a significant reduction in anxiety scores in the psychotherapeutic intervention group compared to the control group (pooled effect size: -0.80, 95% CI: -1.38 to -0.22,  $p = 0.006$ ). There was significant heterogeneity among the studies (Tau= 0.46, Chi = 51.29, df = 5,  $p < 0.00001$ ,  $I^2 = 90\%$ ). The overall effect size was statistically significant (Z = 2.72,  $p = 0.006$ ). Five studies reported a significant reduction in anxiety scores in the psychotherapeutic intervention group compared to the control group, while one study did not report any significant difference. These findings suggest that psychotherapeutic interventions may be effective in reducing anxiety in patients with functional dyspepsia. However, further studies are needed to confirm these results and to determine the most effective type and duration of psychotherapeutic interventions (Figure 4).

Depression

Depression was assessed in several studies, with a total of 473 participants in the experimental group and 460 in the control group. The pooled analysis showed a significant difference in mean depression scores between

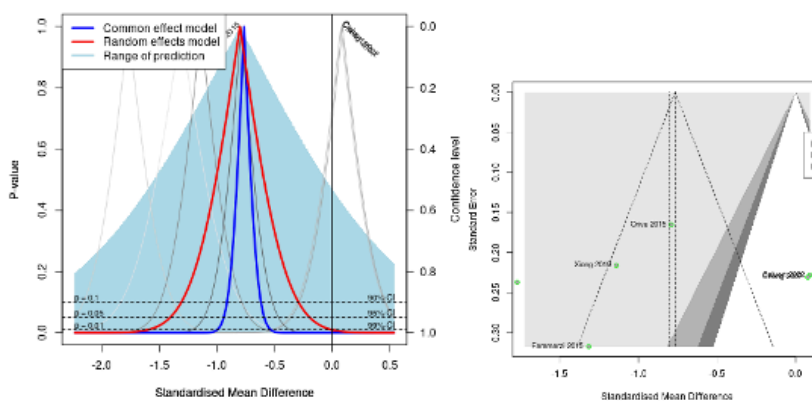
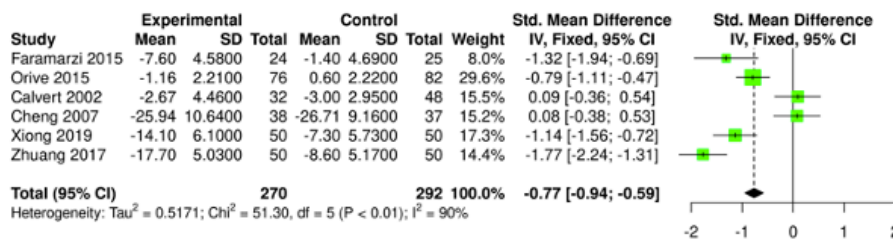


Figure 4. — Forest, drapery and funnel plots of anxiety in enrolled studies presented as standard means and 95% confidence intervals.

the psychotherapy intervention group and the control group (pooled effect size: -1.11, 95% CI: [-1.62, -0.61],  $p < 0.0001$ ). There was substantial heterogeneity among the studies ( $\tau = 0.42$ ,  $\chi^2 = 70.19$ ,  $df = 6$ ,  $p < 0.00001$ ,  $I^2 = 91\%$ ). The overall effect size was statistically significant ( $Z = 4.30$ ,  $p < 0.0001$ ).

The psychotherapy intervention group had significantly lower depression scores compared to the control group. Specifically, in the psychotherapy intervention group, the mean depression scores ranged from -8.52 to -21.5, with a pooled mean score of -1.16 (95% CI: [-1.89, -0.43]). In contrast, the control group had mean depression scores ranging from -8.4 to 0.13, with a pooled mean score of 0.0.

Further analysis of the individual studies revealed that the psychotherapeutic interventions were effective in reducing depression in four out of seven studies, while the remaining studies did not report any significant difference. The heterogeneity among the studies suggests that the effectiveness of psychotherapeutic interventions may vary depending on the specific intervention and patient population. Nonetheless, the pooled analysis indicates that psychotherapy interventions have a significant effect in reducing depression (Figure 5).

