OPEN

Placebo Response Rates in Acupuncture Therapy Trials for Functional Dyspepsia

A Systematic Review and Meta-Analysis

Jie Liu, MD, Gengqing Song, MD, PhD,† Yizhou Huang, MD,* Chaolan Lv, PhD,* Ying Wang, MD,‡ Dandan Wu, MD,‡ Chenyu Sun, MD,§ Meng Jing, MD,‖ and Yue Yu, MD, PhD*‡*

Background: Functional dyspepsia (FD) is a functional digestive disease with limited management selection. Previous studies revealed that acupuncture therapy is effective for FD. However, because sham controls were not implemented in most clinical trials following acupuncture therapy, it is difficult to differentiate overall treatment responses from placebo. This study aims to quantify placebo responses in clinical trials in which FD patients received sham manual acupuncture (MA) and sham electroacupuncture (EA).

Materials and Methods: Randomized controlled trials of MA and EA for FD patients were searched in PubMed, Web of Science, Cochrane Library, and Embase databases, as well as 4 Chinese language databases from inception to January 2021. RevMan 5.20 software was used for pooled analysis of symptom scores and quality of life. The symptom scores were combined using standard mean difference (SMD) or weighted mean difference (WMD) with a 95% confidence interval (CI). The quality of included studies was tested using modified Jadad scale and Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) checklist. Egger's test, Begg's test, and sensitivity analyses were conducted using Stata 11.0 statistical software. The protocol of this study is registered in PROSPERO as CRD42021233858.

Results: After screening, the current systematic review included 13 randomized controlled trials, of which 8 studies were used in the meta-analysis. Regarding subjective outcomes, the combined effect of sham MA on FD symptoms was [SMD = −0.42, 95% CI (−0.72, −0.12); $P = 0.005$], whereas sham EA treatment was [SMD = −0.54, 95% CI (−0.81, −0.27); $P < 0.001$]. The combined effect on FD quality of life of post-sham MA group was [SMD = −0.32, 95% CI (−0.52, −0.12); $P = 0.002$]. With regard to objective outcomes, the combined effect of sham EA on dominant frequency was [WMD = −0.11, 95% CI (−0.30, −0.08); $P = 0.24$], while the combined effect of sham EA on dominant power was [WMD = −3.35, 95% CI (−8.04, 1.35); $P = 0.16$].

Conclusions: Sham MA and sham EA remarkably improve symptoms and quality of life scores of FD without influencing objective outcomes, highlighting the significance of sham controls in acupuncture therapy clinical trials.

Key Words: functional dyspepsia, manual acupuncture, electroacupuncture, sham, placebo

(*J Clin Gastroenterol* 2022;56:299–310)

Functional dyspepsia (FD), as one of the frequent functional gastrointestinal disorders (FGIDs), is prevalent among populations.[1] Ford et al[2] conducted a meta-analysis including 100 separate study populations and found a pooled prevalence of 20.8% [95% confidence interval (CI): 17.8%-23.9%]. FD can be divided into 2 subtypes based on diagnostic criteria of Rome IV.[3] Postprandial distress syndrome (PDS) is characterized by postprandial fullness and early satiation, whereas epigastric pain syndrome (EPS) is characterized by epigastric pain or burning sensation.[4] Suffering from FD symptoms persistently negatively influences on patient's psychological status and quality of life.[5] Moreover, FD imposed a significant economic burden on society. In 2017, the total cost for FD children's medical care was around $ 5.79 billion in America.[6]

Acupuncture, as a type of traditional Chinese medicine modalities, is one of the most widely practiced worldwide.[7] Electroacupuncture (EA) is developed based on manual acupuncture (MA) and is well-accepted in western countries.[8] Overall, acupuncture therapies, including MA, EA, other related therapies, are clinically effective in treating FGIDs.[9–11]

Sham acupuncture is designed as a form of placebo control. For instance, sham MA can be performed by stimulating points away from conventional acupoints or meridians, namely wrong points or nonpoints, while sham EA can be performed in a blinded manner.[12] Sham acupuncture is used to control nonspecific events, such as placebo responses and effects.[13] In detail, placebo effects are defined as any alterations in psychobiological mechanisms underlying a procedure,[14]

Received for publication July 14, 2021; accepted December 1, 2021.

From the *Department of Gastroenterology; ‡South District of Endoscopic Center, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China; †Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH; §Internal Medicine, AMITA Health Saint Joseph Hospital Chicago, Chicago, IL; and ‖Dunedin Public Hospital, Southern District Health Board, Dunedin, New Zealand.

Y.Y. contributed to planning the study. J.L., G.S., Y.H., C.L., Y.W., D.W., C.S., and M.J. collected and assembled the data. J.L., G.S., and C.L. contributed to interpreting the data and drafting the manuscript. J.L., G.S., Y.H., and C.L. contributed equally to this work and should be considered as co-first authors; all authors read and approved the final manuscript.

The study was supported by External Science and Technology Cooperation Planning Projects of Anhui Province (No.1604b0602021).

The authors declare that they have nothing to disclose.

Address correspondence to: Yue Yu, MD, PhD, Division of Life Sciences and Medicine, University of Science and Technology of China, Department of Gastroenterology, the First Affiliated Hospital of USTC, Hefei, Anhui 230001, China (e-mail: yuyuemd@163.com).

DOI: 10.1097/MCG.0000000000001679

while placebo responses are defined as response changes after placebo administration that are responsible for disease progression, symptom fluctuation, and regression to the mean.[15] Briefly speaking, placebo effects refer to psychobiological response to an inert treatment, while placebo responses refer to clinical improvement after receiving an inert treatment. However, placebo effects and responses are potentially involved in the overall treatment response in individuals administered with acupuncture and related therapies.[16] Therefore, a distinction must be made between overall treatment responses and placebo responses.

Although Guo et al[17] found that MA and EA are effective for FD, there has been no report to date focusing on the effect of sham acupuncture therapy. In addition, the outcomes of various studies on the effect of sham acupuncture are either inconsistent or conflicting.[18,19] Comparing subjective and objective outcomes before and after sham MA and sham EA could assist in verifying their placebo responses on FD. As a result, this systematic review and meta-analysis was designed to evaluate placebo responses following sham MA and sham EA treatment in FD patients.

MATERIALS AND METHODS

Search Strategy

In the current retrieval, Chinese and English databases were searched by combining subject terms and free word. The overall databases include 4 English online data repositories consisting of PubMed, Web of Science, Cochrane Library, and Embase database, and 4 Chinese language databases constituting CNKI (China National Knowledge Infrastructure), CBM (Chinese Biomedicine), and the WanFang Database and Chinese Scientific Journals Database (VIP). The searching terms comprised acupuncture therapy (acupuncture; acupoint; electroacupuncture; acupressure; nerve stimulation; ear acupuncture; transcutaneous electrical acustimulation; electrical stimulation) and functional dyspepsia (EPS functional dyspepsia; PDS). By employing the abstraction in PubMed as an example, the concrete retrieval approaches constituted:

#1 functional dyspepsia [Mesh Terms]
#2 functional dyspepsia [Title/Abstract]
#3 PDS [Title/Abstract]
#4 EPS [Title/Abstract]
#5 #1 OR #2 OR #3 OR #4
#6 acupuncture [Mesh Terms]
#7 acupuncture [Title/Abstract]
#8 electroacupuncture [Mesh Terms]
#9 electroacupuncture [Title/Abstract]
#10 acupressure [Title/Abstract]
#11 acupoint [Title/Abstract]
#12 ear acupuncture [Title/Abstract]
#13 electrical stimulation [Title/Abstract]
#14 transcutaneous electrical acustimulation [Title/Abstract]
#15 nerve stimulation [Title/Abstract]
#16 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 #5 AND # 16.

