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Electrical stimulation to treat tinnitus: a meta-analysis and systemic review of randomized controlled trials

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Abstract

Background and aims: Tinnitus is one of the most common otological symptoms that patients experience, and it can be debilitating. No effective drug treatments are available for tinnitus, although considerable research investigating its mechanisms and possible treatments is underway. Electrical stimulation has been considered a promising and well-tolerated therapeutic strategy for tinnitus. This meta-analysis study was aimed to investigate the efficacy, safety and tolerability of electrical stimulation in patients with tinnitus.

Methods: Relevant studies were retrieved from the Embase, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature (CBM), Wanfang and Weipu databases. The Tinnitus Handicap Inventory (THI) and the visual analogue scale (VAS) which focus on loudness and distress evaluation (0–10 points) were used to assess perceived tinnitus suppression after treatment. Subgroup analysis was also performed based on different stimulating areas and methods, follow-up times, tinnitus duration and electrical current intensity. Review Manager 5.4 software was used for data synthesis, and Stata 15.1 software was used for analyses of publication bias and sensitivity.

Results: Our meta-analysis included 11 studies involving a total of 447 patients with tinnitus. The results showed that electrical stimulation significantly reduced THI scores [mean difference (MD) = −9.69; 95% confidence interval (CI) = −14.25, −5.13; $p < 0.0001$; $I^2 = 80\%$] and VAS scores between the two groups (VAS loudness scores, MD = −0.72; 95% CI = −1.20, −0.25; VAS distress scores, MD = −0.90; 95% CI = −1.17, −0.63). In addition, subgroup analysis showed that THI scores in electrical stimulation group of different stimulating areas and methods follow-up times, tinnitus duration and electrical current intensity were generally reduced, regardless of the acute or subacute tinnitus group or left temporoparietal area (LTA) group with no statistical significance between two groups.

Conclusion: Overall, electrical stimulation may be an effective and well-tolerated treatment option for tinnitus.

Keywords: electrical stimulation, meta-analysis, tinnitus, transcranial direct current stimulation, transcutaneous electrical nerve stimulation

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Introduction

Tinnitus is one of the most common and bothersome otological problems; it affects 10–30% of the population and is defined as a sound in the head or ears that occurs in the absence of any external acoustical source.[1] Some patients are not bothered by the sound. However, between 6% and 25% of affected people report symptoms that are severely debilitating, and 2–4% of the tinnitus population suffers from various somatic and psychological disorders, such as depression, anxiety and insomnia, that interfere with their quality of

life.[2] It has been reported that the stronger the tinnitus distress is, the more likely it is that a comorbidity is present.[3] The exact potential mechanism is completely unknown. However, it is plausible that tinnitus originates from a maladaptive homeostatic compensation mechanism that is triggered by auditory deprivation.[4]

Various treatment modalities, including repetitive transcranial magnetic stimulation (rTMS) or direct current stimulation and specific forms of acoustic stimulation (noise/mask, music and coordinated reset), acupuncture and so on, have been investigated to help people with tinnitus. However, no treatments have been proven to effectively modulate the tinnitus percept. That is, its loudness and interventions for the disease are still a subject of ongoing debate.[5–7]

The use of electrical current to alter physiological responses has been recognized as an effective treatment modality since the 1800s;[8] this approach has been used to treat inflammation, chronic pain, edema, depression and spinal disorders with promising outcomes.[8] Electrical stimulation of the cochlea as a treatment for profound hearing loss has been used since 1960,[8,9] and some patients who have participated in experiments in which the cochlea was subjected to electrical stimulation[6] to treat deafness have demonstrated tinnitus suppression.

Despite the development of animal models of tinnitus and the advent of new brain imaging techniques within the last few decades, knowledge about the pathophysiology of tinnitus is still quite controversial;[10] some studies of models have suggested that tinnitus is related to sensory deprivation and may result from altered functionality at many levels, causing abnormal neural activity propagation throughout the auditory network.[11,12] Therefore, electrical stimulation in relevant areas may be effective in suppressing tinnitus. Thus, some invasive and noninvasive treatments, including transcranial direct current stimulation (tDCS), electrical promontory stimulation (EPS), deep brain stimulation (DBS), vagus nerve stimulation (VNS) and transcutaneous electric nerve stimulation (TENS), have been attempted. However, EPS and TENS, as invasive procedures, are usually employed in animal experiments, and their use has lessened recently. Until now, electrical stimulation for the treatment of tinnitus has remained an intriguing therapeutic option; nevertheless, studies investigating the therapeutic effects of tinnitus have continuously been reported.[13]

Few reviews have explored the effectiveness of electrical stimulation in tinnitus management.[14] However, several studies have investigated the effect of electrical stimulation on tinnitus populations. We sought to comprehensively assess this topic and to provide a treatment effect size, as electrical stimulation may represent a promising technology to suppress, by conducting a systematic review and meta-analysis of pertinent published studies in Chinese and English.

Method

Literature retrieval

This study was designed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) statement,[15] and the protocol was reviewed and registered in PROSPERO (ID: CRD42021246082). Two investigators (TY and HL) independently searched for articles in the Embase, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature (CBM), Wanfang and Weipu databases. Medical Subject Headings (MeSH) and free search terms were both used in the literature search. The search strategy used the following key words: 'tinnitus' AND {'electrical promontory stimulation' OR 'deep brain stimulation' OR 'transcranial direct current stimulation', 'vagus nerve stimulation' OR 'transcutaneous electric nerve stimulation' OR 'TENS' OR 'VNS' OR 'tDCS' OR OR 'DBS' OR 'EPS'}. The final search of data was on 1 March 2021.

Study selection

Two investigators (TY and JZ) independently skimmed the identified abstracts and selected articles for full review. The same investigators independently performed full-text reviews (including intensively reading appropriate articles after skimming the references of screened articles). A senior investigator (HL) adjudicated when eligibility could not be agreed upon.

The inclusion criteria were as follows: (1) randomized placebo comparison trials; (2) prospective studies; (3) studies designed for a group of tinnitus

patients who received electrical stimulation (treatment group) including EPS, DBS, tDCS, VNS and TENS *versus* sham (control group) stimulation; (4) quantitative outcomes were not restricted [such as the Tinnitus Handicap Inventory (THI), visual analogue scale (VAS), the tinnitus questionnaire (TQ), the Tinnitus Functional Index (TFI), the tinnitus handicap questionnaire (THQ)]; (5) no region, or age restriction; (6) primary or secondary treatment; and (7) placebo group (sham stimulation) for comparison as a control group.

