Acupuncture for emotional symptoms in patients with functional gastrointestinal disorders: A systematic review and meta-analysis

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Abstract

Background
Patients with functional gastrointestinal disorders (FGIDs) also often have emotional symptoms, such as anxiety and depression. The main drugs used for the treatment of FGIDs mainly target single gastrointestinal symptoms and are not effective in regulating emotional symptoms. Evidence has shown that acupuncture can relieve gastrointestinal symptoms in FGIDs patients, but there is no high-quality evidence to show that acupuncture can relieve psychological symptoms in these patients.

Objectives
To systematically evaluate the clinical efficacy and safety of acupuncture for emotional symptoms in patients with FGIDs.

Methods
Randomized controlled trials (RCTs) published from database inception through July 31, 2021, were retrieved from three English-language databases (PubMed, the Cochrane Central Register of Controlled Trials, and Embase) and five Chinese-language databases (the China National Knowledge Infrastructure, Wanfang, VIP, Chinese Biomedical, and TCM Literature Analysis and Retrieval databases). RCTs that compared acupuncture with sham acupuncture and pharmacotherapy were included in this study. The score on the depression or anxiety scale after treatment were considered as primary outcomes. The 'meta' package (version 4.19–0) in RStudio 1.1.463 was used to analyse the data.

Results
A total of 2151 patients from 24 RCTs were included in this study. Compared with sham acupuncture, acupuncture was not significantly better at relieving anxiety (standardized mean
difference [SMD] -0.35, 95% CI -1.05 to 0.33) and depression (SMD -0.32, 95% CI -0.71 to 0.07) symptoms. Compared with pharmacotherapy, acupuncture was significantly better at relieving anxiety (SMD -0.64, 95% CI -0.93 to -0.35) and depression (SMD -0.46, 95% CI -0.69 to -0.22) symptoms.

Conclusions
This meta-analysis found that acupuncture can alleviate emotional symptoms in FGID patients better than pharmacotherapy. However, it is not clear whether this effect is based on the placebo effect, specific effect or nonspecific effect of acupuncture. The evidence should be proven by rigorously designed RCTs in the future.

PROSPERO registration number
CRD42021271899.

1. Introduction
Functional gastrointestinal diseases (FGIDs), which are defined as gut-brain interaction disorders [1], are the most common types of gastrointestinal diseases [2]. In a large multinational study, researchers found that more than 40% of people worldwide have FGIDs [3]. FGIDs are characterized by morphological and physiological abnormalities, including dysmotility, visceral hypersensitivity, changes in mucosal and immune function, changes in the gut microbiota and processing-related changes in the central nervous system. Irritable bowel syndrome (IBS), functional dyspepsia (FD), functional constipation (FC) and functional diarrhoea (FDr) are the most common FGIDs and may affect quality of life and health care resource utilization. Patients with FGIDs also often have emotional symptoms, such as anxiety and depression. These symptoms often influence each other, leading to recurrence or aggravation of the disease. Therefore, it is important to pay attention to emotional symptoms in patients with FGIDs. The main drugs used for the treatment of FGIDs are kinetic agents, proton pump inhibitors, anticholinergics and antidiarrhoeal drugs. However, these drugs mainly target single gastrointestinal symptoms and are not effective at regulating emotional symptoms. Some studies have shown that antidepressants can be administered to FGID patients [4, 5], but their use is limited because of their adverse reactions.

Complementary and alternative medicine (CAM) is a unique group of medical practices and products, and a large number of patients who suffer from FGIDs turn to CAM to control their symptoms; many of these patients are happy with the therapeutic results [6]. Acupuncture is an important part of CAM and has been practised for thousands of years in China. Evidence has shown that acupuncture can relieve gastrointestinal symptoms of FGIDs [7] and emotional symptoms such as depression [8] and anxiety [9]. However, most studies that have analysed acupuncture for FGIDs focused on gastrointestinal symptoms rather than psychological symptoms. Several studies have shown that acupuncture may relieve gastrointestinal and psychological symptoms better than controls [10–12], but other studies have shown discordant results [13, 14]. Hence, in this study, we summarized evidence from randomized controlled trials (RCTs) and evaluated the effectiveness of acupuncture on relieving emotional symptoms in patients with FGIDs.
2. Methods

2.1 Criteria for considering studies for this review

We included RCTs with parallel groups and excluded conference abstracts, editorials, reviews and case reports or case series, as well as publications reporting duplicate data. All participants included in the study were adults diagnosed with FGIDs, such as FD, IBS, FC or FDr, according to the Rome criteria [1, 15]. The experimental group included patients treated with acupuncture, defined as needle insertion at an acupuncture point, including body acupuncture (manual/electro), ear acupuncture and scalp acupuncture. Studies including other types of acupoint stimulation without needle insertion, such as laser stimulation and transcutaneous electroacupuncture therapy, were excluded. The control group included patients who had been treated with sham acupuncture or medication. The included studies reported the results of validated screening scales for anxiety or depression, such as the self-rating anxiety scale (SAS), self-rating depression scale (SDS), Hamilton rating scale for anxiety (HAM-A), Hamilton rating scale for depression (HAM-D), patient health questionnaire-9 scale (PHQ-9) or generalized anxiety disorder-7 scale (GAD-7). Studies that reported total scores of depression and anxiety obtained through tools such as the hospital anxiety depression scale were excluded.

