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Efficacy of Nonpharmacological Interventions and Combination With Pharmacological Interventions for Gastroesophageal Reflux Disease

A Systematic Review and Network Meta-Analysis

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Background: The efficacy of nonpharmacological therapies for patients with gastroesophageal reflux disease (GERD) has been progressively proved. However, the specific differences in effectiveness among various nonpharmacological interventions and their combinations with pharmacological interventions remain unclear, and the optimal intervention strategy has yet to be conclusively determined.

Methods: Systematic searches were conducted in PubMed, Web of Science, Embase, Cochrane, and CNKI from inception to November 6, 2024. A network meta-analysis was conducted using a random effects consistency model within a Bayesian framework with lower esophageal sphincter (LES) pressure as the primary outcome indicator.

Result: Thirty-three studies involving 10 nonpharmacological interventions were included. Acupoint stimulation with traditional Chinese medicine (TCM) (SMD = 5.83, 95% CI: 1.23 to 10.16), and breathing training with conventional Western medicine (CWM) (SMD = 3.88, 95% CI: 0.45 to 7.52) significantly improved LES pressure and reduced esophageal acid exposure time (AET) (SMD = −5.01 to −3.32). In terms of safety, acupoint stimulation with TCM (logOR = −2.51, 95% CI: -5.91 to −0.19) exhibited a significant advantage over CWM. However, acupoint stimulation combined with TCM and breathing training with CWM did not demonstrate a significant improvement in GERD health-related quality of life questionnaire (HRQL) scores.

Conclusion: Acupoint stimulation combined with TCM and breathing training with CWM, when compared with CWM and other nonpharmacological interventions, is considered a potential adjunctive therapeutic approach for GERD, demonstrating both efficacy and safety. However, methodological limitations necessitate cautious interpretation of results.

Key Words: gastroesophageal reflux disease, fundoplication, acupoint stimulation, network meta-analysis

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Gastroesophageal reflux disease (GERD) is characterized by troublesome symptoms or specific complications caused by the reflux of gastric content.[1,2] Heartburn and acid regurgitation are typical symptoms of GERD, and they are present across all three phenotypes of the condition.[3] In addition to the typical symptoms, GERD is accompanied by various intraesophageal and extraesophageal complications. Dysphagia, reflux-induced esophageal stricture, and esophageal ulcers are common intraesophageal complications. Barrett's esophagus and esophageal adenocarcinoma are severe complications of GERD.

The pathogenesis of GERD is closely associated with the impairment of the antireflux barrier function. The lower esophageal sphincter (LES) is the primary barrier against reflux, and transient lower esophageal sphincter relaxations (TLESRs) are the main pathogenic mechanism of GERD.[4] TLESRs contribute to acid reflux, while impaired peristalsis delays esophageal clearance, thereby increasing the duration of esophageal acid exposure.[5] In addition, 8% to 20% of patients with GERD have concurrent gastroparesis, and delayed gastric emptying leads to an increased gastric pressure gradient, which can also cause TLESRs resulting in GERD.[6] Obesity, NSAID use, smoking, and age over 50 are risk factors for GERD, which directly or indirectly compromising the integrity of the antireflux barrier and increasing the risk of its development.[7]

Statistics indicated that the global prevalence of GERD ranged between 8% and 33%, showing a yearly increase and exhibiting significant regional variations.[8–10]

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M.H., Z.Y., and X.S.: contributed to the study's conception and design. H.L., P.L., L.W., and J.Y.: conducted data retrieval and extraction. M.H., H.H., and Z.Y.: performed the data analysis. M.H.: drafted the manuscript. All authors interpreted the results and participated in substantial revisions and refinement of the manuscript. J.F. and X.S.: read and approved the final manuscript.

The data analyzed in this network meta-analysis are obtained from the studies included in the review. We have provided citations for each included study in the supplementary material, Supplemental Digital Content 1, http://links.lww.com/JCG/B266.

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Currently, proton pump inhibitors (PPIs) are recommended as the first-line therapy for GERD in guidelines.[11] With long-term use of PPIs, ample evidence suggests that PPIs increase the incidence of chronic kidney disease (CKD), intestinal infections, and fractures.[12] PPIs resistance is the challenge in GERD, and up to 40% of patients report that PPIs fail to adequately relieve symptoms such as heartburn and acid regurgitation.[13] Over 90% of patients exhibit typical GERD symptoms within 1 year after discontinuation of PPIs therapy.[14]

In recent years, nonpharmacological interventions and combined therapy for GERD, including fundoplication, acupuncture, breathing training, low-FODMAP diet, acupoint stimulation with traditional Chinese medicine (TCM, specifically denotes Chinese herbal medicine), and breathing training with conventional Western medicine (CWM), are widely used in the management of GERD. However, the evidence regarding the effectiveness of certain nonpharmacological interventions remains limited and contradictory. Fundoplication is the gold standard surgical intervention for GERD, and providing a viable alternative to long-term PPIs therapy.[15] However, there are concerns regarding its potential side effects.[16] Acupoint stimulation, encompassing various forms such as acupuncture, electroacupuncture, acupoint pressure, and transcutaneous electrical acupoint stimulation (TEAS), is widely used in the treatment of GERD. Several meta-analyses have indicated that both acupuncture alone and acupuncture combined with pharmacological treatment, significantly outperform pharmacotherapy.[17] Nevertheless, due to the limitations in the quality of the included studies, the evidence remains at a relatively low level. Other studies[18,19] suggest that breathing training may be a useful therapeutic approach. The efficacy of drug therapy in conjunction with breathing training requires further research. Furthermore, a study in 2024 indicated that the impact of a low-FODMAP diet on GERD symptom improvement remains controversial.[20]

The efficacy of nonpharmacological interventions for GERD is still in the preliminary stages of validation, and comprehensive evaluations of the efficacy of nonpharmacological interventions and their combinations with pharmacological interventions remain lacking. Previous pairwise comparison studies predominantly used GERD-specific symptom scales as outcome measures, resulting in a lower grade of evidence in these studies. Therefore, this study aims to use esophageal parameters as objective indicators to comprehensively evaluate the efficacy and safety of various nonpharmacological interventions and their combinations with pharmacological interventions through network meta-analysis, and further provide evidence-based medical support for the treatment of GERD.