Studies with the following characteristics were excluded: (1) those that were not in English or Chinese; (2) those that had no key information such as the lack of suitable comparator and main quantitative outcomes; and (3) those that were animal experimental investigations, case reports, meeting abstracts and comments and review articles.

Data extraction and outcome definitions

Two investigators (TY and JZ) independently extracted data, and any disagreements were discussed with the third investigator (HL) or subsequently resolved *via* consensus. For each selected publication, the following baseline and study characteristics were extracted: publication year, country, first author, sample size and participant characteristics (age, sex, types of tinnitus and so on); treatment conditions (such as type of stimulation treatment, stimulation intensity, stimulation location and adjuvant therapy); and treatment efficacy (including all types of quantitative scores and scale changes, follow-up duration and side effects conditions). Some studies provided only baseline data and the mean and standard deviation after treatment of quantitative scores. However, the differences were obtained by calculation.

Risk-of-bias assessment

Two investigators (TY and SY) independently undertook a risk of bias assessment, and any doubts were resolved by the third investigator (HL). We evaluated the risk of bias of trials according to the Cochrane handbook (http://handbook.cochrane.org). In addition, we applied the revised Jadad's scale to calculate the quality of every enrolled study. In particular, the following domains were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. We judged each domain as having a low, unclear or high risk of bias. In the review of randomization, every study that contained the exact randomized method, we scored as 'low risk'; however, when the study did not report the exact randomized method, but indicated that the studies were carried out under randomized, controlled designs, we scored them as 'unclear', which was similar to other scoring in allocation of randomization, blind method, incomplete outcome data and selective reporting. The Jadad scale was used to calculate the quantity of every enrolled study.

Statistical outcomes

The study outcomes were changes in magnitude estimates of loudness, tinnitus-related distress and the THI. The THI is a three-label category scale questionnaire (functional, emotional and catastrophic) involving 25 items to generate a total score. Patients can be classified into five grades based on a transformation into a 100-point scale: slight (0–16), mild (18–36), moderate (38–56), severe (58–76) and catastrophic (78–100).[12] The VAS was used to evaluate tinnitus loudness and distress. Tinnitus loudness was rated using a 10-point VAS, where 0 is no tinnitus and 10 is tinnitus as loud as possible. Tinnitus distress was rated using a 10-point VAS, where 0 is no distress and 10 is suicidal quality of distress.[16] TQ sum score ranges from 0 to 84, with a higher score indicating a severe distress.[17] TFI is a 25-item questionnaire scoring the severity and negative impact of tinnitus by cognitive eight domains (i.e. intrusiveness, sense of control, cognitive complaints, sleep disturbance, auditory difficulties, relaxation, quality of life and emotional distress) with the total score ranging from 0 to 100 and higher scores indicating higher levels of disturbance.[18]

Statistical analysis

Review Manager 5.4 (Cochrane) and Stata 15.1 were used for statistical analysis. We pooled data and used the mean difference (MD) with 95% confidence intervals (CIs) for continuous outcomes: changes in the THI and VAS scores.

Heterogeneity between studies was evaluated using the I^2 value to represent the chance that

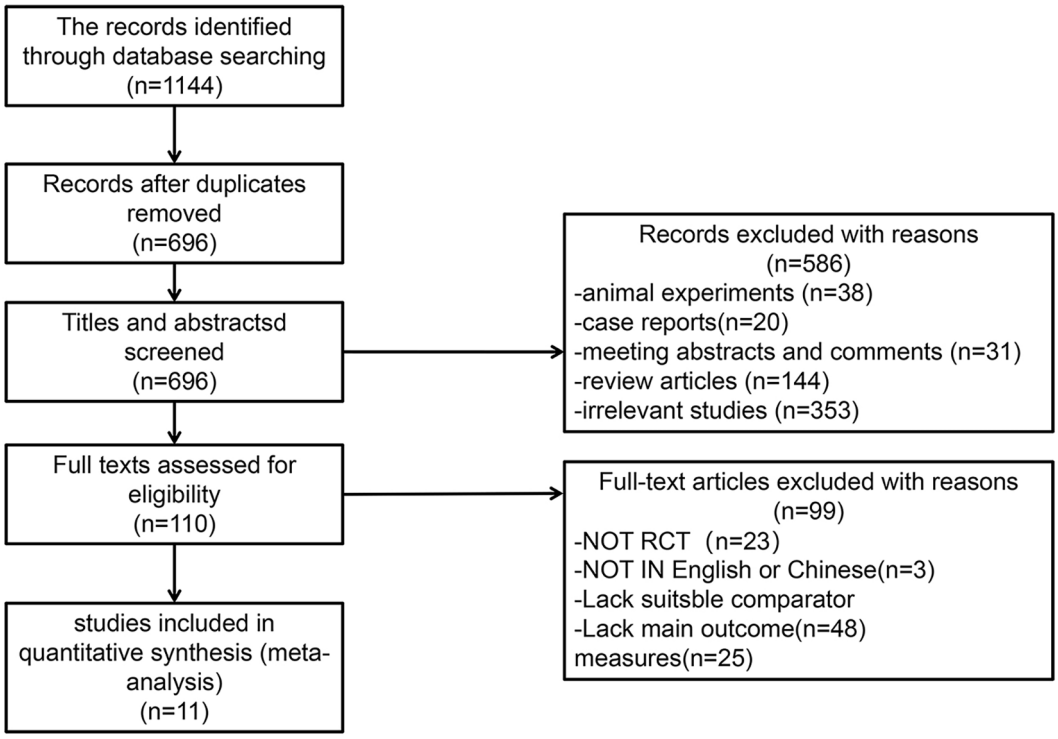

Figure 1. Flow diagram of the selection of the included studies.

variability between different effect estimates exceeded expectations; heterogeneity was categorized as follows using the Nordic Cochrane Centre (2011) reference: I^2 = 0–40%, no important heterogeneity; I^2 = 30–60%, moderate heterogeneity; I^2 = 50–90%, substantial heterogeneity; and I^2 = 75–100%, considerable heterogeneity. If the I^2 statistic was above 50% and the Cochrane Q statistic had a value of $p < 0.1$, a random-effects model was used. If no considerable heterogeneity among studies was apparent, a fixed-effect model was used. Funnel plots and Egger's test were used to assess potential publication bias ($n \geqslant 10$). All statistical analyses were carried out with Review Manager 5.4 (The Cochrane Collaboration).