2.2 Search strategy and study selection

Studies included in the review were retrieved from three English-language (PubMed, the Cochrane Central Register of Controlled Trials, and Embase) and five Chinese-language databases (the China National Knowledge Infrastructure, Wanfang, VIP, Chinese Biomedical and TCM Literature Analysis and Retrieval databases); RCTs published from the time of database inception to July 31, 2021, were retrieved. The search procedure is shown in S1 Table in S1 File. In addition, we searched Google Scholar and the ChiCTR clinical trial registration platform and manually searched journal articles and conference proceedings in the library of Shandong University of Traditional Chinese Medicine.

Two investigators (JX and LW) independently screened the study titles and abstracts and full texts when necessary. A third reviewer (XZ) made the final decision when a disagreement occurred between the two initial investigators.

2.3 Data extraction and quality assessment

Two investigators (MS and XW) independently extracted the data using a predesigned form. The name of the author, year of publication, inclusion and exclusion criteria, number of patients, type of acupuncture, acupoints, treatment used in the control group and outcome measures were recorded. We used the GetData Graph Digitizer to extract numerical data from figures. Data that could not be extracted from the original publications were requested from the corresponding authors or searched for in other reviews. Two investigators (JX and LW) independently assessed the risk of bias using a revised tool to assess the risk of bias in randomized trials (RoB 2) [16], and the RCTs were classified as having 'low risk', 'some concerns' or 'high risk'. A third investigator (HY) resolved any disagreements.

2.4 Statistical analysis

We calculated risk ratio (RR) with 95% confidence intervals (CI) for dichotomous data and standardized mean difference (SMD) with 95% CI for continuous data. The primary outcome measure was the score on the depression or anxiety scale after treatment. The heterogeneity of the studies was evaluated using the \( \chi^2 \) test and \( I^2 \) statistic. Fixed-effect and random-effect
models were used for the meta-analyses. We used the estimates of the random-effects model when high heterogeneity ($I^2 \geq 50\%$ or $p < 0.1$) was present; otherwise, we used the fixed-effect model estimates. We preferred analysed the data based on the intention-to-treat sample. In addition, patients treated with acupuncture in some RCTs were divided into different groups according to acupuncture point. Since the acupoints used in each group were commonly used acupuncture points for the treatment of FGIDs, we combined the results of different acupuncture groups to obtain information representative of the real clinical efficacy. To explore possible clinical heterogeneity, we performed subgroup analyses by disease, type of acupuncture and whether acupoints for tranquilization were included. Sensitivity analysis was performed with the leave-1-out function to confirm the robustness of our results. Publication bias was assessed using contour-enhanced funnel plots and Egger’s test for outcomes when at least 10 trials were included. Quality of evidence was summarized with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach and is presented in ‘Summary of findings’ tables [17]. All the analyses in this review were conducted using the ‘meta’ package (version 4.19–0) [18] in R Studio 1.1.463.

3. Results
3.1 Study selection
A total of 954 reports were retrieved through database searching; 531 duplicate publications and 328 were excluded after title and abstract screening. After reviewing the full texts of the remaining studies, 25 reports from 24 studies that met the inclusion criteria were included in the systematic review or qualitative analysis (Fig 1).

3.2 Characteristics of the included RCTs
We analysed a total of 2151 patients from 24 RCTs [10–14, 19–38]. Two of the included RCTs were multicentre studies, and 22 were single-centre studies. The sample sizes of the studies ranged from 34 to 348, and the duration of treatment lasted 2–10 weeks. Regarding treatment groups, 17 studies used electroacupuncture, and 7 studies used manual acupuncture. Regarding control groups, 20 studies used pharmacotherapy, and 4 studies used sham acupuncture. There were two four-arm trials [22, 26] and two three-arm trials [13, 14, 37]. Seventeen studies reported SAS scores, 17 studies reported SDS scores, 4 studies mentioned HAM-A scores, 5 studies reported HAM-D scores, and 1 study reported PHQ-9 and GAD-7 scores. Detailed characteristics of the research are summarized in Table 1.

3.3 Risk of bias assessment
Based on the revised tool to assess the risk of bias in randomized trials (RoB 2) [16], the overall risk of bias in 3 studies was low, in 20 studies was of some concern and in 1 study was high. The randomization process, deviations from intended interventions and measurement of the outcome were the main causes of risk of bias. S1 and S2 Figs in S1 File summarize the quality evaluations of the included studies.

3.4 Acupuncture versus sham acupuncture
Four RCTs compared acupuncture with sham acupuncture, and all the sham acupuncture groups received minimal acupuncture (pierced the skin 2–3 mm) at nonacupoints.