METHODS

The study protocol was registered in PROSPERO (CRD42024541744). The systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-NMA) guidelines.[21]

Search Strategy

The search was conducted in Embase, Web of Science (Core Collection), PubMed, Cochrane, and CNKI. The search time was restricted from the establishment date of each database to November 6, 2024. The retrieval strategy combined Mesh subject terms and free terms, with the subject terms adjusted in accordance with the features of the database. After refining the search parameters through preliminary searches, GERD was determined as the subject term, and its subtypes including nonerosive reflux disease and reflux esophagitis, as well as typical symptoms include heartburn and acid regurgitation, were expanded as free-text terms for comprehensive retrieval. Nonpharmacological interventions, such as acupuncture, breathing exercises, and fundoplication, were categorized for targeted retrieval. The detailed search terms and retrieval records were shown in Table S1 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266).

Eligibility Criteria

Studies meeting the following criteria were included: (1) Participants included in the studies were diagnosed with GERD and aged over 18 years. (2) The experimental group received at least one nonpharmacological intervention, while the control group was limited to conventional western medicine, with no restrictions on dosage or duration. (3) Conventional western medicine in the experimental group must match those in the control group, except when traditional Chinese medicine is used in the experimental group. (4) The primary outcome was LES pressure, while secondary outcomes included esophageal acid exposure time (AET), GERD health-related quality of life (HRQL), and the incidence of adverse events. (5) Randomized controlled trials (RCTs) were included and with no language restrictions.

Exclusion criteria: (1) Barrett's esophagus or GERD with Hiatal Hernia. (2) Infant GERD and pediatric GERD studies. (3) For studies with multiple publications or identical data, include the earliest published study. (4) Studies with incomplete data or data that cannot be extracted. (5) Studies with inaccessible full text.

Data Extraction and Quality Assessment

Two researchers (M.H. and L.W.) independently screened the titles and abstracts of studies based on the inclusion and exclusion criteria. After independently screening the title and abstract of the study based on inclusion criteria, 2 researchers (M.H. and L.W.) reviewed the full texts of preliminarily eligible studies to assess their inclusion eligibility. Discrepancies will be resolved through group discussion or, if necessary, with the assistance of the corresponding author (X.S.). Two reviewers (J.Y and P.L.) independently utilized a standardized data extraction form to extract data from eligible studies meeting the criteria, focusing on the basic characteristics, demographic characteristics of the participants, study designs, and outcome measures. For studies that did not report the means and SDs, means and SDs were estimated if needed.[22,23]

Risk of Bias Assessment

Two researchers (M.H. and Yu) conducted independent bias risk assessments for the included studies using the revised Cochrane Risk of Bias Tool (ROB2).[24] ROB2 includes the following 5 domains: (1) randomization process; (2) deviation from intended interventions; (3) missing outcome data; (4) measurement of the outcome; (5) selection of the reported result. Each domain in the ROB2 tool has three levels of risk: low risk, high risk, and unclear risk. Disagreements were resolved through discussion, and if consensus was not reached, a third-party expert (X.S.) was consulted.

Statistical Analysis

Pairwise Meta-Analysis

Pairwise meta-analysis was conducted by Stata 17. In multiarm studies, we used the "splitting the shared group" method recommended by the Cochrane Handbook to divide the sample size of the common intervention group. A random-effects model was first used for pairwise meta-analysis of each outcome to detect heterogeneity. Heterogeneity is assessed by the I^2 statistic and P-value. If $I^2 > 50\%$ and $P < 0.05$, a random-effects model is applied to combine the data. Otherwise, the fixed effects model was applied. For outcomes with high heterogeneity, leave-one-out analysis[25] was conducted to explore potential sources of heterogeneity. Following the analysis, certain studies were excluded to reduce overall heterogeneity, and a sensitivity analysis was conducted to assess and compare the pooled effect sizes before and after exclusion. Effect sizes were reported as standardized mean difference (SMD) for continuous data and odds ratio (OR) for dichotomous data, with all results presented with 95% CI.

Network Meta-Analysis

Network meta-analysis (NMA) within the Bayesian framework was conducted using the gemtc package in R version 4.4.3. Considering the moderate to high heterogeneity among studies, effect values were estimated using the Bayesian inference method with a random-effects model, based on the Markov Chain Monte Carlo (MCMC) simulation. The initial iteration count was set to 50,000, with a burn-in period of 10,000 iterations. Convergence of the model was evaluated using the Brooks-Gelman-Rubin diagnostic plot and the Potential Scale Reduction Factor (PSRF). If the diagnostic plot showed convergence with curves remaining stable, and the PSRF approached 1, the random-effects model was deemed to have reached approximate convergence. Convergence was considered acceptable when the PSRF was below 1.2. If convergence was not achieved, the number of iterations was increased until stability was reached.

After the random-effects model achieved stable convergence, effect sizes were estimated. Standardized mean difference (SMD) values were calculated for continuous data, while log odds ratios (logOR) were determined for binary data, with all results reported with 95% CI. A 95% CI for SMD or logOR that excludes 1 was interpreted as indicating a statistically significant difference between interventions.

The surface under the cumulative ranking curve (SUCRA) was used to evaluate the relative ranking of different interventions comprehensively. On the basis of SUCRA values, a cluster analysis was performed to identify the optimal intervention across different outcomes. To ensure the reliability of the results, publication bias was assessed using Egger's test and adjusted funnel plots.

Grading the Certainty of Evidence

The Grading of Recommendations, Assessment, Development, and Evaluations methodology is used to assess the credibility of evidence. This method evaluates 5 potential sources of bias in each comparison: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. On the basis of these 5 biases or limitations, the evidence level is progressively downgraded, ultimately categorizing the evidence into 4 levels: high, moderate, low, and very low.

RESULT

Study Selection

A total of 9104 studies were identified across 5 databases. After screening titles and abstracts, 6699 studies that were irrelevant to clinical research or GERD were excluded. Subsequently, 260 studies were selected for full-text review, 226 studies were excluded as they did not meet the predefined inclusion and exclusion criteria. Finally, 34 studies were included in the meta-analysis (Fig. 1).