Results

Search results and the characteristics of the included studies

We obtained 1144 articles, of which 696 were duplicate results and were therefore discarded. Title and abstract review of the remaining 586 studies yielded 99 full-text candidates. After excluding literature according to the aforementioned criteria, 11[19–29] final studies were included. These studies were published from 2013 to 2020 and were conducted in China, Brazil, Terkel, Switzerland, Iran, Korea and New Zealand. The process of selecting the included studies is presented in Figure 1.

Study descriptions and patient characteristics are summarized in Table 1. The treatment and outcome details in the selected studies are shown in Tables 2 and 3.

Risk-of-bias assessment

The revised Jadad scale scores of the included studies are listed in Table 3. The Jadad scale scores of all included studies ranged from 3 to 6. More specifically, 45.5% (n = 5) of the studies[20,21,23,24,26] had a Jadad score of 4 points, and 18.2% (n = 2)[22,27] had a Jadad score of 6 points. Figures 2 and 3 illustrate the methodological quantity of the included studies. All included studies maintained random sequence generation. However, only three studies described the specific methods that were used. Two studies[20,22] clearly described concealment of allocation. Regarding blinding of participants and personnel, eight

Table 1. Characteristics of the included studies and participants.

Author	Country	Types of tinnitus	Sex (M/F)		Age		Sample size		Tinnitus duration		Laterality of tinnitus (R/L/B)	
					T	C	T	C	T	C	T	C
Wu and colleagues[19]	China	Idiopathic tinnitus	19/15	16/18	37.25 ± 12.49	40.73 ± 10.66	34	34	4.29 ± 2.15 M	4.97 ± 2.39 M	NA	
Souza and colleagues[20]	Brazil	Individuals free from any neurological and/or organic comorbidities	2/10	6/6	44.58 ± 16.20	55.50 ± 9.72	12	12	24 (12–33) M	30 (6.75–126) M	4/6/2	3/4/5
Tutar and colleagues[21]	Turkey	Subjective tinnitus	22/38		41.17 ± 10.75		20	20	31 ± 49 M		NA	
Li and colleagues[22]	China	Acute tinnitus	14/9	17/6	46.8 ± 11.6	48.4 ± 14.1	23	23	3.7 ± 1.4 M	4.0 ± 1.6 M	3/5/15	4/7/12
Yadollahpour and colleagues[23]	Iran	Intractable chronic tinnitus	11/14	7/8	47.52 ± 7.51	47.67 ± 7.96	25	15	7.48 ± 3.99	7.60 ± 3.60	8/4/13	3/5/7
Yadollahpour and colleagues[24]	Iran	Chronic intractable tinnitus	11/14	8/9	46.68 ± 6.87	47.53 ± 7.56	25	17	7.8 ± 2.84 y	8.11 ± 2.8 y	11/4/10	6/5/6
Cavalcanti[25]	Brazil	Chronic tinnitus	9/9		54.72 (45–70)		9	9	12.86 (1–30) M		9 (Bilateral)	
Pal and colleagues[26]	Switzerland	Chronic (⩾1 year) nonpulsatile subjective tinnitus	12/9	12/9	51.6 ± 12.2	48 ± 9.9	21	21	63.1 ± 64.9 M	71 ± 102.3 M	0/0/21	0/0/21
Forogh and colleagues[27]	Iran	Chronic tinnitus	7/4	7/4	49.81 ± 4.14	46.63 ± 5.26	11	11	9 ± 3.67 y	6.54 ± 1.44 y	3/1/7	0/3/8
Lee and colleagues[28]	Korea	Chronic, subjective tinnitus	26/9	13/7	46.6 ± 13.9	45.6 ± 11.5	45	20	24.44 ± 19.79 M		20/25/0	8/12/0
Shekhawat and colleagues[29]	New Zealand	Chronic tinnitus (more than 2 years)	18/2	18/2	58.5 ± 6.4	59.85 ± 9.6	20	20	19.78 y	16.55 y	18/1/1	16/3/1

B, bilateral; C, control group; F, female; L, left side; M, male; M, month; NA, not available; R, right side; T, treatment group; y, year.
Data are presented as mean ± standard deviation.

Table 2. Details of the treatment condition.

Author	Type of stimulation treatment		Stimulus frequency		stimulus intensity		Location of stimulation		Treatment duration		Protocol (number of treatment)		Adjuvant therapy
	T	C	T	C	T	C	T	C	T	C	T	C	
Wu and colleagues[19]	Concha auriculae electroacupuncture		4–20 Hz	-	4–10 mA	-	Cavity of auricular concha [auricular branch of the vagus nerve (ABVN)]	Ear marginal scapha of the left ear	30 min		3 times for 1 week		Oral mecobalamin 0.2 mg Tid for 12 weeks
Souza and colleagues[20]	Transcranial direct current stimulation		Delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta (12.5–30 Hz) and gamma (30.5–60 Hz)	-	2 mA	-	PFC + LTA		20 min		5 consecutive days		NA
Tutar and colleagues[21]	Transcutaneous electrical nerve stimulation		200 Hz	-	10–30 mA	-	Cymba conchae where there is rich ABVN		30 min		10 sessions in 1 month, maximum of 4 days between each session		NA
Li and colleagues[22]	Transcutaneous electrical nerve stimulation		2/100 Hz	-	NA		A pair of electrodes was placed on the left and right C2 nerves dermatomes		30 min		3 times weekly for a total of 4 weeks		Parenteral intramuscular therapy of 1-ml vitamin B12 (2500 mcg) weekly for a total of 4 weeks
Yadollahpour and colleagues[23]	Transcranial direct current stimulation		NA		2 mA	-	The anode was placed over left AC (halfway T3–F7) and cathode over right AC (halfway T4–F8) with 35-cm^2 electrodes.		20 min		Over 5 consecutive days per week for 2 consecutive weeks (total, 10 sessions)		NA
Yadollahpour and colleagues[24]	Transcranial direct current stimulation		NA		2 mA	-	Anode was placed over the right DLPFC (F4), and the cathode over the left DLPFC (F3)		20 min		Over 5 consecutive days per week for 2 consecutive weeks (total, 10 sessions)		NA
Cavalcanti[25]	Transcranial direct current stimulation		NA		2 mA	-	PFC		20 min (10 s ramp-in and ramp-out each)	A ramp-in period of 10 s, after which the current was turned off for the remainder of the session	5 consecutive daily sessions		NA
Pal and colleagues[26]	Transcranial direct current stimulation		NA		2 mA	1 mA	PFC		20 min	For 90 s in a ramp-like fashion	5 days (1× session/day: Monday–Friday)		NA
Forogh and colleagues[27]	Transcranial direct current stimulation		NA		2 mA	-	LTA		20 min	4 s after the initial ramp-up, the current was directly ramped down to 0	5 sessions of stimulation in 5 consecutive days.		NA
Lee and colleagues[28]	Transcutaneous electrical stimulation		50 Hz	-	15 mA	-	Five sites that on the auricle of the ear with tinnitus.		30 s for each point		Twice a week for a total of 8 therapy sessions over 4 weeks		No other treatments for tinnitus including medications or psychotherapy were administered
Shekhawat and colleagues[29]	Transcranial direct current stimulation		NA		2 mA	-	LTA		20 min		5 consecutive sessions with 24-h gap		All the participants were fitted bilaterally with GN ReSound Live 571 open-fit hearing aids on the day following the final brain stimulation session