3.4.1 Anxiety. The pooled results indicated that acupuncture was not significantly better at relieving anxiety symptoms than sham acupuncture ($SMD = -0.35, 95\% CI = -1.05$ to 0.33, $I^2 = 85\%$, Fig 2A). For better visualization, we also constructed a drapery plot [39] (S3 Fig in
The GRADE quality of the evidence was low (Table 2). Sensitivity analysis confirmed the robustness of the results (S4 Fig in S1 File). In addition, the subgroup analysis based on disease showed that acupuncture may be superior to sham acupuncture in relieving anxiety symptoms in patients with IBS (SMD -0.5, 95% CI -0.95 to -0.06), but there was no significant
| Studies | Disease                  | Sample Size | Mean Age±SD | Sex (Male/Female) | Experimental Group | Control Group     | Treatment duration | Outcome          |
|---------|--------------------------|-------------|-------------|-------------------|---------------------|--------------------|--------------------|-------------------|
|         |                          | E C E C     | E C         |                   | Acupoints           | Method of acupuncture |                   |                   |
| Yang2011| Functional dyspepsia     | 30 30       | 37.6±9.8    | 38.4±10.1         | 13/17               | Zusanli, Neiguan   | EA                 | Domperidone 2W SAS, SDS |
| Li2011  | Irritable bowel syndrome | 35 35       | 39.1±11.80  | 37.93±11.45       | 15/20               | Tianshu, Zusanli, Sanyinjiao, Taichong, Baihui, Yintang | EA                 | Pinaverium bromide 4W SAS, SDS |
| Chen2012| Irritable bowel syndrome | 30 34       | 40.5±8.75   | 41.9±10.01        | 11/19               | Baihui, Shenting, Neiguan, Shenmen, Zhongwan, Tianshu, Qihai, Sanyinjiao, Taichong | EA                 | Bacillus licheniformis + Flupentixol and Melitracen Tablets 4W HAMA, HAMD |
| Peng2013| Irritable bowel syndrome | 20 20       | 47.5±3.2    | 45.8±4.0          | 8/12                | Zusanli, Tianshu   | EA                 | Mosapride 4W SAS, SDS |
| Zhong2013| Functional constipation  | 170 62      | 43.85±17.79 | 41.97±18.07       | 13/49               | 1: Tianshu, Dachangshu | EA                 | Mosapride 4W SAS, SDS |
|         |                          |             |             |                   |                     | 2: Quchi, Shangjuxu |                    |                   |
|         |                          |             |             |                   |                     | 3: Tianshu, Dachangshu, Quchi, Shangjuxu |                    |                   |
| Wu2013  | Functional constipation  | 23 18       | 27.91±8.91  | 28.39±9.68        | 8/15                | Quchi, Shangjuxu   | EA                 | Mosapride 4W SAS, SDS |
| Xiong2014| Functional constipation  | 67 41       | NR          | NR                | NR                  | Quchi, Shangjuxu   | EA                 | Mosapride 4W SAS, SDS |
| Zheng2014| Irritable bowel syndrome| 261 87      | 41.25±16.99 | 42.29±18.3        | 52/34               | 1: Tianshu, Dachangshu | EA                 | Loperamide Hydrochloride 4W SAS, SDS |
|         |                          |             |             |                   |                     | 2: Quchi, Shangjuxu |                    |                   |
|         |                          |             |             |                   |                     | 3: Tianshu, Dachangshu, Quchi, Shangjuxu |                    |                   |
| Tian2014| Functional diarrhoea     | 37 16       | 39.77±15.44 | 39.27±16.88       | NR                  | Tianshu, Dachangshu | EA                 | Loperamide Hydrochloride 4W SAS, SDS |
| Da2014  | Functional constipation  | 18 16       | 51.22±22.84 | 38.38±19.61       | 4/14                | Tianshu, Fujie, Shangjuxu | EA                 | SA 8W SAS, SDS |
| Jin2015 | Functional dyspepsia     | 28 28       | 49.29±10.32 | 48.25±11.40       | 11/17               | Zusani, Taixi, Zulingqi, Neiguan, Shenmen | MA                 | SA 4W SAS, SDS |
| Yuan2015| Functional dyspepsia     | 31 32       | 44.21±21.12 | 39.21±25.12       | 13/18               | Gongsun, Neiguan   | MA                 | Domperidone 4W HAMA, HAMD |