The retrieval time of each database is from the establishment of the database to June 1, 2021. At the same time, the reference of related literatures and reviews are retrieved manually to ensure that there is no omission, and the randomized controlled trials (RCTs) on acupuncture therapy treatment of FD published in the literature are statistically analyzed. The protocol of this systematic review has been prospectively registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (reference no. CRD42021233858).

Study Selection

Studies that meet the following criteria were eligible for inclusion: (1) study participants: the subjects were clinically diagnosed as FD patients in compliance with Rome II, III, or IV; (2) study design: RCTs with full text and published in English and Chinese; (3) outcomes: observation indicators have been clearly defined: such as symptom scale score, quality of life score, etc. Literatures should provide accurate comprehensive statistical indicators: Sample Size, Mean, SD; (4) intervention and comparison: study interventions included acupuncture therapy with a placebo sham acupuncture control; Exclusion criteria: (1) Nonrandomised controlled trials; (2) Duplicate publications; (3) Studies without sufficient data; (4) Pediatric patients (age below 16).

Literature Quality Evaluation

All included studies were evaluated by modified Jadad scale with regard to quality and methodology, where a higher score (total score of 7), suggests increasing rigorousness of a trial's methodological design.[20] The contents of the evaluation included: whether the random allocation method was correct, whether the allocation concealment was implemented, whether the blind method was applied whether the number and reasons for withdrawal are described.

Assessment of Sham Acupuncture Treatment Protocol

The detailed sham acupuncture treatment protocol of each RCT was assessed according to STRICTA checklist (Standards for reporting interventions in clinical trials of acupuncture: https://stricta.info/). STRICTA is a validated 6-item checklist with 17 subitems, including acupuncture rationale, needling details, treatment regimen, other treatment components, practitioner background, and control or comparator interventions. The methodology used in STRICTA includes that if an item is completely reported, the answer is "positive." The reporting rate (N = reported RCTs/13) was divided into 3 degrees: high (N $\geq$ 80%), low (N <50%), and moderate (N = 50%-80%).

Data Extraction

Literature screened by 2 reviewers (J.L. and Y.W.) according to the inclusion and exclusion criteria mentioned above separately. When disagreements arise, they consult and negotiate with the third participant (Y.Y.) to resolve the issue. The following data were extracted: first author's name, the time of publication, the participants of the experimental and control group, interventions, duration (weeks), outcomes, STRICTA list, description of MA/EA, and sham control.

Statistical Analysis

Heterogeneity test was performed with RevMan 5.20 software (Cochrane Collaboration, London, United Kingdom). The symptom scores and quality of life score were combined by standard mean difference (SMD) or weighted mean difference (WMD) with 95% CI of continuous variable analysis statistics. Q test and I^2 test were used to analyze the heterogeneity of the studies included in this meta-analysis. If $P > 0.100$ and $I^2 < 50\%$, it was considered that there was small heterogeneity among the studies, and the fixed-effect model

TABLE 1. Included Functional Dyspepsia Trials and Study Characteristics

References	Country	Patients (T/C)	Diagnostic Criteria	Study Duration	Sham Duration	Interventions T	Interventions C	Sham Description	Outcome Measurements	Follow-up
References included in this meta-analysis and systematic review										
Xu et al[18]	China	8/8	Rome III	30 min	30 min	EA	Sham EA	Acupoint for PC6 was located at about 15-20 cm away from PC6 (up to the elbow and outside coastal margin of the forearm not on any meridian) and the sham-point for ST36 was located at 10-15 cm down from and to the lateral side of ST36 not on any meridian	1. Gastric slow waves* 2. HRV 3. Total symptom scores*	Not mentioned
Zheng et al[19]	China	100/100	Rome III	4 wk	4 wk	EA	Sham EA	The sham electroacupuncture group received acupuncture at 4 sham points	1. Response rate 2. LDQ scores* 3. NDSI	Follow-up for 24 wk
Jin et al[22]	China	28/28	Rome III	30 d	30 d	MA	Sham MA	Acupoints in different dermatomes but close proximity of the aforementioned acupoints were used in the distal portion of extremities correspondingly	1. DSSS* 2. SF-36* 3. SDS 4. SAS 5. Gastrin 6. FGSW 7. PVGSW	Follow-up for 3 mo
Zeng et al[23]	China	34/30	Rome III	4 wk	4 wk	MA	Sham MA	The sham acupuncture treatment was performed on 4 nonacupuncture points	1. NDLQI score* 2. SID	Not mentioned
Wang et al[24]	China	36/41	Rome III	4 wk	4 wk	MA	Sham MA	Nonacupoints are away from conventional acupoints or meridians	1. Symptom severity assessment 2. SF-36*	Follow-up for 3 mo
Ma et al[25]	China	32/29	Rome III	12 d	12 d	MA	Sham MA	Nonacupoints are 10 cm away from conventional acupoints or meridians	1. SF-36* 2. NDI symptom score* 3. Response rate 4. NDLQI score*	Follow-up for 1 mo
Wang et al[26]	China	34/34	Rome III	4 wk	4 wk	MA	Sham MA	Nonacupoints are 2 cm away from conventional acupoints or meridians	1. NDI symptom score* 2. NDLQI score* 3. Response rate	Follow-up for 6 mo
Liu et al[27]	China	27/27	Rome II	5 wk	2 wk	EA	Sham EA	6 cm above the kneecap where no acupoints were present	1. HRV 2. Gastric slow waves* 3. Neuropeptide level 4. Plasma motilin	Not mentioned

TABLE 1. (*continued*)

References	Country	Patients (T/C)	Diagnostic Criteria	Study Duration	Sham Duration	Interventions T	Interventions C	Sham Description	Outcome Measurements	Follow-up
References included in this systematic review										
Wang et al[28]	China	138/140	Rome IV	4 wk	4 wk	MA	Sham MA	Nonacupoints are away from conventional acupoints or meridians	1. Postprandial fullness symptom score	Follow-up for 12 wk
Yang et al[29]	China	117/112	Rome IV	4 wk	4 wk	MA	Sham MA	Nonacupoints are away from conventional acupoints or meridians	1. Response rate 2. Elimination rate	Follow-up for 12 wk
Tu et al[30]	China	21/21	Rome IV	4 wk	4 wk	MA	Sham MA	Sham acupuncture group received superficial needling (to ~2 mm depth) at locations not corresponding to traditional acupuncture points, without manual stimulation or elicitation of de qi sensation	1. Response rate 2. Symptom severity assessment 3. HADS	Not mentioned
Ma et al[31]	China	118/120	Rome III	4 wk	4 wk	MA	Sham MA	Nonacupoints with a shallow puncture was performed as sham acupuncture group. On-acupoints were punctured perpendicularly, 0.5-1 cm unilaterally	1. Response rate 2. Symptom severity assessment	Follow-up for 12 wk
Ji et al[32]	China	14/14	Rome III	5 wk	2 wk	EA	Sham EA	The sham-point for PC6 was about 15 cm up (to the elbow) and lateral to PC6 and the sham-point for ST36 was about 10 cm down (to the knee joint) and lateral to ST36	1. Symptom severity assessment 2. SAS, SDS	Not mentioned

*Outcome measurements applied this meta-analysis.