AC, auditory cortex; C, control group; DLPFC, dorsolateral prefrontal cortex; LTA, left temporoparietal area; NA, not available; PFC, prefrontal cortex; T, treatment group.

Table 3. Summary of the treatment outcomes.

Author	Group	Questionnaire		Score, mean (SD)			Jadad score	*p* value	Follow-up period	Side effects
				Baseline	Poststimulation	Difference				
Wu and colleagues[19]	T	THI		49.76 (4.80)	28.09 (3.64)	−21.67 (4.34)	3	<0.05	12 weeks after postintervention	NA
	C			48.56 (4.20)	29.19 (1.91)	−19.37 (3.64)				
	T	SDS		45.34 (2.72)	43.47 (3.13)	−1.87 (3.64)				
	C			44.91 (1.81)	42.22 (1.60)	−2.69 (1.71)				
	T	SAS		48.89 (4.28)	41.96 (3.07)	−6.93 (3.82)				
	C			51.20 (1.81)	45.63 (2.13)	−5.57 (1.99)				
	T	SF-36	Physical	50.40 (3.87)	66.33 (5.56)	15.93 (4.94)				
	C			50.04 (4.71)	62.26 (5.08)	12.22 (4.91)				
	T		Social function	50.84 (3.98)	67.96 (6.19)	17.12 (5.43)				
	C			51.43 (5.92)	65.01 (5.13)	13.58 (5.57)				
	T		Physical function	49.64 (4.65)	71.29 (6.46)	21.65 (5.50)				
	C			49.27 (5.49)	63.88 (5.12)	14.61 (5.31)				
	T		Emotion	51.48 (3.96)	75.3 (7.11)	23.82 (6.17)				
	C			49.49 (5.51)	71.63 (5.33)	22.14 (5.42)				
	T		Somatoform pain	51.41 (5.04)	74.25 (5.57)	19.67 (4.82)				
	C			50.67 (5.49)	70.34 (3.54)	11.31 (4.33)				
	T		Metal health	49.83 (2.92)	61.14 (4.97)	7.91 (8.51)				
	C			50.39 (5.32)	58.30 (4.05)	12.35 (4.54)				
	T		General health	49.98 (4.05)	62.33 (4.90)	12.35 (4.54)				
	C			50.69 (5.54)	55.96 (4.96)	5.27 (5.27)				
	T		Vitality	49.98 (6.78)	71.75 (5.45)	21.77 (6.22)				
	C			51.08 (3.74)	68.81 (5.85)	17.73 (5.13)				
Souza and colleagues[20]	T	THI		52 (7.9)	35 (5.1)	−17 (6.94)	4	<0.0001	5 days after postintervention	NA
	C			44 (5.8)	42 (7.3)	−2 (6.68)				
	T	VAS		7.5 (0.4)	7 (0.6)	−0.5 (0.53)				
	C			7.5 (0.6)	4.2 (0.8)	−3.3 (0.72)				
Tutar and colleagues[21]	T	DASS	Depression	13.10 (7.80)	4.35 (2.54)	−8.75 (7.11)	4	<0.05	4 weeks after postintervention	NA
	C			13.10 (5.82)	9.45 (5.83)	−3.65 (3.44)				
	T		Anxiety	13.50 (6.08)	4.40 (3.09)	−9.10 (6.11)				
	C			13.50 (4.99)	10.30 (5.56)	−3.20 (2.98)				
	T		Stress	15.95 (6.04)	6.64 (3.32)	−9.50 (5.48)				
	C			15.85 (6.23)	12.45 (5.62)	−3.40 (3.58)				

(Continued)

Table 3. (Continued)