Studies Characteristics

Table S2 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266) summarizes the baseline characteristics of the 35 included studies. The included studies were published from 2001 to 2024, involving a total of 2985 participants. The participants had a mean age of 44.9 years and an average disease duration of 5.4 years. The control group received CWM, which consisted of either PPIs alone or a combination of PPIs and prokinetic agents. The experimental group encompassed 11 different types of interventions, including acupoint stimulation, acupoint stimulation with CWM, acupoint stimulation with TCM, acupoint stimulation combined with both CWM and TCM, breathing training with CWM, acupoint stimulation with breathing training, acupoint stimulation with breathing training and CWM, a low-FODMAP diet with CWM, Nissen fundoplication, transoral incisionless fundoplication (TIF) and stretta therapy. The duration of nonsurgical interventions ranged from 2 to 8 weeks, while the follow-up period for fundoplication and stretta therapy lasted between 6 months and 3 years. Table S3, Supplemental Digital Content 1, http://links.lww.com/JCG/B266 summarizes the acupoint selection protocols and treatment frequency distributions across 22 acupoint stimulation trials. Treatment frequency varied markedly among studies, ranging from once weekly at the lowest to twice daily at the highest. Statistical analysis of high-frequency acupoint usage (Table

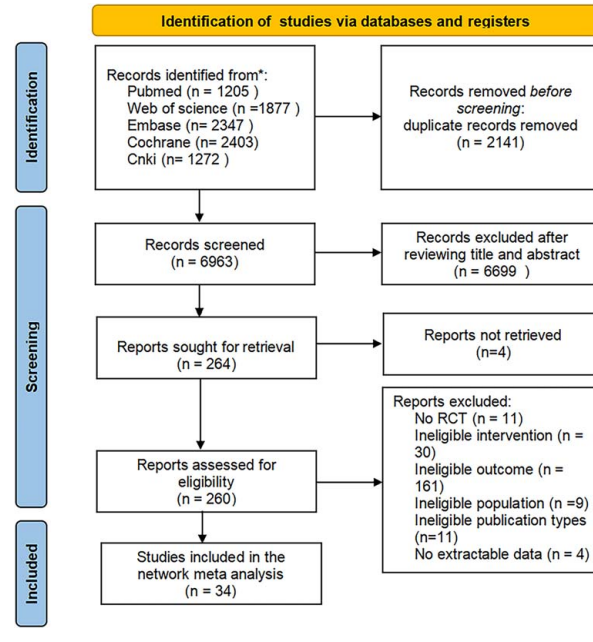

FIGURE 1. PRISMA flow chart of study selection.

S4, Supplemental Digital Content 1, http://links.lww.com/JCG/B266) identified, in descending order of selection rate, the following 8 points: ST36, CV12, PC6, BL18, BL21, BL20, BL19, LR3.

Risk of Bias Assessment

Figure S1 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266) and Figure 2 present the risk of bias in the 34 included studies. Among the included studies, 26 adequately reported the randomization procedures, such as random number tables, stratified block randomization, computer-generated randomization, and lottery-based allocation. Eight studies were evaluated to have a moderate risk of bias due to the lack of detailed description of the randomization procedure. In light of the inherent characteristics of nonpharmacological interventions, it was hard to implement double-blinding for both patients and investigators. In addition, only 4 studies explicitly reported the use of the intention-to-treat principle in their data analysis. These factors contribute to some concerns in the risk of deviations from intended interventions. Two studies using Nissen fundoplication as the intervention conducted follow-ups lasting 3 months and 3 years, respectively. Both studies reported a high dropout rate among participants and were assessed as having moderate and high risk of bias due to missing data. All studies used consistent outcome measurement methods for both experimental and control groups, and comprehensively reported all predefined outcome measures included in their trial designs. Thus, the risks of outcome measurement and selective reporting were assessed as low risk.

Figure S2 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266) and Table S5 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266) present the outcomes of the comparison-adjusted funnel plot and Egger's test. The results revealed that the funnel plot exhibited a largely symmetrical distribution, and the Egger's test did not reach statistical significance, indicating no substantial evidence of publication bias.

Pairwise Meta-Analysis

Compared with CWM, improvements in LES pressure were observed in interventions incorporating acupoint stimulation with CWM, breathing training with acupoint stimulation, low-FODMAP diet with CWM, and Nissen fundoplication (SMD = 0.47 to 1.26). In the pairwise meta-analysis focusing on esophageal AET, significant heterogeneity was observed between nonpharmacological interventions and CWM. A leave-one-out sensitivity analysis indicated that the studies by Lin B2023 and Wu XM2022 had a substantial impact on the overall results (Figs. S3, S4, Supplemental Digital Content 1, http://links.lww.com/JCG/B266). Considering the potential influence and heterogeneity caused by the studies, the studies by Lin B in 2023 and Wu XM in 2022 on esophageal AET were excluded, and sensitivity analyses were performed on the results before and after the exclusion. The results of the analysis showed that the overall heterogeneity before exclusion was 91.8% (SMD = −0.73, 95% CI: −1.15 to −0.32). Following the exclusion, heterogeneity decreased to 68.4% (SMD = −0.30, 95% CI: −0.53 to −0.07). The narrowing of the confidence interval postexclusion suggests increased stability of the results. The final results indicate that breathing training with CWM, acupoint stimulation with TCM, and Nissen fundoplication significantly shortened esophageal AET (SMD = −3.16 to −0.38). In terms of HRQL values, all nonpharmacological interventions alone and nonpharmacological with CWM demonstrated a positive impact on quality of life compared with CWM. While, regarding adverse event incidence, Nissen fundoplication, TIF and stretta were associated with a significantly higher rate of adverse events compared with CWM (OR = 4.56 to 21.42). In contrast, acupoint stimulation alone, acupoint stimulation with TCM, and acupoint stimulation with both TCM and CWM exhibited lower adverse event rates compared with CWM (OR = 0.11 to 0.95). The pairwise meta-analysis is detailed in Table 1.