C indicates control group; DSSS, dyspeptic symptom sum score; EA, electroacupuncture; EGG, electrogastrogram; FGSW, frequency of gastric slow waves; HAMD, Hamilton Depression Scale; HRV, heart rate variability; LDQ, Leeds dyspepsia questionnaire; MA, manual acupuncture; NDI, Nepean dyspepsia index; NDLQI, Nepean dyspepsia life quality index; NDSI, Nepean dyspepsia symptom index; PVGSW, propagation velocity of gastric slow waves; SAS, Self-rating anxiety scale; SDS, Self-rating depression scale; SF-36, 36-item short form health survey; SID, symptom index of dyspepsia; T, trial group.

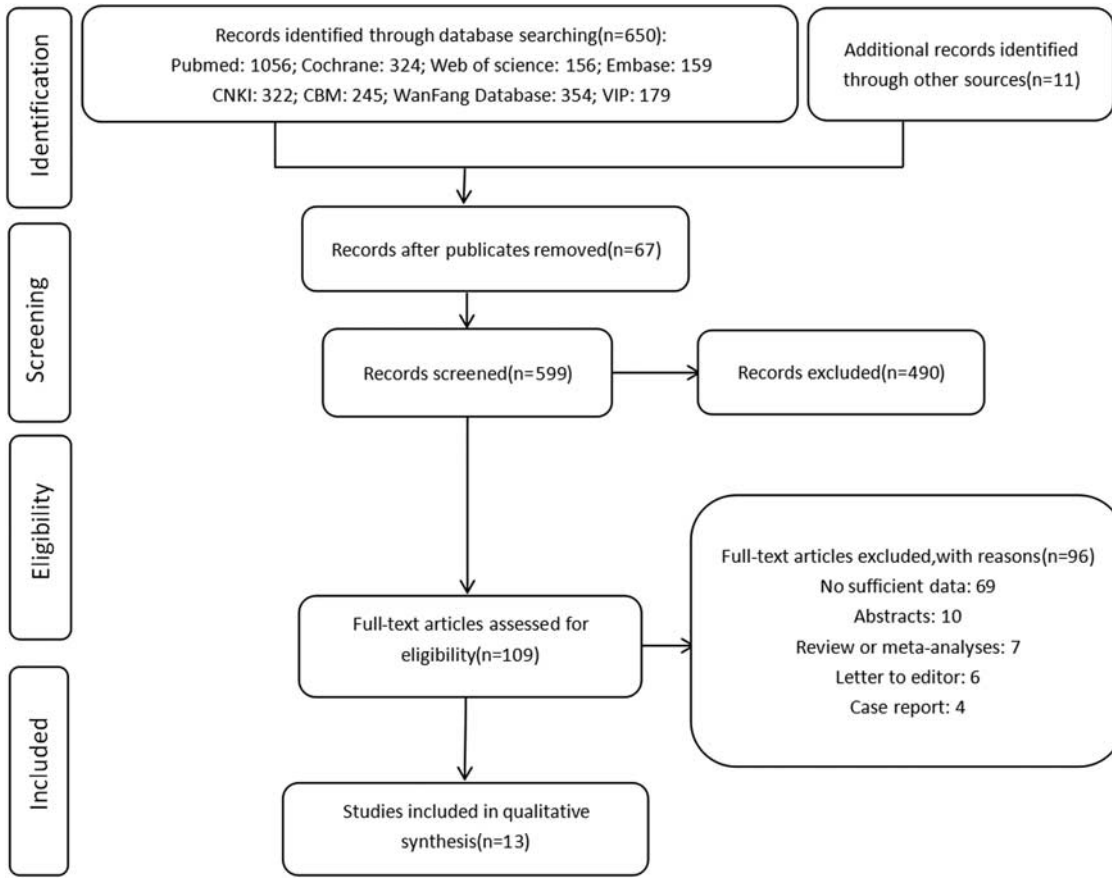

FIGURE 1. Flow chart representing the selection of studies. CBM indicates Chinese Biomedicine; CNKI, China National Knowledge Infrastructure; VIP, WanFang Database and Chinese Scientific Journals Database.

was chosen; otherwise, the random effect model was used.[21] All included studies performed with a baseline (pre-sham) along with a post-sham acupuncture group. Outcomes data were recorded for this meta-analysis when 2 or more trials documented a similar outcome, including symptom scale score, quality of life score, etc. In detail, the data of Nepean dyspepsia index (NDI), dyspeptic symptom sum score, gastric cardinal symptom index were included for FD symptom following sham MA and sham EA in the current meta-analysis. Outcomes meta-analyzed for quality of life of FD included SF-36 score, Nepean dyspepsia life quality index (NDLQI). The outcomes for each included study are summarized in Table 1. Sensitivity assessments were performed to explore the robustness of this meta-analysis. Meanwhile, the Egger's test and Begg's test along with the funnel plots were used to explore the risk publication bias.[33] Subgroup assessments were carried out as per the different scales if the heterogeneity shown $P < 0.100$ and $I^2 > 50\%$, given that there was large heterogeneity among

TABLE 2. Detailed Quality Assessment of Included Studies Using Modified Jadad Score

References	Randomization	Concealment of Allocation	Double Blinding	Description of Withdrawals and Dropouts	Total Jadad Score
Xu et al[18]	2	0	0	0	2
Zheng et al[19]	2	1	1	1	5
Jin et al[22]	1	0	0	1	2
Zeng et al[23]	1	0	1	1	3
Wang et al[24]	2	0	0	0	2
Ma et al[25]	2	0	0	1	3
Wang et al[26]	2	0	0	0	2
Liu et al[27]	1	0	2	0	3
Wang et al[28]	2	0	0	1	3
Yang et al[29]	2	2	2	1	7
Tu et al[30]	2	2	0	1	5
Ma et al[31]	2	2	1	1	6
Ji et al[32]	2	0	0	0	2

TABLE 3. Detailed Quality Assessment of Acupuncture Treatment Protocol

Items	Item Details	Positive References	%
1. Acupuncture rationale	1.1) Style of acupuncture	18,19,22–32	100
	1.2) Reasoning for treatment provided	18,19,22–32	100
	1.3) Extent to which treatment was varied	18,19,22–32	100
2. Details of needling	2.1) Number of needle insertions per subject per session	22–26,28–31	69.23
	2.2) Names of points used	18,19,22–32	100
	2.3) Depth of insertion	22–26,28–31	69.23
	2.4) Response sought	22,23,25,28–31	53.85
	2.5) Needle stimulation	22–26,28–31	69.23
	2.6) Needle retention time	22–26,28–31	69.23
	2.7) Needle type	22–26,28–31	69.23
3. Treatment regimen	3.1) Number of treatment sessions	18,19,22–32	100
	3.2) Frequency and duration of treatment sessions	18,19,22–32	100
4. Other components of treatment	4.1) Details of other interventions administered to the acupuncture group	None	0
	4.2) Setting and context of treatment	None	0
5. Practitioner background	5.1) Description of participating acupuncturists	22–26,28–31	69.23
6. Control or comparator interventions	6.1) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	18,19,22–32	100
	6.2) Precise description of the control or comparator	18,19,22–32	100

the studies. Egger's test, Begg's test and sensitivity analyses were assessed with the Stata 11.0 statistical software (Stata Corp., College Station, TX).