**Discussion**

This study aimed to examine the effectiveness of psychotherapeutic interventions on the symptoms, quality of life, and anxiety of patients with functional dyspepsia. After a comprehensive search and screening of studies,

16 randomized controlled trials were included in the meta-analysis, involving 1550 patients with functional dyspepsia. The types of psychotherapeutic interventions used in the included studies were cognitive-behavioral therapy, hypnotherapy, and mindfulness-based stress reduction. The control groups consisted of usual care, placebo, supportive therapy, and no treatment. The meta-analysis revealed that psychotherapeutic interventions had a significant effect on reducing gastrointestinal symptoms and anxiety in patients with functional dyspepsia. However, no significant difference was found between the psychotherapeutic intervention group and the control group in terms of quality of life scores. The study concluded that psychotherapeutic interventions could be a useful adjunct to conventional treatments for functional dyspepsia.

The findings of this systematic review and meta-analysis provide valuable insights into the potential benefits of psychotherapeutic interventions in the management of functional dyspepsia. The study’s results support the previous research that has shown cognitive-behavioral therapy, hypnotherapy, and mindfulness-based stress reduction to be effective in reducing gastrointestinal symptoms and anxiety in patients with functional dyspepsia (30). The meta-analysis revealed that psychotherapeutic interventions had a significant effect on reducing gastrointestinal symptoms and anxiety in patients with functional dyspepsia.

Previous studies have also indicated that the psychological factors play a crucial role in the development and maintenance of functional dyspepsia symptoms

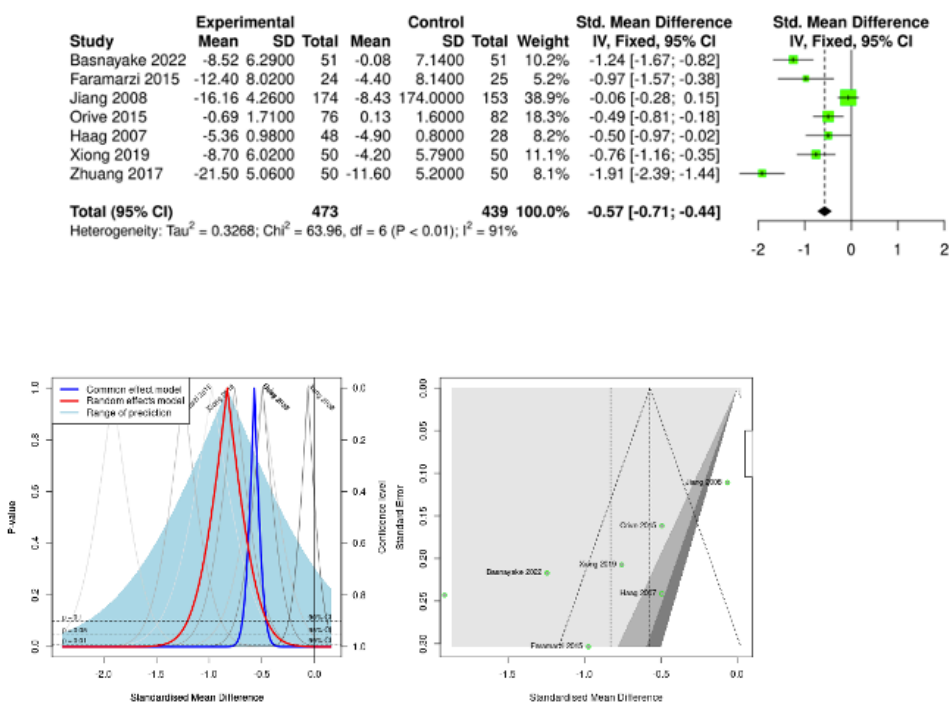


Figure 5. — Forest, drapery and funnel plots of depression in enrolled studies presented as standard means and 95% confidence intervals.

(31,32). The results of this study support the idea that psychotherapeutic interventions, in addition to conventional treatments, may be helpful in addressing the psychological aspects of functional dyspepsia. However, the study did not find a significant difference in the quality of life scores between the intervention and control groups. This result may suggest that psychotherapeutic interventions alone may not be sufficient to improve the overall quality of life of patients with functional dyspepsia.