Network Meta-Analysis

Primary Outcome LES Pressure

Figure 3A presents the LES pressure network plot, which is derived from the data of 18 RCTs that comprise a total of 1566 participants. These studies encompass 9 types of interventions, including CWM, acupoint stimulation, acupoint stimulation with breathing training, acupoint stimulation with CWM, breathing training with CWM, acupoint stimulation with TCM, acupoint stimulation and breathing training with CWM, low-FODMAP diet with CWM, and Nissen fundoplication. The highest number of studies compared acupoint

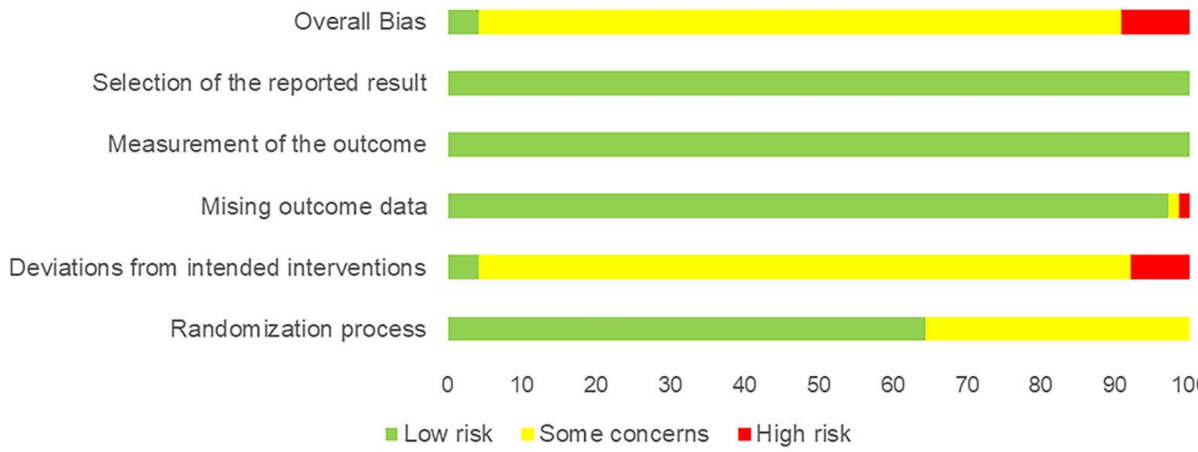

FIGURE 2. Risk of bias summary of the included trials.

TABLE 1. Pairwise Comparison of Nonpharmacological Interventions

Comparison	Number	SMD (95% CI)	I^2 (%)	P
Pairwise meta-analysis of LES pressure				
APS	2	0.28 (−0.15, 0.71)	43.7	0.18
APS+CWM	5	1.26 (0.83, 1.68)	83.5	0.000
BT+CWM	3	1.75 (1.30, 2.20)	0.0	0.800
APS+TCM	2	1.28 (−0.26, 2.83)	93.8	0.000
APS+BT+CWM	2	1.17 (−0.12, 2.46)	72.6	0.056
LFD+CWM	1	0.47 (0.06, 0.88)	—	—
APS+BT	1	0.31 (−0.16, 0.79)	—	—
LNF	2	1.21 (0.95, 1.47)	0.0	0.606
Overall	18	1.08 (0.81, 1.35)	82.9	0.000
Pairwise meta-analysis of esophageal AET				
APS	4	−0.24 (−0.64, 0.15)	75	0.007
BT+CWM	1	−3.16 (−4.55, −1.77)	—	—
LFD+CWM	2	−0.17 (−0.52, 0.19)	0.0	0.857
APS+TCM	1	−0.52 (−0.84, −0.21)	—	—
NF	3	−0.38 (−0.61, −0.15)	0.0	0.915
RF	1	0.42 (−0.25, 1.08)	—	—
TIF	1	−0.07 (−0.60, 0.46)	—	—
Overall	13	−0.30 (−0.53, −0.07)	68.4	0.000
Pairwise meta-analysis of HRQL				
AP	2	−1.32 (−1.72, −0.93)	0.0	0.784
BT+CWM	1	−1.71 (−2.46, −0.96)	—	—
APS+CWM	1	−2.36 (−2.87, −1.85)	—	—
APS+TCM	4	−0.99 (−1.23, −0.76)	0.0	0.565
APS+TCM+CWM	2	−1.25 (−1.71, −0.79)	41.4	0.191
APS+BT	1	−1.15 (−1.67, −0.64)	—	—
TIF	2	−1.47 (−1.97, −0.96)	27.8	0.239
Overall	12	−1.32 (−1.55, −1.08)	60.4	0.003
Pairwise meta-analysis of adverse events (OR)				
APS	2	0.11 (0.01, 0.92)	0.0	0.605
APS+CWM	1	0.95 (0.13, 7.09)	—	—
APS+TCM	3	0.17 (0.04, 0.68)	0.0	0.995
APS+TCM+CWM	1	0.14 (0.02, 1.18)	—	—
NF	2	21.42 (2.84, 161.66)	0.0	0.718
RF	1	9.60 (0.50, 184.26)	—	—
TIF	1	4.56 (0.23, 88.77)	—	—
Overall	11	0.79 (0.22, 2.80)	62.2	0.003

The intervention in all control groups were CWM. Esophageal AET: PH < 4%.

APS indicates acupoint stimulation; BT, breathing training; CWM, conventional Western medicine; LFD, low-FODMAP diet; NF, Nissen fundoplication; RF, stretta; TCM, traditional Chinese medicine; TIF, transoral incisionless fundoplication.

stimulation with CWM to CWM alone. The consistency model results indicated that, compared with CWM, 5 of the 8 evaluated interventions, with the exceptions of acupoint stimulation alone, the low-FODMAP diet with CWM, and acupoint stimulation with breathing training, effectively increased LESP (SMD = 3.88 to 7.77) (moderate to very low certainty evidence, Table S9, Supplemental Digital Content 1, http://links.lww.com/JCG/B266). Furthermore, Nissen fundoplication demonstrated greater effectiveness in enhancing LES pressure compared with acupoint stimulation (SMD = 6.82, 95% CI: 0.75-13.04) and the low-FODMAP diet with CWM (SMD = 7.44, 95% CI: 0.06-14.82). However, no statistically significant differences were identified among the other interventions in their efficacy for improving LES pressure levels (Table 2). The efficacy of 9 intervention measures was ranked, with Nissen fundoplication (SUCRA = 90.8%) showing the greatest impact on LES pressure, followed by acupoint stimulation with TCM (SUCRA = 75.9%) and acupoint stimulation with breathing training and CWM (SUCRA = 75.9%) (Fig. S5, Supplemental Digital Content 1, http://links.lww.com/JCG/B266).