RESULTS

Study Included

A total of 109 relevant literatures were retrieved from both English and Chinese databases and screened strictly according to inclusion and exclusion criteria. Finally, 13 studies of RCT were included. Among the 13 RCTs,[18,19,22–32] 5 reported the sham MA and sham EA efficacy on overall FD symptoms, 5 studies with 6 records reported sham MA efficacy on FD quality of life. All of the control groups were treated with sham MA or sham EA for FD. The process and results of literature screening are shown in Figure 1. The basic information of 13 literatures are included in Table 1 specifically. The quality evaluation of the included literatures is evaluated by Jadad scale score and shown in Table 2.

Study Characteristics and Quality Assessment

All studies were published between 2008 to 2021, of which 13 studies were RCTs. All the trials were carried out in China and 9 were published in English, while the remaining studies were published in Chinese. Four studies were conducted with sham EA and the remaining studies with sham MA. A further comprehensive description of the study information is provided in Table 1, while the literature quality evaluation ratings across every study by Jadad score is shown in Table 2. The reporting quality of included trials ranged from low to high. According to STRICTA checklist, the proportion of included studies elucidating other treatment components was 0%, while the proportion of included studies elucidating resting items were all above at 50% (Table 3). In summary, the quality of included studies was considered moderate to high, with Jadad scores of 2 or higher.[20]

Description of Sham MA and Sham EA

The methods of applying sham acupuncture vary across different studies. Tu et al[30] described sham MA as superficial insertion of electrodes/needles compared with deep insertion in treatment group, whereas remaining studies reported that sham MA and sham EA treatments were performed on nonacupuncture points.[18,19,22–29,31,32] However, needle insertion location with distance away from conventional acupoints or meridians varies across included literature. The sham description extracted from included studies is detailed in Table 1.

Heterogeneity Test and Combined Effect Analysis

Subjective Outcomes Following Sham MA or Sham EA Treatment

FD Overall Symptom: 2 studies reported sham MA on FD symptoms using NDI,[25,26] while 1 study reported sham MA on FD symptoms using dyspeptic symptom sum score.[22] Because the heterogeneity test indicated that sham MA on FD symptom was ($Q = 3.90$, $P = 0.140$, $I^2 = 49.00\%$), a fixed-effect model was used. The combined effect of sham MA treatment group on FD symptoms was [SMD = −0.42, 95% CI (−0.72, −0.12); $P = 0.005$] (Fig. 2).

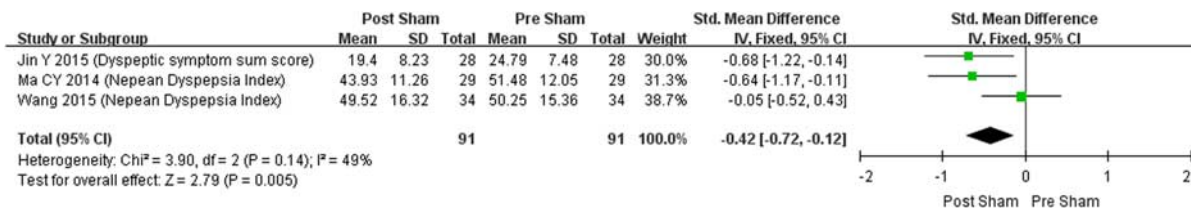

FIGURE 2. Forest plot of the improvement regarding functional dyspepsia overall symptoms by sham manual acupuncture. Hollow diamonds represent pooled standard mean difference. CI indicates confidence interval. full color online

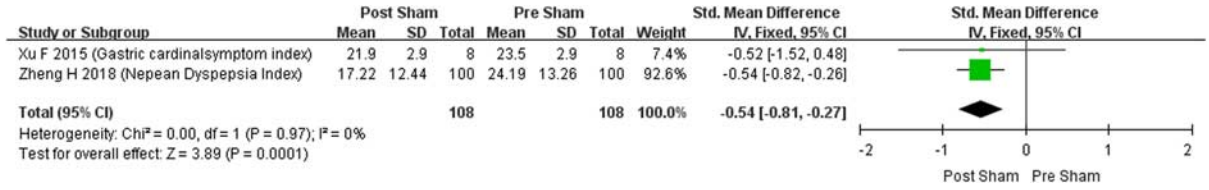

FIGURE 3. Forest plot of the improvement regarding functional dyspepsia overall symptoms by sham electroacupuncture. Hollow diamonds represent pooled standard mean difference. CI indicates confidence interval. full color online

Regarding EA treatment, 1 study reported sham EA on FD symptoms using NDI,[19] while 1 study reported sham EA on FD symptoms using gastric cardinal symptom index.[18] Because the heterogeneity test of sham EA on FD symptoms was ($Q = 0.00$, $P = 0.970$, $I^2 = 0.00\%$), a fixed-effect model was applied. The combined effect of sham EA treatment group on FD symptoms was [SMD = −0.54, 95% CI (−0.81, −0.27); $P < 0.001$] (Fig. 3).

FD Quality of Life: 5 studies reported 6 records on the effects of sham MA on FD quality of life, 3 using SF-36 and the other 3 using NDLQI.[22–26] Because the heterogeneity test indicated that sham MA on FD symptoms was (Q = 8.17, $P = 0.15$, $I^2 = 39.0\%$), a fixed-effect model was applied. The combined effect of sham MA treated group on FD quality of life was [SMD = −0.32, 95% CI (−0.52, −0.12); $P = 0.002$], as illustrated in Figure 4. The pooled effect of sham EA on FD quality of life could not be calculated as only one study[19] reported it.

Objective Outcomes Following Sham EA Treatment

Two studies examined the effects of sham EA on gastric slow waves.[18,27] The heterogeneity test result of sham EA on dominant frequency was ($Q = 17.49$, $P < 0.001$, $I^2 = 94.00\%$), indicating that a random effect model should be used. The combined effect of sham EA on dominant frequency was [WMD = −0.11, 95% CI (−0.30, −0.08); $P = 0.24$] (Fig. 5). Meanwhile, the heterogeneity test result of sham EA on dominant power was ($Q = 24.62$, $P < 0.001$, $I^2 = 96.00\%$), implying that a random effect model should be applied. The combined effect of sham EA on dominant power was [WMD = −3.35, 95% CI (−8.04, 1.35); $P = 0.16$] (Fig. 6). The effect of sham MA on objective outcomes could not be pooled because no more than 2 similar results were included.

Sensitivity Analysis

In addition, we conducted a sensitivity analysis to examine robustness of this meta-analysis. The sensitivity analysis revealed that no study had a remarkable effect on the pooled effect regarding FD symptoms, FD quality of life, and gastric slow waves.

Subgroup Analysis

Meanwhile, subgroup analyses were performed to investigate heterogeneity. WMD with 95% CI and heterogeneity test results of SF-36 scale subgroup were [WMD = 2.49, 95% CI (0.38, 4.61); $P = 0.02$, $Q = 0.93$, P heterogeneity = 0.63, $I^2 = 0.00\%$], while the results of NDLQI scale subgroup were [WMD = 2.81, 95% CI (−1.79, 7.41); $P = 0.23$, $Q = 7.99$, P heterogeneity = 0.02, $I^2 = 75.00\%$]. The results indicated that heterogeneity may originate from different scales used by researchers (Fig. 7).