Author	Group	Questionnaire		Score, mean (SD)			Jadad score	*p* value	Follow-up period	Side effects
				Baseline	Poststimulation	Difference				
	T	THI		33.05 (21.09)	8.60 (4.89)	−24.45 (19.12)				
	C			37.95 (20.96)	28.65 (14.99)	−9.30 (18.7)				
Li and colleagues[22]	T	THI		31.8 (12.6)	NA	−11.6 (11.24)	6	<0.01	4 weeks after postintervention	No adverse events related to the verum TENS or sham TENS intervention occurred in either group
	C			30.2 (14.3)		−2.9 (2.79)				
	T	TSS		22.8 (7.7)		−9.3 (9.01)				
	C			21.1 (6.9)		−3.1 (3.0)				
	T	TQ		20.1 (9.5)		−13.8 (13.37)				
	C			19.3 (8.4)		−3.5 (3.39)				
	T	SF-12	Physical	77.6 (16.2)		11.3 (10.93)				
	C			79.3 (17.0)		2.5 (2.41)				
	T		Mental	80.1 (15.4)		12.6 (12.2)				
	C			81.6 (14.4)		3.0 (2.91)				
Yadollahpour and colleagues[23]	T	THI		71.28 (10.57)	46.4 (15.36)	−24.88 (13.61)	4	NA	1 h, 1 week and 1 month after postintervention	Itching, tingling, scalp pain, burning, pinching, fatigue, headache, skin irritation, discomfort
	C			71.6 (9.57)	66.73 (14.3)	−4.87 (12.62)				
	T	VAS	Loudness	7.36 (0.81)	5.6 (1.78)	−1.76 (0.97)				
	C			7.46 (0.92)	6.8 (1.52)	−0.67 (0.61)				
	T		Distress	7.68 (0.56)	5.92 (1.25)	−1.76 (0.70)				
	C			7.07 (1.22)	7.67 (0.62)	−0.6 (0.61)				
Yadollahpour and colleagues[24]	T	THI		69.88 (9.45)	47.24 (12.45)	−22.75 (11.25)	4	NA	1 h, 1 week and 1 month after postintervention	NA
	C			69.82 (9.45)	61.94 (13.51)	−7.88 (12.01)				
	T	VAS	Loudness	7.44 (0.96)	5.88 (1.79)	−1.56 (0.83)				
	C			7.58 (0.94)	7.18 (1.24)	−0.41 (0.29)				
	T		Distress	7.72 (0.61)	6.48 (1.19)	−1.24 (0.58)				
	C			7.65 (0.61)	7.17 (1.29)	−0.47 (0.68)				
Cavalcanti[25]	T	THI		48.0 (26.0)	46.0 (28.0)	−2.0 (27.06)	3	NA	5 days after postintervention	With no untoward effects
	C			52.0 (25.0)	49.0 (25.0)	−3.0 (25.0)				
	T	VAS		7 (2.4)	7.3 (1.6)	0.3 (2.12)				
	C				7.3 (1.8)	0.3 (2.16)				

(Continued)

Table 3. (Continued)

Author	Group	Questionnaire		Score, mean (SD)			Jadad score	*p* value	Follow-up period	Side effects
				Baseline	Poststimulation	Difference				
Pal and colleagues[26]	T	THI		46.7 (20.0)	42.1 (20.3)	−4.6 (20.15)	4	NA	5 days after postintervention; 1 month after last intervention; 3 months after last intervention	No other side effects were reported. All patients experienced occasional 'tingling', which was most commonly of short duration, with no pain or discomfort
	C			46.4 (18.2)	45.8 (18.7)	−0.6 (18.46)				
	T	VAS	Intensity	57.0 (20.3)	57.2 (18.6)	0.2 (19.51)				
	C			59.4 (19.8)	59.4 (18.2)	0.0 (19.05)				
	T		Distress	55.2 (25.8)	48.2 (21.7)	−7.0 (24.01)				
	C			54.2 (25.4)	46.4 (24.5)	−7.8 (24.96)				
	T	STSS		10.6 (2.6)	10.6 (2.6)	0.0 (2.6)				
	C			10.1 (1.7)	10.3 (2.2)	0.2 (2.0)				
	T	CGI		NA	4.0 (0.7)	NA				
	C				4.1 (0.6)					
	T	HAD		14.6 (7.6)	12.4 (7.3)	−2.2 (7.45)				
	C			15.1 (6.3)	15.3 (6.9)	0.2 (6.62)				
Forogh and colleagues[27]	T	THI		58.6 (28.1)	55.8 (23.2)	−2.8 (26.0)	6	0.729	After fifth session; 2 weeks after stimulation	NA
	C			53.7 (20.0)	53.4 (30.9)	−0.3 (27.14)				
	T	VAS	Loudness	5.3 (2.6)	5.1 (2.5)	−0.2 (2.55)		0.964		
	C			5.2 (2.5)	4.8 (2.8)	−0.4 (2.66)				
	T		Distress	5.6 (2.5)	5.0 (2.2)	−0.6 (2.36)		0.339		
	C			4.7 (2.3)	4.2 (2.4)	−0.5 (2.35)				
Lee and colleagues[28]	T	THI		49.4 (9.9)	42.8 (8.7)	−6.6 (9.36)	3	<0.05	After 4-week sessions	Mild side effects were seen in eight patients including four patients with dizziness, three patients with headache and one patient with facial numbness. However, side effects dissipated after cessation of treatment
	C			44.5 (6.5)	45.2 (7.9)	−0.7 (7.30)		>0.05		
	T	VAS	Duration	6.9 (1.6)	5.6 (2.1)	−1.3 (1.9)		<0.05		
	C			6.5 (1.2)	6.1 (1.5)	−0.4 (1.37)		>0.05		

(Continued)

Table 3. (Continued)

Author	Group	Questionnaire		Score, mean (SD)			Jadad score	*p* value	Follow-up period	Side effects
				Baseline	Poststimulation	Difference				
	T		Loudness	6.7 (1.7)	5.8 (1.9)	−0.9 (1.81)		<0.05		
	C			6.2 (1.9)	5.6 (1.6)	−0.6 (1.77)		>0.05		
	T		Annoyance	6.7 (1.5)	5.4 (2.2)	−1.3 (1.95)		<0.05		
	C			6.5 (1.7)	5.7 (1.2)	−0.8 (1.51)		>0.05		
	T		Difficulty in activities of daily life	6.8 (1.9)	5.4 (1.9)	−1.4 (1.9)		<0.05		
	C			6.6 (1.7)	6.5 (1.3)	−0.1 (1.54)		>0.05		
Shekhawat and colleagues[29]	T	TFI		−2.5 (2.5)	−6 (3)	−3.5 (2.78)	3	>0.05	During 5 stimulation sessions; before hearing aid fitting; 3 months; 6 months	NA
	C			−3 (3)		−3 (3)				
	T	VAS	Loudness	NA		−0.33 (0.58)				
	C					−0.06 (0.89)				

C, control group; CGI, Clinical Global Impression Scale; DASS, Depression Anxiety Stress Scales; HAD, Hospital Anxiety and Depression scale; LTA, left temporoparietal area; NA, not available; PFC, prefrontal cortex; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; STSS, Subjective Tinnitus Severity Scale; T, treatment group; TENS, transcutaneous electric nerve stimulation; TFI, Tinnitus Functional Index; THI, Tinnitus Handicap Inventory; TQ, tinnitus questionnaire; TSS, Tinnitus Severity Scale; VAS, visual analogue scale; SF, social function.
Data are presented as mean (standard deviation).