Secondary Outcome

Esophageal AET (PH < 4%)

Twelve studies involving 1165 patients were included, evaluating the effects of 8 interventions on esophageal AET. The specific interventions assessed were CWM, acupoint stimulation, low-FODMAP diet with CWM, breathing training combined with CWM, acupoint stimulation with TCM, Nissen fundoplication, TIF and Stretta therapy (Fig. 3b). In reducing esophageal AET, breathing training with CWM was found to be more effective than the other 5 interventions (SMD = −7.60 to −4.43), with the exception of acupoint stimulation with TCM and Nissen fundoplication. In addition, acupoint stimulation with TCM exhibited significant efficacy in shortening esophageal AET, outperforming CWM alone (moderate certainty evidence) (Table S10, Supplemental Digital Content 1, http://links.lww.com/JCG/B266), acupoint stimulation alone, a low-FODMAP diet combined with CWM, and Stretta therapy (SMD = −5.90 to −2.73). Nissen fundoplication was found to be more effective than CWM in reducing esophageal AET (SMD = −2.33, 95% CI: −4.39 to −0.33, moderate certainty evidence).

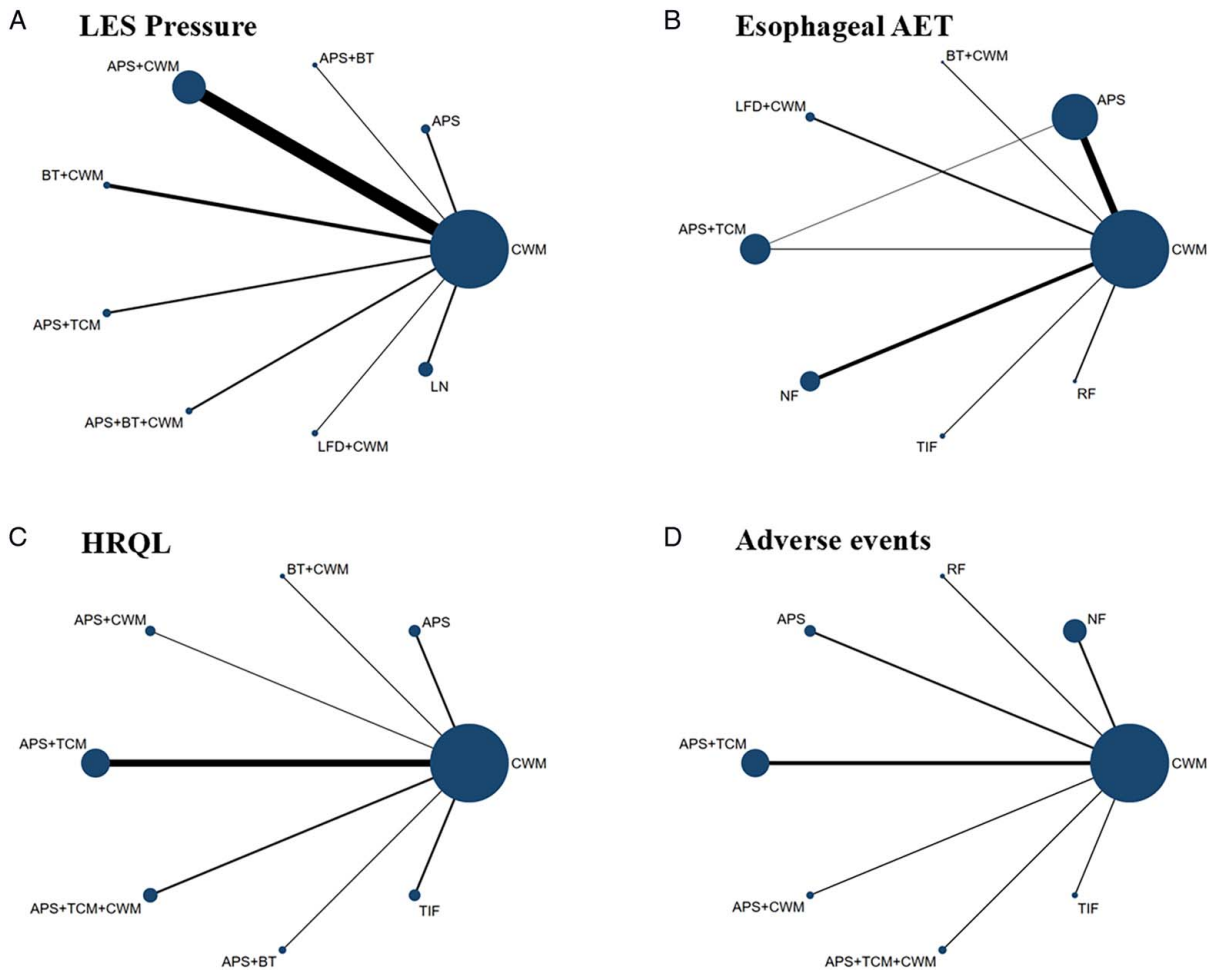

FIGURE 3. Network plot of outcome indicators. A, LES pressure. B, Esophageal AET. C, HRQL. D, Adverse events. APS, acupoint stimulation; BT, breathing training; CWM, conventional Western medicine; LFD, low-FODMAP diet; NF, Nissen fundoplication; RF, stretta; TCM, traditional Chinese medicine; TIF, transoral incisionless fundoplication. Esophageal AET: PH < 4%.

However, no statistically significant differences in therapeutic efficacy were observed when compared with other interventions, with the exception of breathing training with CWM. On the basis of the SUCRA values, breathing training with CWM (SUCRA = 96.9%) was identified as the most effective intervention for shortening esophageal AET, followed by acupoint stimulation with TCM (SUCRA = 82.7%) and Nissen fundoplication (SUCRA = 71.7%). The results of the network meta-analysis and SUCRA values for esophageal AET are provided in Table S6 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266) and Figure S6 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266).

HRQL

Figure 3C and Table S7 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266) summarize the results of the HRQL scores. Overall, 13 studies involving a total of 916 participants assessed the impact of 8 interventions on HRQL scores: CWM, acupoint stimulation, breathing training with CWM, acupoint stimulation with CWM, acupoint stimulation with TCM, acupoint stimulation combined with TCM and CWM, acupoint stimulation combined with breathing training, and TIF. The results indicated that, compared with CWM, 6 of the 7 interventions (moderate to low certainty evidence, Table S11, Supplemental Digital Content 1, http://links.lww.com/JCG/B266), excluding breathing training with CWM, significantly reduced HRQL scores (SMD = −13.26 to −3.87). Furthermore, TIF demonstrated superior efficacy in improving HRQL scores compared with other interventions (SMD = −13.26 to −5.46). Acupoint stimulation alone and acupoint stimulation with breathing training were more effective than breathing training combined with CWM in reducing HRQL scores (SMD = −6.63 to −6.00). The SUCRA revealed that the most effective treatment for HRQL was TIF (SUCRA = 98.7%), acupoint stimulation combined with breathing training (SUCRA = 75.4%), and acupoint stimulation alone (SUCRA = 73.1%), respectively (Fig. S7, Supplemental Digital Content 1, http://links.lww.com/JCG/B266).