(Continued)
| Studies   | Disease                  | Sample Size | Mean Age±SD | Sex (Male/Female) | Experimental Group | Control Group | Treatment duration | Outcome          |
|----------|--------------------------|-------------|-------------|-------------------|---------------------|---------------|--------------------|------------------|
|          |                          | E  | C  | E  | C  | Acupoints | Method of acupuncture |
| Lian2016 | Functional diarrhoea     | 32 | 30 | 33.85±12.55 | 31.60±11.56 | 14/18 | Tianshu, Dachangshu, Quchi, Shangjixu | EA | Loperamide Hydrochloride | 4W | SAS |
| Du2016   | Functional dyspepsia     | 48 | 47 | 44.89±10.12 | 43.28±12.05 | 13/35 | Shenchuan, Sishecang, Shenmen, Baihui, Zusanzii, Zhongwan, Neiguan | EA | Domperidone | 4W | HAMD |
| Ding2016 | Functional diarrhoea     | 48 | 19 | 43.19±17.08 | 41.37±16.74 | 28/17 | Tianshu, Dachangshu | 1: EA with strong stimulation | Loperamide Hydrochloride | 4W | SAS, SDS |
|          |                          |           |             |                   |                     |               | 2: EA with little stimulation |                 |
| Li2017   | Irritable bowel syndrome | 79 | 39 | 46.3±13.2  | 48.9±12.4  | 42/34 | Baihui, Yintang, Tianshu, Zusanzii, Shangjixu, Sanjinjiao, Taichong | MA | Pinaverium bromide | 6W | SAS, SDS |
| Nie2017  | Functional diarrhoea     | 53 | 53 | 46.4±10.8  | 46.1±10.6  | 29/24 | Tianshu, Shangjixu | MA | Loperamide Hydrochloride | 4W | SAS, SDS |
| Shen2018 | Functional dyspepsia     | 32 | 32 | 45.71±11.26 | 44.21±11.59 | 7/27  | Baihui, Yintang, Neiguan, Zhongwan, Tianshu, Qihai, Zusanzii, Sanjinjiao, Taichong | EA | Mosapride | 4W | HAMA, HAMD |
| Zhong2018| Irritable bowel syndrome | 60 | 30 | 31.12±12.74 | 30.22±13.99 | 35/25 | 1: Quchi, Shangjixu | EA | Loperamide Hydrochloride | 4W | SAS, SDS |
|          |                          |            |             |                   |                     |               | 2: Quchi, Shangjixu, Tianshu, Dachangshu |                 |
| Mak2019  | Irritable bowel syndrome | 40 | 40 | 50.85±11.57 | 50.83±14.15 | 20/20 | Neiguan, Shenmen, Zusanzii, Shangjixu, Sanjinjiao, Taichong, Baihui, Yintang | EA | SA | 10W | PHQ-9, GAD-7 |
| Meng2019 | Irritable bowel syndrome | 35 | 35 | 39.3±11.5  | 38.4±13.5  | 16/19 | Taichong, Zusanzii, Shangjixu, Sanjinjiao, Tianshu, Baihui, Yintang | MA | Pinaverium bromide | 4W | SDS |
| Chen2019 | Functional dyspepsia     | 35 | 35 | 40.97±11.70 | 43.59±12.4  | 11/22 | Zhongwan, Tianshu, Zusanzii, Neiguan, Baihui, Yintang | MA | SA | 4W | SAS, SDS |

(Continued)
relief of anxiety symptoms in patients with FD, FC or FDr (Fig 2A). The subgroup analyses based on acupoints and type of acupuncture showed that the inclusion of acupoints for tranquilization or the type of acupuncture did not explain the heterogeneity. It also showed that acupuncture was not more effective than sham acupuncture in reducing anxiety symptoms (S5 and S6 Figs in S1 File).

3.4.2 Depression. The pooled data showed that acupuncture was not significantly better at relieving depression symptoms than sham acupuncture (SMD -0.32, 95% CI −0.71 to 0.07, I² = 54%, Fig 2B), and we also constructed a drapery plot (S7 Fig in S1 File) to visualize the results. The GRADE quality of the evidence was moderate (Table 2). The sensitivity analyses showed that acupuncture reduced depression symptoms more than the control when the study Da2014 was omitted (SMD -0.44, 95% CI -0.84 to -0.03, S8 Fig in S1 File), but the effect was very small. Moreover, the subgroup analysis based on disease showed that acupuncture may not be superior in relieving depression symptoms in patients with IBS, FD, FC and FDr compared with sham acupuncture (Fig 2B). The subgroup analysis based on acupoints showed that acupuncture prescriptions include acupoints for tranquilization, may be more useful in relieving depression symptoms in patients with FGIDs than sham acupuncture (S9 Fig in S1 File). The subgroup analysis based on type of acupuncture showed that no matter electroacupuncture or manual acupuncture could relieve depression symptoms in patients with FGIDs to a greater degree than the control (S8 Fig in S1 File).

3.5 Acupuncture versus pharmacotherapy

3.5.1 Anxiety. The pooled results indicated that acupuncture was significantly better at relieving anxiety symptoms than pharmacotherapy (SMD -0.64, 95% CI -0.93 to -0.35, I² = 86%, Fig 3). A drapery plot was constructed to visualize the results (S11 Fig in S1 File). The GRADE quality of the evidence was low (Table 2). The sensitivity analyses confirmed the robustness of the results (S12 Fig in S1 File). Moreover, the subgroup analysis (Fig 3) showed that acupuncture was better than pharmacotherapy at relieving anxiety symptoms in patients with FD (SMD -1.47, 95% CI -2.46 to -0.48), IBS (SMD -0.64, 95% CI -1.17 to -0.11), FC (SMD -0.22, 95%CI -0.43 to -0.01) and FDr (SMD -0.53, 95% CI -0.78 to -0.29). The results of the other subgroup analyses showed that this effect was independent of the inclusion of tranquilization acupoints (S13 Fig in S1 File) and the type of acupuncture (S14 Fig in S1 File).
3.5.2 Depression. The analysis of pooled data indicated that acupuncture was significantly better at improving depression symptoms than pharmacotherapy (SMD -0.46, 95% CI -0.69 to -0.22, \( I^2 = 79\% \), Fig 4); we constructed a drapery plot to visualize the results (S15 Fig in S1 File). The overall quality of the evidence was low (Table 2). The sensitivity analyses confirmed the robustness of the results (S16 Fig in S1 File). In addition, the subgroup analysis (Fig 3)