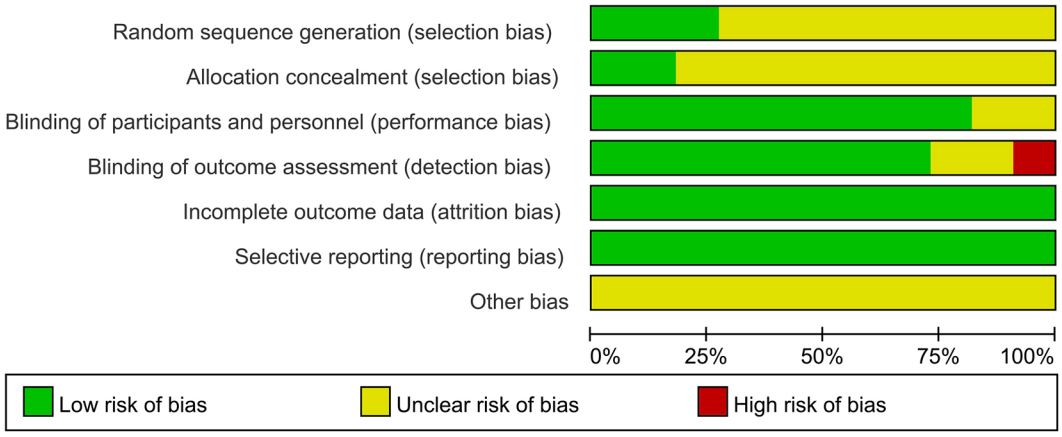

Figure 2. Risk of bias graph.

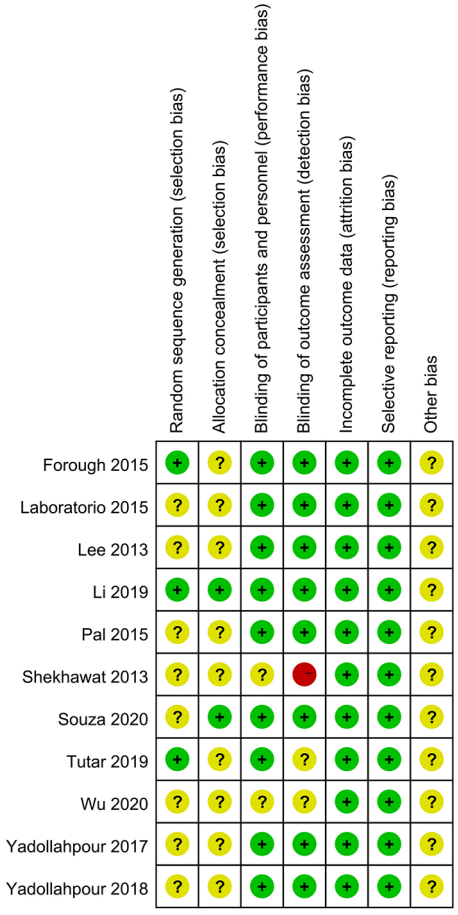

Figure 3. Risk of bias summary.

studies[20,22–28] had an explicit double-blind design, one study[21] had a single-blind design and two studies[19,29] did not clearly describe the blinding method that was used. In the domain of incomplete outcome data and selective reporting, all the studies were judged as 'low'. Other biases sometimes included unknown risk, so we scored all the other biases as 'unclear'.

Meta-analysis of THI in patients with tinnitus after electrical stimulation

Among these studies, 10 with a total of 407 participants assessed the subjective severity of tinnitus by the THI, which was available for analysis using a random-effects model, with substantial heterogeneity among studies ($I^2 = 80\%$, $p < 0.00001$). The results exhibited statistically significant differences between the electrical stimulation group and the sham stimulation group (MD = −9.69; 95% CI = −14.25, −5.13; $p < 0.0001$), as shown in Figure 4. To address high heterogeneity, we conducted subgroup analysis and categorized patients by follow-up time, stimulation intensity, stimulation area and tinnitus duration before treatment.

The electrical stimulation group had a significant change in the THI score compared with the sham stimulation group in the short-term follow-up period (MD = −10.77; 95% CI = −16.21, −5.33), with substantial heterogeneity ($I^2 = 65\%$).[20,23–28] Five studies[21–23,26,27]provided data on changes in the THI scores in the medium-term follow-up period. Pooled analysis of the data showed significant improvement in THI scores (MD = −11.36; 95% CI = −17.33, −5.39). Two studies[19,26] assessed the effect of real stimulation treatment on tinnitus severity and disability using the THI in the long-term follow-up period. There was a significant effect of real stimulation on the THI compared with sham stimulation in

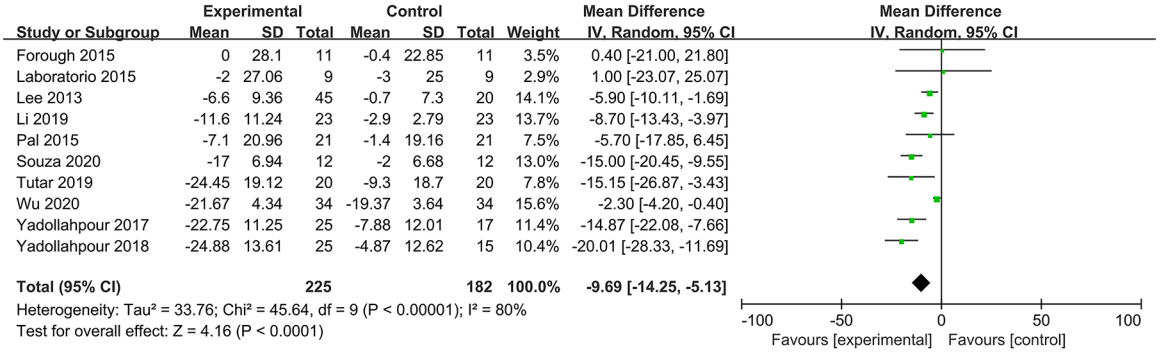

Figure 4. Analysis comparing electrical stimulation *versus* sham stimulation for the THI change scale score in tinnitus patients.
CI, confidence interval; IV, inverse variance; THI, Tinnitus Handicap Inventory.