Adverse Events

A total of 11 trials were included to evaluate the incidence of clinical adverse events associated with CWM, acupoint stimulation, acupoint stimulation combined with CWM, acupoint stimulation with TCM, acupoint stimulation combined with TCM and CWM, Stretta, TIF and Nissen fundoplication (Fig. 2D). The results revealed that compared

TABLE 2. League Table of Primary Outcomes

LES pressure (SMD, 95% CI)								
CWM	0.93 (−3.27, 5.25)	0.52 (−5.54, 6.47)	4.10 (1.42, 6.76)	3.88 (0.45, 7.52)	5.83 (1.23, 10.16)	5.79 (1.12, 11.39)	0.34 (−5.48, 6.31)	7.77 (3.29, 12.19)
−0.93 (−5.25, 3.27)	APS	−0.42 (−7.69, 6.90)	3.17 (−1.85, 8.17)	2.94 (−2.44, 8.55)	4.87 (−1.36, 10.96)	4.87 (−1.32, 12.14)	−0.60 (−7.92, 6.70)	6.82 (0.75, 13.04)
−0.52 (−6.47, 5.44)	0.42 (−6.90, 7.69)	APS+BT	3.58 (−2.93, 10.11)	3.37 (−3.51, 10.44)	5.29 (−2.30, 12.57)	5.26 (−2.01, 13.69)	−0.16 (−8.55, 8.31)	7.24 (−0.22, 14.74)
−4.10 (−6.76, −1.42)	−3.17 (−8.17, 1.85)	−3.58 (−10.11, 2.93)	APS+CWM	−0.21 (−4.55, 4.34)	1.68 (−3.56, 6.88)	1.67 (−3.54, 8.00)	−3.73 (−10.15, 2.69)	3.66 (−1.50, 8.83)
−3.88 (−7.52, −0.45)	−2.94 (−8.55, 2.44)	−3.37 (−10.44, 3.51)	0.21 (−4.34, 4.55)	BT+CWM	1.92 (−3.96, 7.46)	1.92 (−3.86, 8.47)	−3.53 (−10.44, 3.22)	3.90 (−1.82, 9.44)
−5.83 (−10.16, −1.23)	−4.87 (−10.96, 1.36)	−5.29 (−12.57, 2.30)	−1.68 (−6.88, 3.56)	−1.92 (−7.46, 3.96)	APS+TCM	0.03 (−6.15, 7.39)	−5.46 (−12.66, 2.04)	1.99 (−4.26, 8.39)
−5.79 (−11.39, −1.12)	−4.87 (−12.14, 1.32)	−5.26 (−13.69, 2.01)	−1.67 (−8.00, 3.54)	−1.92 (−8.47, 3.86)	−0.03 (−7.39, 6.15)	APS+BT+CWM	−5.46 (−13.67, 1.75)	1.96 (−5.34, 8.22)
−0.34 (−6.31, 5.48)	0.60 (−6.70, 7.92)	0.16 (−8.31, 8.55)	3.73 (−2.69, 10.15)	3.53 (−3.22, 10.44)	5.46 (−2.04, 12.66)	5.46 (−1.75, 13.67)	LFD+CWM	7.44 (0.06, 14.82)
−7.77 (−12.19, −3.29)	−6.82 (−13.04, −0.75)	−7.24 (−14.74, 0.22)	−3.66 (−8.83, 1.50)	−3.90 (−9.44, 1.82)	−1.99 (−8.39, 4.26)	−1.96 (−8.22, 5.34)	−7.44 (−14.82, −0.06)	NF

APS indicates acupoint stimulation; BT, breathing training; CWM, conventional Western medicine; LFD, low-FODMAP diet; NF, Nissen fundoplication; RF, stretta; TCM, traditional Chinese medicine; TIF, transoral incisionless fundoplication.

with CWM and other nonpharmacological treatments, Nissen fundoplication (logOR = 28.66 to 72.59), Stretta (logOR = 27.39 to 72.51), and TIF (logOR = 23.09 to 64.23) are associated with a higher incidence of adverse events, while acupoint stimulation (logOR = −64.23 to −35.92) had the lowest incidence of adverse events (moderate to very low certainty evidence, Table S12, Supplemental Digital Content 1, http://links.lww.com/JCG/B266). The safety of the 8 treatments was ranked based on SUCRA. Acupoint stimulation ranked highest in safety (SUCRA = 99.6%), followed by acupoint stimulation with TCM (SUCRA = 76.9%) and acupoint stimulation combined with TCM and CWM (SUCRA = 75.1%). The results of the network meta-analysis and SUCRA values for adverse events are provided in Table S8 and Figure S8 (Supplemental Digital Content 1, http://links.lww.com/JCG/B266).

Cluster Analysis

LES Pressure and Esophageal AET

Cluster analysis was conducted on 6 shared interventions included in both LESP and esophageal AET. The *x*-axis represents the SUCRA values for the effectiveness of interventions in improving LES pressure, while the *y*-axis corresponds to the esophageal AET improvement SUCRA values. The results of the cluster analysis revealed that the 6 interventions were classified into 3 categories, among which Nissen fundoplication, acupoint stimulation combined with TCM, and breathing training with CWM exhibited relatively superior therapeutic efficacy, as depicted in Figure 4.