### Table: Acupuncture versus Sham Acupuncture

| Study           | Disease = Functional constipation | Disease = Functional dyspepsia | Disease = Irritable bowel syndrome |
|-----------------|-----------------------------------|--------------------------------|-----------------------------------|
| Da2014          | 18/16                             | Jin2015/Chen2019                | Mak2019/119/118                   |
| Age range (yr)  | 40/79.60                          | 28/62.20/33                    | 40/3.98/3.2500                    |
| Mean (SD)       | 40.00/8.6200                      | 52.20/11.4000                  | 6.08/4.8800                      |
| Outcome         | 16/36.00                          | 38.47/8.5500                   | 119/118                          |
| Total Mean      | 18/16                             | Jin2015/Chen2019                | Mak2019/119/118                   |
| Standardised Mean Difference | 0.57 [-0.11; 1.26]   | -1.36 [-1.95; -0.78]           | -0.36 [-1.05; 0.33]              |
| SMD             | 0.57 [-0.11; 1.26]                | -0.73 [-1.96; 0.50]            | -0.36 [-1.05; 0.33]              |
| 95%-CI          | 23.0%                             | 24.5%                          | 100.0%                           |
| Weight          | 23.0%                             | 26.0%                          | 50.6%                            |

Fig 2. Forest plot of comparison: Acupuncture versus sham acupuncture, outcome: Severity of anxiety and depression at the end of treatment. A: anxiety, B: depression.

https://doi.org/10.1371/journal.pone.0263166.g002
showed that acupuncture was better than pharmacotherapy at relieving anxiety symptoms in patients with FD (SMD -1.13, 95% CI -1.82 to -0.44), IBS (SMD -0.33, 95% CI -0.64 to -0.02) and FDr (SMD -0.39, 95% CI -0.67 to -0.11), but not FC (SMD -0.11, 95% CI -0.32 to 0.10). The other subgroup analyses indicated that this effect had nothing to do with the inclusion of tranquilization acupoints (S17 Fig in S1 File) or acupuncture type (S18 Fig in S1 File).

### 3.6 Adverse events

Nine studies reported adverse events, and 4 of them reported 0 adverse events in all groups. No serious adverse events occurred in the 9 studies. Five studies compared acupuncture and pharmacotherapy and reported the number of adverse events. The pooled result indicated that there were no statistically significant differences between the groups (RR 0.56, 95%CI 0.26 to 1.19, Fig 5).
3.7 Publication bias

The contour-enhanced funnel plots (S19 Fig in S1 File) and Egger’s test (P = 0.004) for the effects of acupuncture versus pharmacotherapy on anxiety suggested possible publication bias. After adding 1 studies based on the Duval & Tweedie trim-and-fill method [40], the SMD was statistically significant both before and after trim-and-fill analysis. Moreover, the contour-enhanced funnel plots (S20 Fig in S1 File) and Egger’s test (P = 0.027) for the effects of acupuncture versus pharmacotherapy on depression showed potential publication bias. The trim-and-fill method was used to add 2 studies, and the SMD was statistically significant as before trim-and-fill analysis.

4. Discussion

This meta-analysis included 2151 patients from 24 RCTs. We compared acupuncture versus sham acupuncture and pharmacotherapy. The pooled results showed that acupuncture was relatively effective in relieving anxiety and depression symptoms in patients with...
Fig 4. Forest plot of comparison: Acupuncture versus pharmacotherapy, outcome: Severity of depression at the end of treatment.

https://doi.org/10.1371/journal.pone.0263166.g004

Fig 5. Forest plot of comparison: Acupuncture versus pharmacotherapy, outcome: Adverse events.

https://doi.org/10.1371/journal.pone.0263166.g005
FGIDs, but the current evidence does not explain whether this effect is a placebo effect. However, heterogeneity and high risk of bias reduced our level of certainty regarding this evidence.