Publication Bias Analysis

No obvious publication bias was detected using funnel plots (Figs. 8 and 9), Egger's test, and Begg's test regarding sham MA and sham EA on FD symptoms, respectively. Meanwhile, no publication bias was detected using Egger's test ($t = 3.49$, $P = 0.073$) and Begg's test ($t = 0.68$, $P = 0.497$) for sham MA on FD quality of life (Fig. 10). Similarly, no publication bias was found for sham EA on dominant frequency and dominant power (Figs. 11 and 12, respectively). Table 4 summarizes the publication bias associated with each outcome as determined by Egger's and Begg's tests.

DISCUSSION

According to Rome IV criteria, FD is among the major FGIDs.[1] Individuals with FD exhibit numerous upper gastrointestinal manifestations consisting of abdominal pain, distension, heartburn, and early satiety, without organic causes. Because of its recurrence and persistence, FD leads to a decrease in quality of life, along with a considerable economic burden.[34] The current therapeutic options for FD are unsatisfactory so that nearly 50% patients tend to look for complementary medicine.[35] Acupuncture therapy constitutes an internationally well-known alternative treatment that has been used to treat various diseases in China for more than 2500 years, and it can

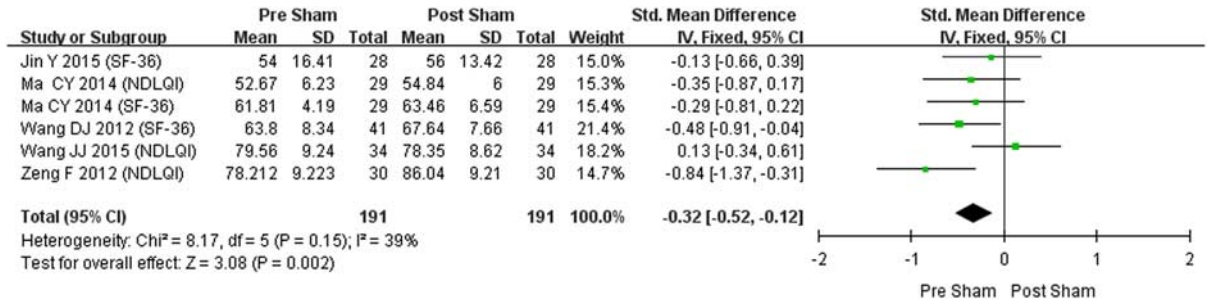

FIGURE 4. Forest plot of the improvement regarding functional dyspepsia quality of life by sham manual acupuncture. Hollow diamonds represent pooled standard mean difference. CI indicates confidence interval. full color online

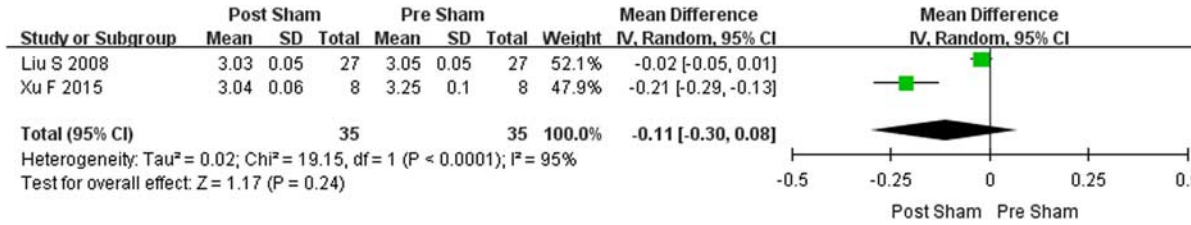

FIGURE 5. Forest plot of effect estimates of sham electroacupuncture on dominant frequency. Hollow diamonds represent pooled weighted mean difference. CI indicates confidence interval. full color online

be a complex, multimodal, effective management for FGIDs.[36] Previous studies showed that the therapeutic influence of acupuncture and EA was significantly superior to that of sham controls.[37] This systematic review and meta-analysis is the first meta-analysis of RCTs, demonstrating that sham MA and sham EA are associated with statistical significance regarding both improvements in the symptoms and quality of life of FD patients. However, dominant frequency and dominant power cannot be significantly improved for FD patients following sham EA treatment. Our findings quantified placebo responses in these clinical trials using sham MA and sham EA in control groups and demonstrated that sham MA and sham EA improve subjective outcomes but do not influence objective outcomes. In addition, the findings suggested important implications for interpreting the results of uncontrolled acupuncture studies and other related therapies. When designing future clinical trials, the impact of placebo responses and effects on the overall treatment response must be considered.

The actual treatment efficacy of acupuncture cannot be elicited if no sham controls were implemented; so it is essential to treat nonplacebo controlled trials with cautions.[38,39] In the past, favorable outcomes had been reported frequently in non-sham-controlled trials following acupuncture and related therapies for FD.[40–44] For example, Ko et al[40] reported that total NDI scores of FD patients were remarkably declined in the acupuncture group in contrast with the waitlist control group ($P=0.03$). Among the NDI items, fullness after eating ($P=0.02$), discomfort ($P=0.01$), burping ($P=0.02$), and burning ($P=0.02$), were remarkably improved in the acupuncture group in contrast with the waitlist control group. In a clinical study conducted by Qiang et al,[43] patients were grouped randomly into EA group and western medicine group and the placebo effect was not taken into account. As mentioned above, one of the main deficits in these studies[40–44] is lack of placebo control. Therefore, the conclusion from these studies[40–44] indicate the uncertainty of acupuncture therapy to improve the symptoms of FD patients, so future studies are needed by using stringent research design, including standard management of placebo. In this systematic review and meta-analysis, this sham placebo contribution in dyspepsia symptom as well as quality of life was analyzed quantitatively as the number of sham-controlled trials have increased in recent years, and the results were consistent with previous research, which highlights the significance of sham controls in clinical trails.[39]

Placebo responses along with inert treatment may affect self-reporting of FD symptoms because subjective improvements in manifestations serve a pivotal role in acupuncture therapy trials.[20] In view of this, the improvements, such as dyspepsia symptom and quality of life were likely to be related to "subjective outcomes." However, Jin et al[22] found that individuals with FD exhibited remarkable improvements in the level and frequency of serum gastrin, as well as the gastric slow waves' propagation velocity ($P=0.0002$, 0.0078, and 0.0180, respectively.) after 1 month's acupuncture treatment. Liu et al[27] found that the high frequency resulting from the spectral assessment of variability in the heart rate was remarkably elevated with both acute EA (76% increment, $P=0.01$) and chronic EA (75% increment, $P=0.025$). Nonetheless, such an increment was not documented in the sham EA treatment. Ji et al[32] concluded that gastric emptying and gastric accommodation were remarkably increased with 2-week EA and not sham EA. Of note, no significant improvements in "objective outcomes," for example, serum gastrin concentration, gastric slow waves, heart rate variability and gastric accommodation, were identified in many previous sham-controlled studies, suggesting that sham EA, similar to other placebo effect, may just evoke a psychological response in FD patients.[45,46] In the current study, although we found that sham MA and sham EA are effective for FD, outcomes from all included studies showed that MA and EA were superior to sham-group including some objective outcomes, such as serum gastrin concentration, gastric slow waves, heart rate variability. Most notably, this meta-analysis comprehensively evaluates the effects of sham EA on gastric slow waves, demonstrating that dominant frequency and power cannot be significantly improved following sham EA treatment. However, the certain mechanism of this response is not fully understood and remains to be studied furtherly.