Efficacy and Safety

Cluster analysis was conducted to evaluate the efficacy and safety of different interventions based on their SUCRA values. The clustering results indicated that, in terms of the efficacy parameters LES pressure and esophageal AET, the combination of acupoint stimulation and TCM achieved a cohesive integration of clinical efficacy and safety. For the HRQL, acupoint stimulation alone exhibited superior efficacy and safety. Notably, Nissen fundoplication

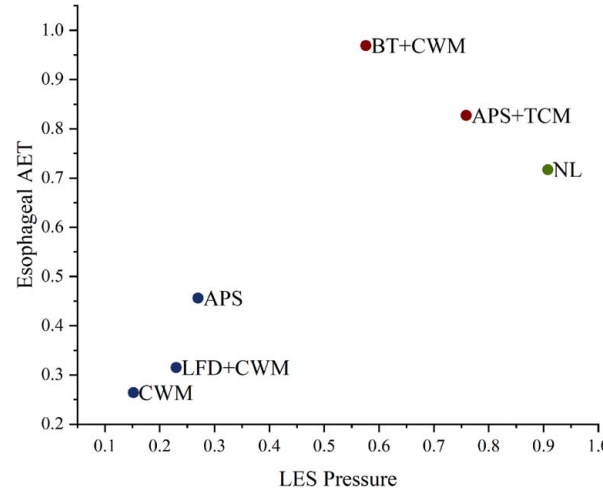

FIGURE 4. Cluster analysis plot for SUCRA of LES pressure and esophageal AET. APS indicates acupoint stimulation; BT, breathing training; CWM, conventional Western medicine; LFD, low-FODMAP diet; NF, Nissen fundoplication; TCM, traditional Chinese medicine. Esophageal AET: PH < 4%.

demonstrated superior efficacy, ranking among the top interventions, but its safety remained comparatively inferior (Figs. S9–S11, Supplemental Digital Content 1, http://links.lww.com/JCG/B266).

DISCUSSION

To our knowledge, this study represents the first NMA to systematically and comprehensively assess the efficacy of nonpharmacological interventions for GERD based on esophageal parameters. According to the results of the NMA, several preliminary trends have been identified. The combination of nonpharmacological and pharmacological treatments, as well as standalone nonpharmacological interventions, demonstrated superior efficacy in increasing LES pressure, reducing esophageal AET, and improving the quality of life in patients with GERD compared with CWM. Among these treatments, Nissen fundoplication, acupoint stimulation combined with TCM, and breathing training with CWM have shown particularly significant efficacy in improving esophageal parameters. Previous studies have confirmed that fundoplication can restore normal esophageal parameters in patients with GERD and provide sustained reflux symptom remission.[11] This conclusion aligns with the findings of the present study. Furthermore, among nonpharmacological interventions, TIF appears to offer a potential advantage in reducing HRQL scores and may be the most effective intervention for improving quality of life in GERD patients, with the highest ranking probability. The study only included 2 types of fundoplication procedures: Nissen fundoplication and TIF. In terms of reducing esophageal AET, Nissen fundoplication showed significantly better outcomes compared with TIF, corroborating the results of a 2018 study.[26] Although previous studies have compared various fundoplication (eg, Nissen, Toupet, Dor), considerable controversy persists regarding their comparative efficacy and postoperative complications. Current evidence indicates that Toupet fundoplication demonstrates comparable efficacy to both Nissen and Dor procedures in controlling gastroesophageal reflux, while offering the distinct advantage of significantly reducing postoperative complications such as dysphagia and gas-related symptoms.[27,28] Furthermore, studies have shown that compared with Toupet fundoplication, the Dor provides less comprehensive relief of reflux symptoms and is associated with higher reoperation rates, although both techniques demonstrate similar long-term dysphagia outcomes.[29] Collectively, Toupet fundoplication achieves an optimal balance between effective reflux control and reduced postoperative complications.[30,31]

As a nonsurgical intervention, Stretta techniques constitutes a viable alternative to fundoplication procedures. This study demonstrates comparable efficacy between stretta, TIF, and Nissen fundoplication in improving esophageal acid exposure time. However, the present analysis did not include stretta in the LESP comparison. Existing evidence suggests TIF may be superior to stretta in enhancing LESP.[32,33] Further research is needed to clarify the relative impact of stretta and fundoplication on esophageal parameters.

Notably, Nissen fundoplication, TIF, and stretta are associated with a significantly increased incidence of adverse events compared with other interventions. Frequently reported adverse events include dysphagia and gas-bloat syndrome, while severe complications involve mortality, perforation, and chest pain.[34,35] To optimize the balance between therapeutic efficacy and potential adverse effects, guidelines issued by organizations such as the AGA, SAGES, and ACG have delineated standardized criteria for patient selection in fundoplication. These guidelines[14,36] include a subset of GERD patients who experience adverse effects or complications associated with PPI therapy, as well as those with refractory GERD. Comprehensive preoperative impedance-pH monitoring is used to confirm the persistence of reflux symptoms and to rule out significant esophageal motility disorders.

Given the limitations of fundoplication, it is imperative to explore additional adjunctive therapeutic strategies. The results of the NMA indicated that acupoint stimulation combined with TCM showed great potential in improving esophageal parameters. Multiple meta-analyses[37–39] have indicated that acupoint stimulation combined with TCM and acupoint stimulation alone demonstrate significantly greater clinical efficacy and symptom improvement than CWM, while also contributing to a notable reduction in the recurrence rate of GERD. With regard to the therapeutic mechanism of GERD, several studies[40,41] concluded that TEAS can activate the vagus nerve and strengthen the excitability of the vagus nerve. For GERD patients with gastrointestinal motility disorders and gastroparesis, it can regulate gastric slow-wave activity, increase the LES pressure, and thereby relieve acid reflux event.[42] In addition, acupuncture can modulate the release of motilin and gastrin through stimulating the vagus nerve by the dorsal motor nucleus of the vagus and activating the sympathetic nervous system through the celiac ganglia, thus improving gastrointestinal dysfunction.[43] In contrast, TCM demonstrates superior efficacy over PPIs in alleviating symptoms of acid regurgitation and heartburn in GERD patients, while also significantly reducing the recurrence rate.[44,45] Current research indicates that TCM exerts therapeutic effects on GERD by modulating multiple targets within GERD-related signaling pathways, exhibiting anti-inflammatory properties, suppressing oxidative stress, and reducing esophageal hypersensitivity.[46,47] Compared with fundoplication, acupoint stimulation with TCM is associated with a lower incidence of adverse events. Moreover, Traditional Chinese Medicine therapies encompass a broad range of therapeutic applications and have shown benefits in managing refractory GERD and certain esophageal syndromes.[48]