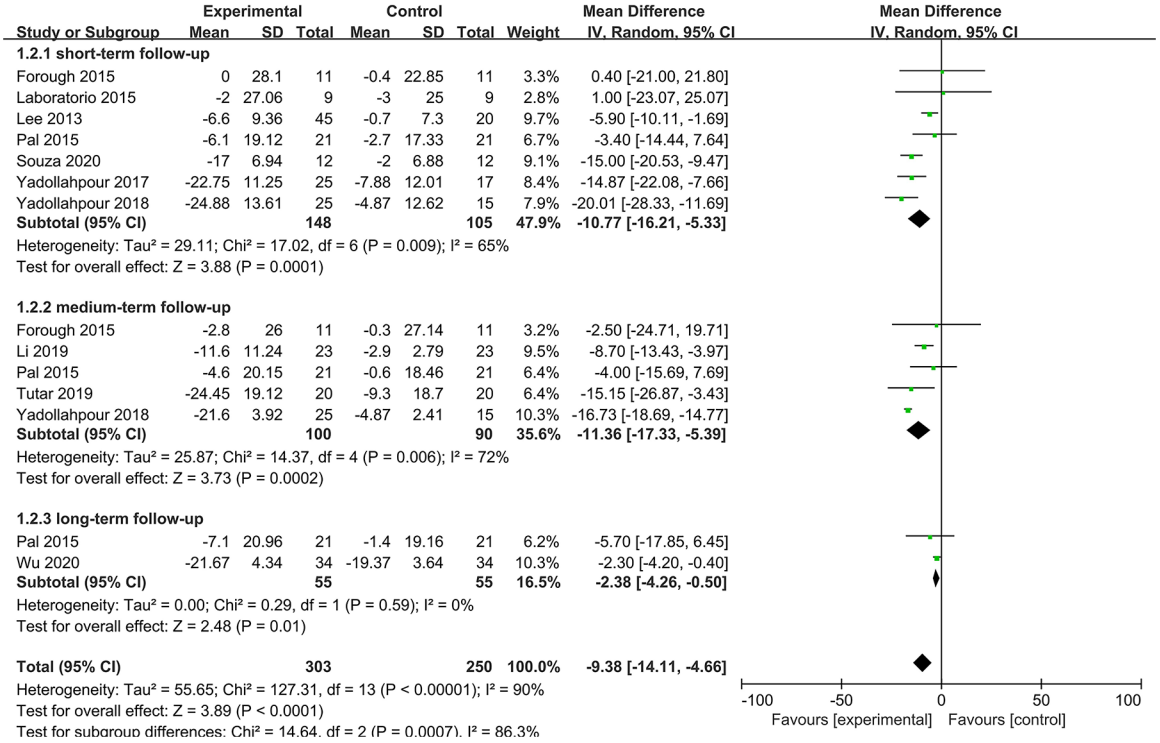

Figure 5. Subgroup analysis of the THI change scale score comparing electrical stimulation with sham stimulation by follow-up period.
CI, confidence interval; IV, inverse variance; THI, Tinnitus Handicap Inventory.

the long-term follow-up period (MD = −2.38; 95% CI = −4.26, −0.50), with no heterogeneity (I^2 = 0%) (Figure 5). The heterogeneity in these three groups was decreased, especially the in long-term follow-up group (I^2 = 0) which indicated that different follow-up times may be a source of the heterogeneity.

In the subgroup analysis for the tinnitus duration (Figure 6), the MD of the THI score changes between electrical stimulation and sham stimulation was −5.12 (95% CI = −11.35, 1.11; I^2 = 83%; p = 0.11) in the acute or subacute tinnitus group (score ⩽6 as recent onset tinnitus), and −11.66 (95% CI = −16.51, −6.81; I^2 = 58%; p < 0.00001) in the chronic tinnitus group (score >6 as chronic and persistent tinnitus), showing that this factor may lead to some heterogeneity and that the therapeutic effect may be not so good in acute or subacute tinnitus.

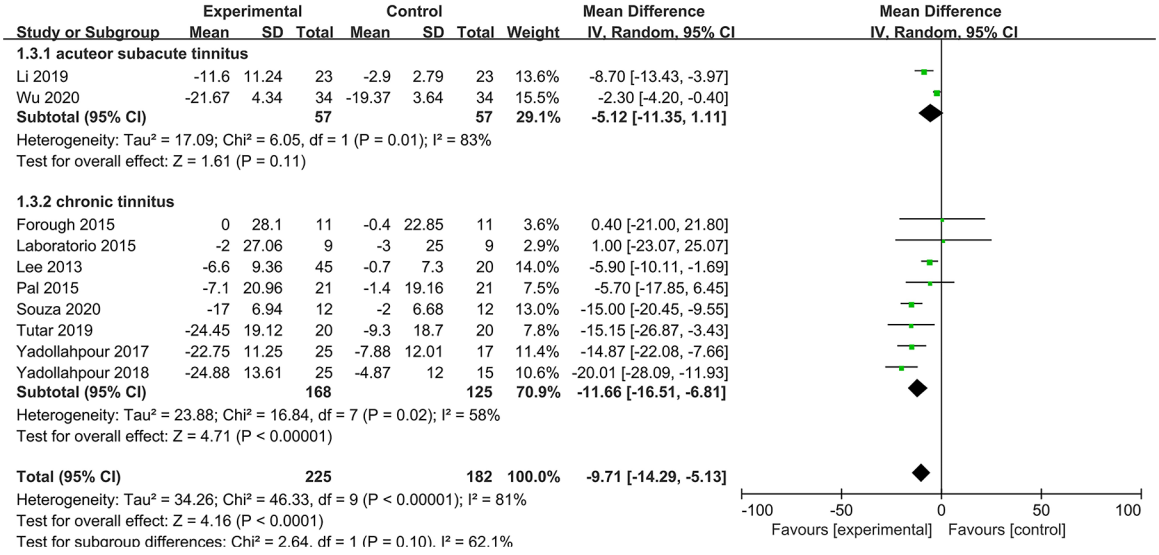

Figure 6. Subgroup analysis of the THI change scale score comparing electrical stimulation with sham stimulation by tinnitus duration.
CI, confidence interval; IV, inverse variance; THI, Tinnitus Handicap Inventory.