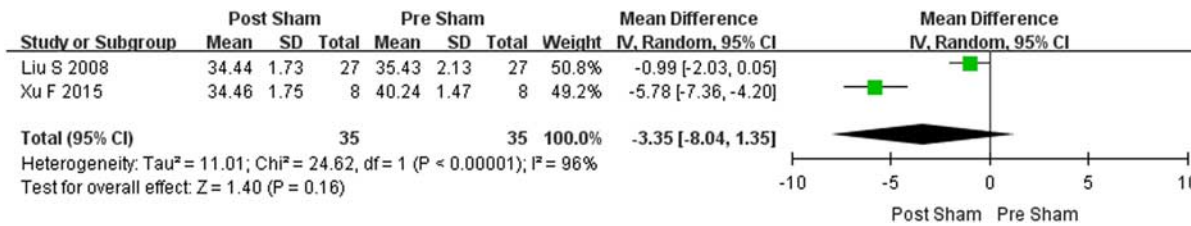

FIGURE 6. Forest plot of effect estimates of sham electroacupuncture on dominant power. Hollow diamonds represent pooled standard mean difference. CI indicates confidence interval. full color online

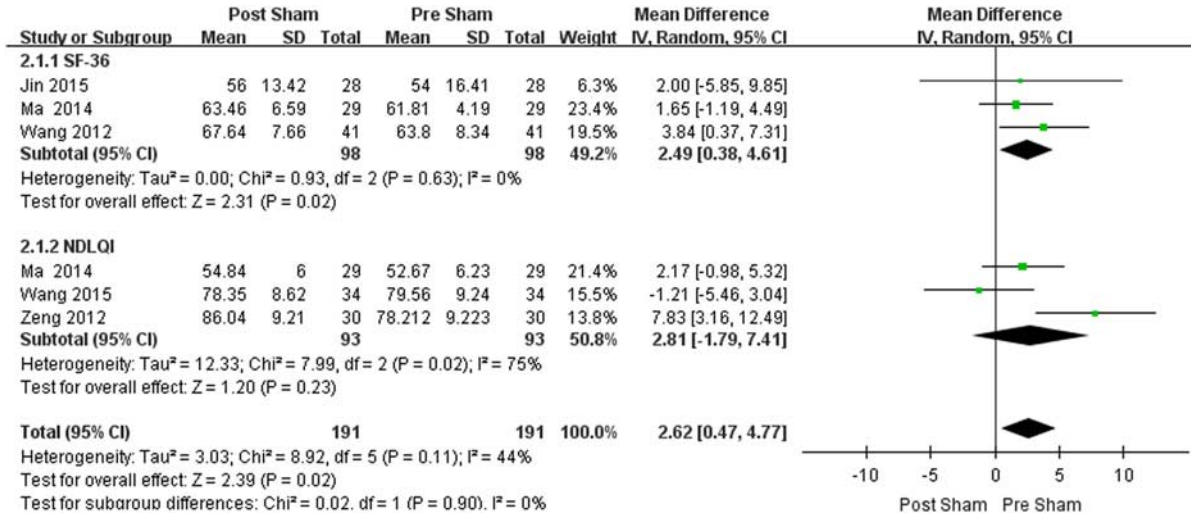

FIGURE 7. Subgroup analysis for different scales used in studies. Hollow diamonds represent pooled weighted mean difference. CI indicates confidence interval; SF-36, 36-item short form health survey; NDLQI, Nepean dyspepsia life quality index. full color online

Although 13 studies were eligible for analysis in our review, only the data from 8 studies can be merged.[18,19,22–27] Our findings demonstrate that sham MA and sham EA is linked to a decrease in FD symptom severity and an increase of quality of life in individuals with FD. However, a small heterogeneity was detected when combining extracted data of FD symptom and quality of life. The subgroup analysis results suggested that different scales used by included studies may be one of the sources of heterogeneity. Meanwhile, we think the heterogeneity may originate from the various methods of sham acupuncture applied in different clinical trials as well as a wide variety in selection of acupoints and acupuncture manipulation. Admittedly, it was inappropriate to compare, as well as abstract data from the different sham acupuncture arm of every trial given the heterogenous nature of the incorporated modalities of sham acupuncture treatment. Notably, it is difficult to determine an overall typical placebo response rate because of the lack of a control comparison. Consequently, it is a challenge for further studies to delineate, as well as quantify an overall placebo response rate attributed to sham acupuncture by comparing similar approaches of sham acupuncture.

Although studies included in this meta-analysis reported that the sham acupuncture treatment was performed on non-acupuncture points,[18,19,22–29,31,32] it is observed that the descriptions regarding how to perform sham acupuncture were different in these studies. In particular, the location of needle insertion with distance away from the conventional acupoints or meridians is variable. For example, nonacupoints that 10 cm away from conventional acupoints or meridians are applied in the trail by Ma et al[25] and Wang et al[26] described sham acupoints as 2 cm away from the conventional meridians or acupoints. A standard blinded sham therapy could pose a difficult challenge in practice to acupuncture trials. In order to conduct RCTs for differentiating overall treatment responses from placebo, a viable and credible sham acupuncture device is required. Recently, blunt acupuncture needles retracting into their handles have been introduced as a potentially valuable solution for blinding research subjects. Park sham device,[47] as the most representative type of sham acupuncture device, includes a flange with adhesive tape and a guide tube for placing placebo needle on acupuncture point. In addition, some recent studies have used Streitberger's needle,[48] a needle-foam device with a toothpick.[49,50] The insertion and removal

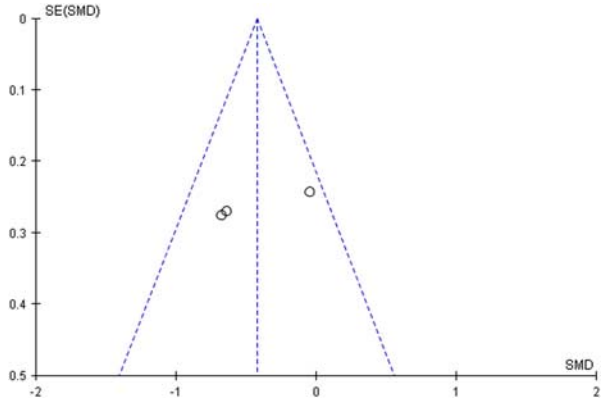

FIGURE 8. Funnel plot of the improvement regarding functional dyspepsia overall symptoms by sham manual acupuncture. SMD indicates standard mean difference. full color online

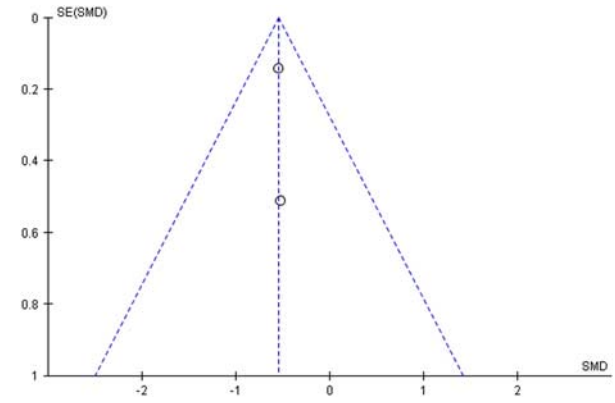

FIGURE 9. Funnel plot of the improvement regarding functional dyspepsia overall symptoms by sham electroacupuncture. SMD indicates standard mean difference. full color online