Regarding the therapeutic differences among various acupoint stimulations for GERD, only a 2018 meta-analysis[49] investigated 7 interventions, including manual acupuncture, fire needle, and catgut embedding. The results demonstrated that acupuncture combined with chiropractic manipulation showed the optimal therapeutic efficacy, with a low quality of evidence. Further refinement needed on efficacy differences among acupoint stimulation therapies. In addition to the inherent diversity of acupoint stimulation therapy itself, the acupoint selection protocols also demonstrate remarkable variability. The acupoint selection protocols for GERD can be classified into 2 main categories[50]: The first protocol mainly focuses on acupoints from the Conception Vessel, Stomach Meridian of Foot-Yangming, and Bladder Meridian of Foot-Taiyang. Acupoints including CV12, ST36, PC6, and BL21 form the core acupoint combination, demonstrating high application frequency in clinical practice. The acupoint combination may exert therapeutic effects through the following mechanisms: (1) Endocrine Modulation Mechanism: elevates serum levels of motilin and gastrin, accelerating gastric emptying and reducing reflux risk.[51] (2) Autonomic Nervous System

Regulation Mechanism: suppresses sympathetic overexcitation while enhancing vagal tone, thereby normalizing gastrointestinal motility.[52] (3) Central Nervous System Integration Mechanism: targets the brainstem to activate multiple neuromodulatory pathways—including nitric oxide (NO) signaling, CCK-A receptors, and mu-opioid receptors. This significantly reduces TLESR frequency while simultaneously improving gastrointestinal motor and secretory functions.[53,54] The second protocol primarily utilizes acupoints along the Governing Vessel, specifically targeting tender points located beneath the spinous processes of T1-T9 vertebrae. The Governor Vessel courses along the spinal column and exhibits close anatomic relationships with spinal nerves. Stimulation of tender points beneath T1-T9 spinous processes modulates visceral function through integrated neurohumoral regulation and autonomic nervous system mechanisms.[55]

However, in terms of HRQL improvement, while acupoint stimulation combined with TCM exhibited greater efficacy than CWM, it remained less effective when compared with acupoint stimulation therapy alone. Furthermore, it was observed that standalone nonpharmacological interventions, such as fundoplication, acupoint stimulation combined with breathing training, and acupoint stimulation alone, resulted in greater improvements in quality of life compared with combined nonpharmacological and pharmacological treatment strategies. This might be ascribed to the following reasons: prolonged and continuous use of PPIs in patients with GERD has been associated with potential adverse effects during treatment, as well as the cumulative burden of long-term medication use, both of which may significantly compromise patients' quality of life. In contrast, nonpharmacological treatment strategies alone have been shown to effectively control reflux symptoms, reducing the dependency on medication, and consequently leading to improvements patients' quality of life.

A 2020 study[56] indicated that breathing training alleviates reflux symptoms in GERD patients and reduces the frequency of acid-suppressive medication usage. Subsequently, the study by Ong et al[57] revealed that breathing training effectively controlled reflux symptoms, even in patients with refractory GERD, and significantly improved the quality of life scores of GERD patients. Our study further demonstrated that the combination of breathing training and CWM is effective in significantly reducing esophageal AET. Other studies have shown that breathing exercises enhance diaphragmatic muscle tension, thereby improving the function of the antireflux barrier.[19,58] This mechanism is regarded as one of the critical pathways through which breathing exercises contribute to the alleviation of GERD symptoms. Regarding the incidence of adverse events, none of the 3 studies included in our analysis reported any occurrences of related adverse events. Considering its demonstrated safety and efficacy, the combination of breathing training and CWM is considered suitable for the majority of GERD patients. Furthermore, for individuals who experience fear or aversion toward acupuncture, this combined approach may represent a more preferable therapeutic option.

This study also preliminarily observed the overall efficacy of combining acupoint stimulation with breathing training and CWM in improving LES pressure. Given the current limited and fragmented understanding of this combined therapy, we propose that future studies extensively incorporate such integrative treatment interventions, further exploring the benefits of combined approaches, such as acupoint stimulation, breathing training, and CWM, as well as acupoint stimulation, breathing training, and TCM. These studies would offer more diverse options for the clinical management of GERD. It is worth emphasizing that during the literature screening process, we observed that the majority of clinical trials on GERD predominantly rely on symptom assessment scales, such as the reflux diagnostic questionnaire and the gastroesophageal reflux disease questionnaire, as key outcome measures for evaluating therapeutic efficacy. However, these assessment scales are characterized by a high degree of subjectivity, which introduces potential bias in the evaluation of therapeutic efficacy and may impact the accuracy and objectivity of trial outcomes. Consequently, in accordance with the pathophysiology of GERD, this study incorporated RCTs that utilized 2 objective esophageal parameters, namely LES pressure and esophageal AET, as efficacy evaluation criteria. Therefore, in future clinical trials, we recommend incorporating high-resolution esophageal manometry parameters, in addition to GERD-related scales, as objective measures to evaluate the efficacy of interventions on improving reflux barrier function and alleviating symptoms.

This study also has some limitations. First, the number of included literature was relatively limited, and there is a paucity of literature related to some therapeutic approaches, which may not accurately and comprehensively assess the efficacy and safety of nonpharmacological interventions. Second, constrained by the limited number of available studies, we used the umbrella term "acupoint stimulation" to collectively analyze various intervention modalities including manual acupuncture, electroacupuncture, and catgut embedding, and did not further distinguishing between specific acupoint selection protocols or treatment frequencies. It should be emphasized that significant differences exist among these acupoint stimulation therapies regarding their mechanisms of action, as well as the potential effects of different acupoint combinations and treatment frequencies on therapeutic outcomes. Therefore, the interpretation of these research findings should carefully consider these methodological limitations. Third, some studies included a relatively small sample size of patients, which might have impacted the strength of evidence. Fourth, due to the absence of sufficient direct evidence, the conclusions of this study were predominantly based on indirect comparisons. Lastly, the absence of long-term follow-up data limited this study in evaluating the sustained efficacy of nonpharmacological interventions. As a result, a substantial number of high-quality RCTs will be required in the future to further validate the short-term and long-term efficacy of nonpharmacological interventions.

CONCLUSIONS

In conclusion, our study provided evidence supporting the efficacy of fundoplication in improving esophageal parameters, and reducing the HRQL scores in patients with GERD, while being accompanied by a relatively higher risk of adverse events. Comparatively, acupoint stimulation combined with TCM and breathing training with CWM are considered potential adjunctive therapeutic options for GERD, demonstrating both efficacy and safety, but the certainty of evidence ranges from moderate to low. However, methodological limitations necessitate cautious interpretation of results.

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