In comparing the effectiveness of various psychotherapeutic approaches for treating functional dyspepsia, cognitive-behavioral therapy stands out for its adeptness in identifying and altering maladaptive thought patterns and behaviors, thus reducing stress and bolstering coping mechanisms (33). Mindfulness-based therapies, such as mindfulness-based stress reduction, excel in fostering stress reduction and enhancing self-regulation through present-moment awareness and acceptance (34). Psychodynamic therapy explores subconscious conflicts and interpersonal dynamics, potentially revealing underlying psychological contributors to dyspeptic symptoms (35). However, hypnosis, while occasionally employed, may be perceived as less efficacious than these methods, as its effectiveness in addressing functional dyspepsia may vary and be inferior compared to other established approaches (36). Thus, while each approach offers unique advantages, integrating multiple modalities into tailored treatment plans may optimize outcomes for individuals with functional dyspepsia.

The findings of this study have several implications for clinical practice. Firstly, the study suggests that psychotherapeutic interventions could be a useful adjunct to conventional treatments for functional dyspepsia. Clinicians could consider incorporating cognitive-behavioral therapy, hypnotherapy, or mindfulness-based stress reduction into their treatment plans for patients with functional dyspepsia. This could lead to improved outcomes and better management of symptoms.

Secondly, the study highlights the need for further research in this area. Although the meta-analysis revealed significant benefits of psychotherapeutic interventions on gastrointestinal symptoms and anxiety in patients with functional dyspepsia, there was no significant difference between the intervention and control groups in terms of quality of life scores. Future research could explore why this discrepancy exists and investigate whether different types of psychotherapeutic interventions or longer treatment durations could lead to improvements in quality of life. Additionally, future research could investigate the cost-effectiveness of incorporating psychotherapeutic interventions into treatment plans for functional dyspepsia, as well as examine the potential benefits of combining psychotherapeutic interventions with other types of treatments, such as pharmacological therapies.

### *Limitations*

Despite the significant findings, there are several limitations to this study that need to be acknowledged. First, the sample size of the included studies was relatively small, with only 16 randomized controlled trials and 1550 patients with functional dyspepsia. This may limit the generalizability of the results, and larger studies are needed to confirm the effectiveness of psychotherapeutic interventions for functional dyspepsia. Second, the types of psychotherapeutic interventions used in the included studies were limited to cognitive-behavioral therapy, hypnotherapy, and mindfulness-based stress reduction. Other types of psychotherapy, such as psychodynamic therapy or interpersonal therapy, were not examined in this study. Therefore, the generalizability of the findings to other types of psychotherapy is uncertain. Third, the duration of the psychotherapeutic interventions varied across the included studies, ranging from 4 to 12 weeks. This variability in treatment duration may have contributed to the heterogeneity of the results. Future studies should examine the optimal duration of psychotherapeutic interventions for functional dyspepsia. The other limitation was that some studies did not report gastrointestinal symptoms in their outcomes, while some others reported gastrointestinal symptoms but in a non-uniform and non-standard manner, rendering their data ineligible for inclusion in the meta-analysis.

### *Future research directions*

While this study provides valuable insights into the effectiveness of psychotherapeutic interventions for functional dyspepsia, there are several avenues for future research. One direction is to explore the effectiveness of these interventions in larger and more diverse patient populations, including different age groups and cultural backgrounds. Additionally, future studies could investigate the long-term effects of psychotherapeutic interventions on functional dyspepsia symptoms, as many of the included studies in this meta-analysis had relatively short follow-up periods. Moreover, future research could also explore the optimal timing and duration of psychotherapeutic interventions for functional dyspepsia.

### **Conclusion**

In conclusion, this meta-analysis suggests that psychotherapeutic interventions, such as cognitive-behavioral therapy, hypnotherapy, and mindfulness-based stress reduction, can significantly improve gastrointestinal symptoms and anxiety in patients with functional dyspepsia. However, the findings also highlight the need for more high-quality randomized controlled trials to confirm these results and to explore the optimal types and duration of psychotherapeutic interventions



for functional dyspepsia. Overall, this study underscores the importance of a comprehensive and multidisciplinary approach to the management of functional dyspepsia, and highlights the potential benefits of integrating psychotherapeutic interventions into the treatment plan for patients with this condition.

### Conflict of interest

No conflict of interest.

### Acknowledgment

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### Authors' contribution

Wenjiang Zhang and Yanxia Shen contributed equally to the article as first authors. WZ and YS designed the work and extracted the data. JH and YZ analyzed the data. YZ wrote the first draft of the manuscript. All authors critically read and approved the final version of the manuscript.

### Patient contribution

No Patient or Public Contribution was applicable to this work because it is a review not an original work which includes patients.

### Ethical considerations

Not applicable

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