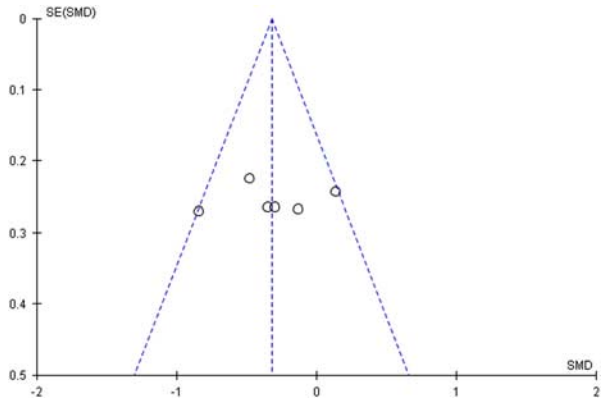

FIGURE 10. Funnel plot of the improvement regarding functional dyspepsia quality of life by sham manual acupuncture. SMD indicates standard mean difference. full color online

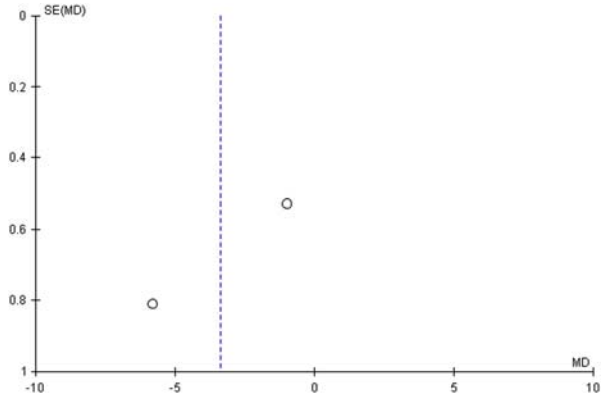

FIGURE 11. Funnel plot of effect estimates of the sham electroacupuncture on dominant frequency. full color online

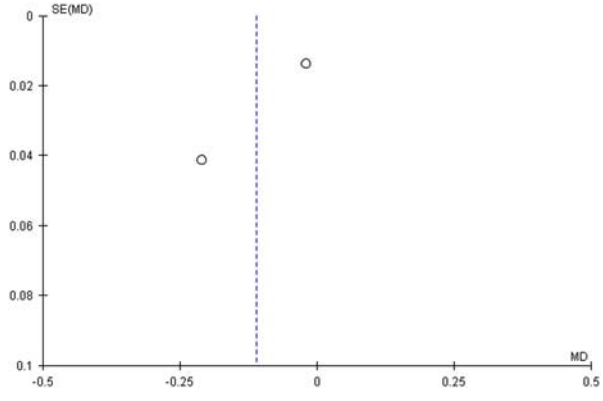

FIGURE 12. Funnel plot of effect estimates of sham electroacupuncture on dominant power. full color online

TABLE 4. Publication Bias of Outcomes by Egger's Test and Begg's Test

	Egger's Test		Begg's Test	
Outcomes	***t***	***P***	***Z***	***P***
Sham MA on FD symptom	0.77	0.361	0.74	0.458
Sham EA on FD symptom	0.40	0.718	0.58	0.417
Sham MA on FD quality of life	3.49	0.073	0.68	0.497
Sham EA on dominant frequency	1.25	0.313	1.15	0.295
Sham EA on dominant power	1.35	0.194	1.48	0.145

EA indicates electroacupuncture; FD, functional dyspepsia; MA, manual acupuncture.

model has recently been invented for clinical studies,[51] which can distinguish between verum acupuncture and sham acupuncture by paying attention to the needle's retention time following skin penetration. Finally, the nonacupoint model,[52] which focuses on nonacupoints, is also adopted for sham acupuncture in acupuncture trials, depending on the specificity of the effect on each acupoint. Therefore, these sham devices and needles offer valuable techniques for placebo research and possibly future trial design in this area. The different sham methodologies documented across numerous randomized sham-controlled trials reflect the absence of a gold standard definition for sham acupuncture. In this study, it is believed that there is a lack of consensus regarding what constitutes a high-quality sham control/placebo, allowing for the implementation of defined optimal sham therapies in future randomized sham-controlled trials.

Limitation

Finally, herein, we acknowledge that only sham interventions (pre-sham and post-sham) were included in our analysis so that our study lacks a control comparison. It is generally considered that a control comparison is difficult to implement in placebo investigation. Sham acupuncture outcomes may thus be influenced by confounding factors consisting of natural disease progression along with regression to the mean. Then, the variability in the definition of sham therapy across included studies and further studies would be of interest for further investigation. Meanwhile, although we quantified placebo responses of these clinical trials using sham MA and sham EA for FD, it is very difficult to separate out placebo effects from placebo responses.

CONCLUSION

In summary, sham MA and sham EA remarkably improve manifestations and quality of life scores of FD without influencing objective outcomes. So it reliably explains the treatment effect, it is necessary that sham controls are implemented in clinical trials if possible, and noncontrolled studies should be interpreted with caution. Notably, further studies should be conducted to develop a standard for the sham acupuncture clinical trial design to explore the acupuncture therapeutic effect.

REFERENCES

1. Ford AC, Mahadeva S, Carbone MF, et al. Functional dyspepsia. *Lancet*. 2020;396:1689–1702.
2. Ford AC, Marwaha A, Sood R, et al. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut*. 2015;64:1049–1057.