FGIDs are currently defined as gut-brain interaction disorders, and the associated gastrointestinal symptoms may lead to emotional symptoms, such as anxiety and depression, which can aggravate gastrointestinal symptoms, resulting in a vicious cycle. Therefore, a treatment that can relieve both gastrointestinal symptoms and psychological symptoms in patients with FGIDs will be more beneficial in controlling such symptoms. Acupuncture has been used in China for thousands of years. In recent years, studies have found that acupuncture can be used to treat gastrointestinal diseases as well as emotional symptoms. However, the acupoints used in acupuncture for the treatment of different diseases are often quite different. For example, Tianshu, Zusanli, Quchi, Shangjuxu and other specific acupoints related to the stomach are often used in the treatment of gastrointestinal diseases. Baihui, Yintang, Shenmen and other acupoints for tranquillization are often used in the treatment of emotional symptoms. According to traditional acupuncture theory, it is believed that the functions of acupoints include distal treatment, near treatment and special treatment. Distal-treatment function means that acupoints can treat diseases where the meridians pass, near-treatment function means that acupoints can treat diseases where they are located, and special-treatment function means that some acupoints have a specific effect on some diseases. These effects are called specific effects in clinical practice. In addition, modern studies believe that acupuncture has nonspecific effects, including expectation effects, Hawthorne effects, Pygmalion effects and so on [41]. In the subgroup analysis, this study found that regardless of whether the acupuncture prescription included tranquillization acupoints, its efficacy in relieving psychological symptoms in patients with FGIDs was higher than that of conventional drug therapy, but the result was opposite when compared with sham acupuncture. This suggests that acupuncture to alleviate psychological symptoms in patients with FGIDs may be mostly due to its nonspecific effect, while the pseudoacupuncture method at nonacupoints has not only a placebo effect but also a nonspecific effect. These results can also be explained in terms of the mechanism. Acupuncture at Tianshu, Zusani, and Shangjuxu can regulate the balance of the gut microbiome [42–45], and gut microbiome dysbiosis is an important cause of depression and anxiety [46, 47]. Therefore, acupuncture can also alleviate psychological symptoms that rely on brain-gut axis interactions when the prescription does not include tranquillization acupoints. The mechanism by which acupuncture regulates the brain-gut axis to treat emotional symptoms is a current research hotspot. Compared with pharmacotherapy, acupuncture reduced anxiety and depressive symptoms in patients with FD, IBS and FDr and alleviated anxiety symptoms in patients with FC, but there was no significant difference in the scores for depression symptoms in patients with FC. Four RCTs were included in the FC subgroup analysis. All the RCTs used mosapride as the control; mosapride has antidepressant and antianxiety effects at routine clinical dosages [48]. This showed that acupuncture treatment for depression and anxiety symptoms in patients with FC was at least equivalent to mosapride. In addition, this study found that the type of acupuncture was not related to the effect of acupuncture in the treatment of emotional symptoms in FDIG patients, and both manual acupuncture and electroacupuncture can reduce their psychological symptoms to a greater degree than conventional drugs. In terms of adverse reactions, acupuncture and conventional drugs for the treatment of FGIDs were associated with few adverse reactions, and there was no significant difference between the two. Previous studies have also shown that acupuncture is associated with fewer adverse reactions than antidepressants [8].

To the best of our knowledge, this is the first systematic review of acupuncture treatment for emotional symptoms in FGIDs patients. Our results show that acupuncture is beneficial to...
the improvement of psychological symptoms in patients with FGIDs, and previous studies have shown that acupuncture has an advantage in improving gastrointestinal symptoms in patients with FGIDs [7]. Therefore, this study provides new evidence supporting acupuncture as an alternative intervention scheme for FGIDs.

However, this study has some limitations. First, 23 of the 24 included studies were from mainland China, and 1 study was from Hong Kong, China. Second, only 2 multicentre studies, with a total sample size of more than 200 people, were included; the others were single-centre, small-sample studies. Third, because of the particularity of acupuncture therapy, blinding of subjects and intervention implementers cannot be performed like it can in drug studies, but random sequence generation, distribution concealment, and blinding of outcome evaluators and statistical analysts is feasible. However, there are still deficiencies in the design of these trials, which may lead to bias toward low-quality research methods. Therefore, the conclusions of this study need to be further verified.

5. Conclusion
This meta-analysis found that acupuncture can alleviate emotional symptoms in FGID patients better than pharmacotherapy. However, it is not clear whether this effect is based on the placebo effect, specific effect or nonspecific effect of acupuncture. The evidence should be proven by rigorously designed RCTs in the future.

Supporting information
S1 File. Supplementary S1-S22 Figs and S1, S2 Tables.
(DOCX)

Acknowledgments
We would like to thank American Journal Experts (www.aje.com) for English language editing.

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Data curation: Jin Xian, Mi Sun, Xue Wang.
Formal analysis: Jin Xian, Xue Wang, Xiaoming Zang.
Funding acquisition: Jin Xian, Xin Zhang, Qi-Wen Tan.
Investigation: Huijuan Yu, Qi-Wen Tan.
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Writing – review & editing: Xin Zhang.
References

1. Drossman DA, Hasler WL. Rome IV—Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology. 2016; 150: 1257–1261. https://doi.org/10.1053/j.gastro.2016.03.035 PMID: 27147121

2. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. Gastroenterology. 2016; 150: 1262–1279.e2. https://doi.org/10.1053/j.gastro.2016.02.032 PMID: 27144617

3. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology. 2021; 160: 99–114.e3. https://doi.org/10.1053/j.gastro.2020.04.014 PMID: 32294476

4. Xie C, Tang Y, Wang Y, Yu T, Wang Y, Jiang L, et al. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. PLoS One. 2015; 10: e0127815. https://doi.org/10.1371/journal.pone.0127815 PMID: 26252008

5. Talley NJ, Locke GR, Saito YA, Almazar AE, Bouras EP, Howden CW, et al. Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: A Multicenter, Randomized Controlled Study. Gastroenterology. 2015; 149: 340–349.e2. https://doi.org/10.1053/j.gastro.2015.04.020 PMID: 25921377

6. Deutsch JK, Levitt J, Hass DJ. Complementary and Alternative Medicine for Functional Gastrointestinal Disorders. Am J Gastroenterol. 2015; 110: 350–364. https://doi.org/10.1038/aajg.0000000000000539

7. Wang X, Wang H, Guan Y, Cai R, Shen G. Acupuncture for functional gastrointestinal disorders: a systematic review and meta-analysis. Journal of Gastroenterology and Hepatology. n/a. https://doi.org/10.1111/jgh.15645 PMID: 34342044

8. Smith CA, Armour M, Lee MS, Wang L-Q, Hay PJ. Acupuncture for depression. Cochrane Common Mental Disorders Group, editor. Cochrane Database of Systematic Reviews. 2018 [cited 16 Jul 2021].

9. Li M, Xing X, Yao L, Li X, He W, Wang M, et al. Acupuncture for treatment of anxiety, an overview of systematic reviews. Complement Ther Med. 2019; 43: 247–252. https://doi.org/10.1016/j.ctim.2019.02.013 PMID: 30935538

10. Yuan Xingxing, Wang Bingyu, Yang Lei, Zhang Yali. Clinical Observation on Acupuncture at Gongsun and Neiguan Points for Functional Dyspepsia Patients with Psychological Factors. Journal of Clinical Acupuncture and Moxibustion. 2015; 31: 52–55.

11. Mak ADP, Chung VCH, Yuen SY, Tse YK, Wong SYS, Ju Y, et al. Noneffectiveness of electroacupuncture for comorbid generalized anxiety disorder and irritable bowel syndrome. J Gastroenterol Hepatol. 2019; 34: 1736–1742. https://doi.org/10.1111/jgh.14667 PMID: 30891824

12. Lian Songyong, Zhang Zheng, Tang Chunzhi, Li Yan, Tan Zhenyun. Therapeutic Effect of He-Mu-Shu Point Combination Acupuncture for Patients with Functional Diarrhea and Its Influence of Anxiety. Journal of Guangzhou University of Traditional Chinese Medicine. 2016; 33: 650–653.

13. Zhong Feng, Cao Yue, Luo Rong, Sheng Rongrong, Shi Wenying, Liu Yinghan, et al. Clinical Effect of Electroacupuncture at He-Mu Acupoint Combination in Treatment of DiarrheaPredominant Irritable Bowel Syndrome. Journal of Hunan University of Chinese Medicine. 2018; 38: 435–438.

14. Zhong Feng, Cao Yue, Luo Rong, Sheng Rongrong, Shi Wenying, Liu Yinghan, et al. Clinical Effect of Electroacupuncture at He-XiaHe Acupoint Combination in Treatment of DiarrheaPredominant Irritable Bowel Syndrome. Journal of Anhui University of Chinese Medicine. 2018; 37: 68–71.

15. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology. 2006; 130: 1377–1390. https://doi.org/10.1053/j.gastro.2006.03.008 PMID: 16678553

16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366: i4898. https://doi.org/10.1136/bmj.i4898 PMID: 31462531

17. Schünemann HU, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing ‘Summary of findings’ tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, 2019. pp. 375–402. https://doi.org/10.1002/9781119536604.ch14

18. Schwarzer G. meta: General Package for Meta-Analysis. 2021. https://CRAN.R-project.org/package=meta

19. Li Hao. A Clinical Observation on the effect of su gan jian Pi Acupuncture tretment of diarrhea-dremoninant irritable bowel syndrome. Nanjing University of Chine Medicine. 2011.

20. Jiayao Yang, Dongqing Tao, sullfeng Peng, zhaochong Shi, Wei Hu, Yufang Wu. Effect of electroacupuncture at acupoints on symptoms, mentation and quality of life in patients with functional dyspepsia. Chin J Gastroenterol Hepatol. 2011; 20: 268–271.
21. Chen Yaohua, Chen Xingkui, Yin Xiaojun, Shi Yin. Comparison of the Therapeutic Effects of Electroacupuncture and Probiotics Combined with Deanxit in Treating Diarrhea-Predominant Irritable Bowel Syndrome. Chinese Journal of Integrated Traditional and Western Medicine. 2012; 32: 594–598. PMID: 22679715

22. Zhong Feng. A Multi-center Clinical Randomized Controlled Trial of Acupuncture for Treating Functional Constipation. Chengdu University of TCM. 2013.

23. Wu Qiong, Zhang Zheng, Tang Chunzhi, Zhao Jie, Yu Juan, Lian Songyong, et al. Randomized - Controlled - Study of Acupuncture on Anxiety, Depression and Functional Constipation. Shanxi Journal of Traditional Chinese Medicine. 2013; 29: 29–30;32. https://doi.org/10.3969/j.issn.1000-7156.2013.03.019

24. Peng Suifeng, Yang Jiayao, Shi Tuo, Zhou Xiaoli, Shi Zhaohong. Clinical observation of Electroacupuncture on patients with constipation irritable bowel syndrome. Chinese Journal of Integrated Traditional and Western Medicine on Digestion. 2013; 21: 426–428.

25. Xiong Fan, Wang Ying, Li Shiqi, Tian Man, Zheng Cuihong, Huang Guangying. The Clinical Study of Electro-acupuncture Stimulation for Functional Constipation. Research of Integrated Traditional Chinese and Western Medicine. 2014; 6: 126–130.

26. Huabin Zheng. A Multi-center Clinical Randomized Controlled Trial of Acupuncture for Treating Irritable Bowel Syndrome-Diarrhea. Chengdu University of TCM. 2014.

27. Man Tian. A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Master of medicine. Huazhong University of Science & Technology. 2014.