3. Caballero-Mateos AM[a], Redondo Cerezo E. Dyspepsia, functional dyspepsia and Rome IV criteria. *Rev Esp Enferm Dig*. 2018;110:530–531.
4. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterology*. 2016;150:1380–1392.
5. Aro P, Talley NJ, Agréus L, et al. Functional dyspepsia impairs quality of life in the adult population. *Aliment Pharmacol Ther*. 2011;33:1215–1224.
6. Mani J, Madani S, Thomas R. Economic impact and prognostic factors of functional dyspepsia in children. *J Pediatr Gastroenterol Nutr*. 2020;70:e65–e70.
7. Cai RL, Hu L, Zhou YP. Development history of acupuncture and moxibustion diagnosis and treatment institutions since the founding of the People's Republic of China. *Zhongguo Zhen Jiu*. 2020;40:1351–1354.
8. Chen KB, Huang Y, Jin XL, et al. Electroacupuncture or transcutaneous electroacupuncture for postoperative ileus after abdominal surgery: a systematic review and meta-analysis. *Int J Surg*. 2019;70:93–101.
9. Chen JDZ, Ni M, Yin J. Electroacupuncture treatments for gut motility disorders. *Neurogastroenterol Motil*. 2018;30: e13393.
10. Kim KN, Chung SY, Cho SH. Efficacy of acupuncture treatment for functional dyspepsia: a systematic review and meta-analysis. *Complement Ther Med*. 2015;23:759–766.
11. Han J, Wang HC, Rong PJ, et al. Systematic review and meta-analysis of the therapeutic effect on functional dyspepsia treated with acupuncture and electroacupuncture. *World J Acupunct Moxibustion*. 2021;31:44–51.
12. Yu Y, Wei R, Liu Z, et al. Ameliorating effects of transcutaneous electrical acustimulation combined with deep breathing training on refractory gastroesophageal reflux disease mediated via the autonomic pathway. *Neuromodulation*. 2019; 22:751–757.
13. Marchant J. Placebos: honest fakery. *Nature*. 2016;535:S14–S15.
14. Jonas WB, Crawford C, Colloca L, et al. To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials. *BMJ Open*. 2015;5: e009655.
15. Blease CR, Bishop FL, Kaptchuk TJ. Informed consent and clinical trials: where is the placebo effect? *BMJ*. 2017;356:j463.
16. Kaptchuk TJ. Placebo effects in acupuncture. *Med Acupunct*. 2020;32:352–356.
17. Guo Y, Wei W, Chen JDZ. Effects and mechanisms of acupuncture and electroacupuncture for functional dyspepsia: a systematic review. *World J Gastroenterol*. 2020;26: 2440–2457.
18. Xu F, Tan Y, Huang Z, et al. Ameliorating effect of transcutaneous electroacupuncture on impaired gastric accommodation in patients with postprandial distress syndrome-predominant functional dyspepsia: a pilot study. *Evid Based Complement Alternat Med*. 2015;2015:168252.
19. Zheng H, Xu J, Sun X, et al. Electroacupuncture for patients with refractory functional dyspepsia: a randomized controlled trial. *Neurogastroenterol Motil*. 2018;30:e13316.
20. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–2.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
22. Jin Y, Zhao Q, Zhou K, et al. Acupuncture for functional dyspepsia: a single blinded, randomized, controlled trial. *Evid Based Complement Alternat Med*. 2015;2015:904926.
23. Zeng F, Qin W, Ma T, et al. Influence of acupuncture treatment on cerebral activity in functional dyspepsia patients and its relationship with efficacy. *Am J Gastroenterol*. 2012;107: 1236–1247.
24. Wang DJ, Chang XR, Yan J, et al. Comparative study on therapeutic effect between acupuncture at special acupoints and non-specific acupoints in foot yangming meridian for functional dyspepsia. *Zhongguo Zhen Jiu*. 2012;32:703–708.
25. Ma CY, Huang Q, Wan WJ, et al. Effects of syndrome-differentiation acupuncture on life quality in patients with functional dyspepsia. *Zhongguo Zhen Jiu*. 2014;34: 125–129.
26. Wang JJ, Rong XD, Ding Y. Observation clinical effect of selecting acupoint along channel for treating functional dyspepsia postprandial distress syndrome in 34 cases. *Chong Qing Med*. 2015;44:1918–1920.
27. Liu S, Peng S, Hou X, et al. Transcutaneous electroacupuncture improves dyspeptic symptoms and increases high frequency heart rate variability in patients with functional dyspepsia. *Neurogastroenterol Motil*. 2008;20:1204–1211.
28. Wang Y, Yang JW, Hu H, et al. Improvements in dyspepsia related symptoms after treated with acupuncture in 278 patients with postprandial distress syndrome: a secondary analysis of a multi-center randomized controlled trial. *Zhongguo Zhen Jiu*. 2021;41:583–587.
29. Yang JW, Wang LQ, Zou X, et al. Effect of acupuncture for postprandial distress syndrome: a randomized clinical trial. *Ann Intern Med*. 2020;172:777–785.
30. Tu JF, Yang JW, Wang LQ, et al. Acupuncture for postprandial distress syndrome: a randomized controlled pilot trial. *Acupunct Med*. 2020;38:301–309.
31. Ma TT, Yu SY, Li Y, et al. Randomised clinical trial: an assessment of acupuncture on specific meridian or specific acupoint vs. sham acupuncture for treating functional dyspepsia. *Aliment Pharmacol Ther*. 2012;35:552–561.
32. Ji T, Li X, Lin L, et al. An alternative to current therapies of functional dyspepsia: self-administrated transcutaneous electroacupuncture improves dyspeptic symptoms. *Evid Based Complement Alternat Med*. 2014;2014:832523.
33. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315: 629–634.
34. Stanghellini V. Functional dyspepsia and irritable bowel syndrome: beyond Rome IV. *Dig Dis*. 2017;35(suppl 1):14–17.
35. Lahner E, Bellentani S, Bastiani RD, et al. A survey of pharmacological and nonpharmacological treatment of functional gastrointestinal disorders. *United Eur Gastroenterol J*. 2013;1:385–393.
36. Ma Y, Dong M, Zhou K, et al. Publication trends in acupuncture research: a 20-year bibliometric analysis based on PubMed. *PLoS One*. 2016;11:e0168123.
37. Zhang J, Liu Y, Huang X, et al. Efficacy comparison of different acupuncture treatments for functional dyspepsia: a systematic review with network meta-analysis. *Evid Based Complement Alternat Med*. 2020;2020:3872919.
38. Koog YH, Lee JS, Wi H. Nocebo and placebo effects may not be separate in acupuncture. *J Clin Epidemiol*. 2014;67: 1375–1376.
39. Tan K, Wells CI, Dinning P, et al. Placebo response rates in electrical nerve stimulation trials for fecal incontinence and constipation: a systematic review and meta-analysis. *Neuromodulation*. 2020;23:1108–1116.
40. Ko SJ, Kuo B, Kim SK, et al. Individualized acupuncture for symptom relief in functional dyspepsia: a randomized controlled trial. *J Altern Complement Med*. 2016;22:997–1006.
41. Guo LK, Zhang CX, Guo XF. Long-term efficacy and safety research on functional dyspepsia treated with electroacupuncture and Zhizhu Kuanzhong capsule. *Zhongguo Zhenjiu*. 2011; 31:1071–1077.
42. Pen F, Yang JY, Shi ZH. Electroacupuncture improves gastric motility, autonomic nerve activity and psychological state in patients with functional dyspepsia. *World Chin J Digest*. 2008;16:4105–4109.
43. Qiang LM, Jiang Y. Electroacupuncture for functional dyspepsia and the influence on serum Ghrelin, CGRP and GLP-1 levels. *World J Acupunct Moxibust*. 2018;28:86–90.
44. Zhang CX, Guo LK. Dalitong granule combined with electroacupuncture in the treatment of functional dyspepsia: a randomized controlled trial. *Chin J Integr Med*. 2015;21: 743–750.

45. Finniss DG, Kaptchuk TJ, Miller F, et al. Biological, clinical, and ethical advances of placebo effects. *Lancet*. 2010;375: 686–695.
46. Price DD, Craggs J, Verne GN, et al. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain*. 2007;127:63–72.
47. Park J, White A, Stevinson C, et al. Validating a new non-penetrating sham acupuncture device: two randomised controlled trials. *Acupunct Med*. 2002;20:168–174.
48. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet*. 1998;352:364–365.
49. Kreiner M, Zaffaroni A, Alvarez R, et al. Validation of a simplified sham acupuncture technique for its use in clinical research: a randomised, single blind, crossover study. *Acupunct Med*. 2010;28:33–36.
50. Lao L, Bergman S, Hamilton GR, et al. Evaluation of acupuncture for pain control after oral surgery: a placebo-controlled trial. *Arch Otolaryngol Head Neck Surg*. 1999;125:567–572.
51. Dos Santos Maciel LY, Dos Santos Leite PM, Neto ML, et al. Comparison of the placebo effect between different non-penetrating acupuncture devices and real acupuncture in healthy subjects: a randomized clinical trial. *BMC Complement Altern Med*. 2016;16:518.
52. Yang L, Wang Y, Mo Q, et al. A comparative study of electroacupuncture at Zhongliao (BL33) and other acupoints for overactive bladder symptoms. *Front Med*. 2017;11:129–136.