28. Nili Da. The clinical research of relevance between functional constipation efficacy and psychological disorders treated with acupuncture. Nanjing University of Chinere Medicine. 2014.

29. Jin Y, Zhao Q, Zhou K, Jing X, Yu X, Fang J, et al. Acupuncture for functional dyspepsia: A single blinded, randomized, controlled trial. Evid-Based Complement Altern Med. 2015; 2015. https://doi.org/10.1155/2015/904926 PMID: 26294930

30. Ding Pei. The Clinical trial of Electroacupuncture to treat Functional diarrhea. Huazhong University of Science & Technology. 2016.

31. Du Ruo, Zhang Xinling, Wang Shiyou, Qian Hailiang. Observation of curative effect of Xiaoyao acupuncture on functional dyspepsia. Modern Journal of Integrated Traditional Chinese and Western Medicine. 2016; 25: 1375–1377.

32. Li Jing. Clinical Efficacy Evaluation of Acupuncture with Regulating Mind and Spleen for Diarrhea-dre- dominant Irritable Bowel Syndrome and its Brain Functional Changes in Rs-fMRI. Nanjing University of Chinere Medicine. 2017.

33. Nie Jingtao. Clinical efficacy comparison and safety analysis of combined raising and acupoint matching method and loperamide hydrochloride in the treatment of functional diarrhea. Modern Journal of Integrated Traditional Chinese and Western Medicine. 2017; 26: 192–194.

34. Shen Xuli. The Clinical Effect Observation Electroacupuncture on Postprandial Distress Syndrom with Anxiety and Depression. Shandong University of TCM. 2018.

35. Meng Guojuan. Acupuncture treatment for depressive symptom in diarrhea-predominant irritable bowel syndrome: a randomized controlled study. Journal of Acupuncture and Tuina Science. 2019; 17: 422–426.

36. Chen Huiyi. Clinical Study of Acupuncture on Functional Dyspepsia with Anxiety and Depression. Shanghai University of TCM. 2019.

37. Xu XH, Zhang MM, Wu X, Xu SB, Wang W, Zheng CH, et al. Efficacy of Electro-acupuncture in Treatment of Functional Constipation: A Randomized Controlled Trial. Curr Med Sci. 2020; 40: 363–371. https://doi.org/10.1007/s11596-020-2188-y PMID: 32337698

38. Min Yang, Zou Ran, Zhang Ling, Xu Paide. Clinical study on the effect of acupuncture and moxibustion on mental status of patients with irritable bowel syndrome of liver depression and spleen deficiency. Hebei Journal of Traditional Chinese Medicine. 2020; 51–54.

39. Rücker G, Schwarzer G. Beyond the forest plot: The drapery plot. Research Synthesis Methods. 2021; 12: 13–19. https://doi.org/10.1002/jrsm.1410 PMID: 32336044

40. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56: 455–463. https://doi.org/10.1111/j.0006-341x.2000.00455.x PMID: 10877304

41. Gong Y, Chang H, Gao J-S, Liu C-D, Han B-W, Wu X-K. Progress of researches on non-specific effect of acupuncture. Zhen Ci Yan Jiu. 2019; 44: 693–697. PMID: 31532141

42. Wang X-M, Lu Y, Wu L-Y, Yu S-G, Zhao B-X, Hu H-Y, et al. Moxibustion inhibits interleukin-12 and tumor necrosis factor alpha and modulates intestinal flora in rat with ulcerative colitis. World J Gastroenterol. 2012; 18: 6819–6828. https://doi.org/10.3748/wjg.v18.i46.6819 PMID: 23239920
43. Wei D, Xie L, Zhuang Z, Zhao N, Huang B, Tang Y, et al. Gut Microbiota: A New Strategy to Study the Mechanism of Electroacupuncture and Moxibustion in Treating Ulcerative Colitis. Evid Based Complement Alternat Med. 2019; 2019: 9730176. https://doi.org/10.1155/2019/9730176 PMID: 31354859

44. Wang L-J, Xue T, Wu Y-Q, Zhao J-Y, Wang T-N, Li J-T, et al. Effect of acupuncture on intestinal flora in rats with stress gastric ulcer. Zhongguo Zhen Jiu. 2020; 40: 526–532. PMID: 32394661

45. Sun H, Zhang B, Qian H-H, Chen Z-C. Effect of warm-needle moxibustion intervention on immune function and intestinal flora in patients after colorectal cancer radical operation. Zhen Ci Yan Jiu. 2021; 46: 592–597. PMID: 34369680

46. Foster JA, McVey Neufeld K-A. Gut–brain axis: how the microbiome influences anxiety and depression. Trends in Neurosciences. 2013; 36: 305–312. https://doi.org/10.1016/j.tins.2013.01.005 PMID: 23384445

47. Huang F, Wu X. Brain Neurotransmitter Modulation by Gut Microbiota in Anxiety and Depression. Front Cell Dev Biol. 2021; 9. https://doi.org/10.3389/fcell.2021.649103 PMID: 33777957

48. Krishna V, Bairy KL, Patil N, Sunny SV. Evaluation of the anti-anxiety and antidepressant activities of mosapride in Wistar albino rats. J Basic Clin Physiol Pharmacol. 2019; 30. https://doi.org/10.1515/jbcpp-2018-0089 PMID: 31318691