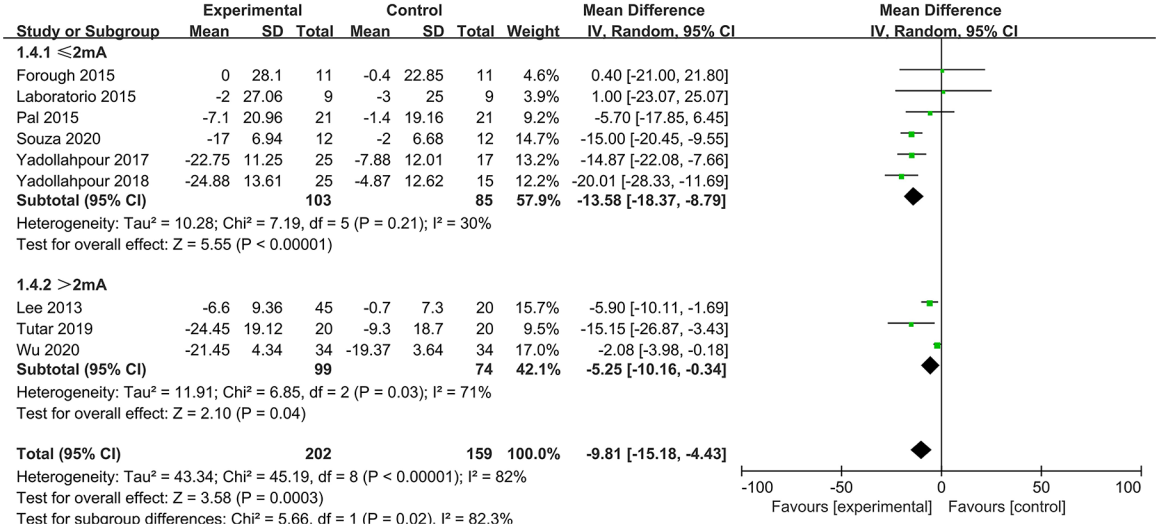

Figure 7. Subgroup analysis of the THI change scale score comparing electrical stimulation with sham stimulation by stimulation intensity.
CI, confidence interval; IV, inverse variance; THI, Tinnitus Handicap Inventory.

As shown in Figure 7, subgroup analysis was stratified by stimulation intensity, that is, less than or equal to 2 mA or greater than 2 mA. The MD of the THI score changes was −13.58 (95% CI = −18.37, −8.79; $I^2 = 30\%$; $p < 0.00001$) for low current stimulation and −5.25 (95% CI = −10.16, −0.34; $I^2 = 71\%$; $p = 0.04$) for high current intensity which demonstrated that higher current intensity may not improve the treatment and that different stimulation intensities may be a source of heterogeneity.

The last two subgroups were defined based on different stimulation areas and methods, and all the patients were divided into tDCS and TENS groups. Four studies[19,21,22,28] assessed the efficacy

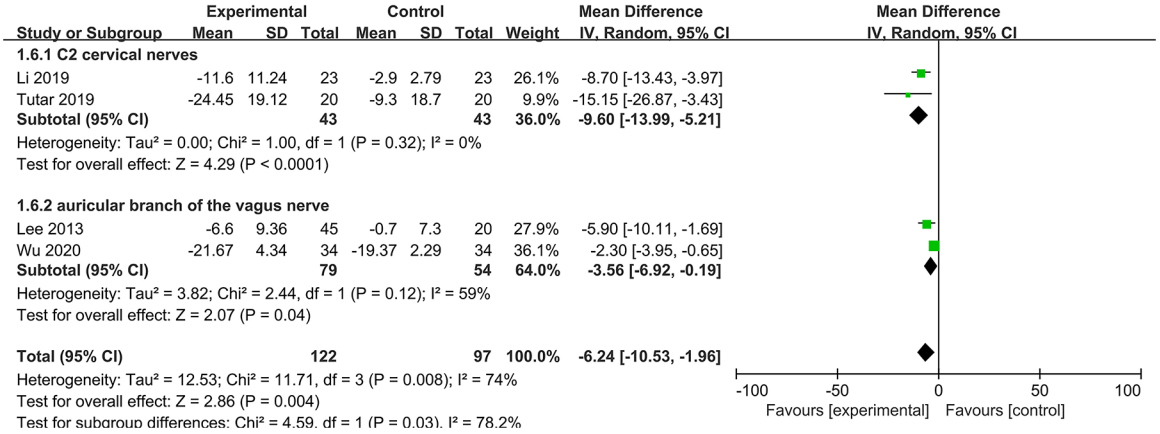

Figure 8. Subgroup analysis of the THI change scale score comparing TENS with sham stimulation by stimulation areas.
CI, confidence interval; IV, inverse variance; TENS, transcutaneous electric nerve stimulation; THI, Tinnitus Handicap Inventory.

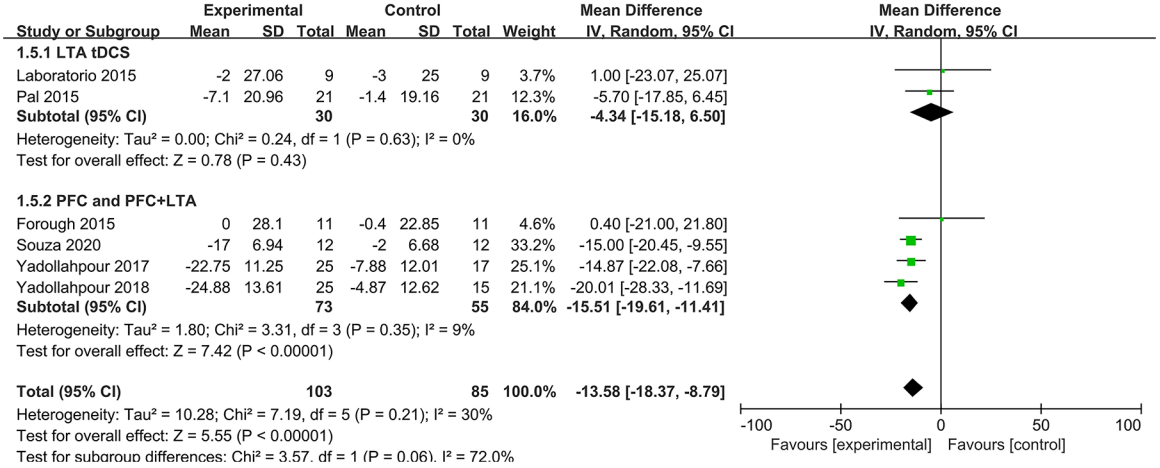

Figure 9. Subgroup analysis of the THI change scale score comparing tDCS with sham stimulation by stimulation areas.
CI, confidence interval; IV, inverse variance; LTA, left temporoparietal area; PFC, prefrontal cortex; tDCS, transcranial direct current stimulation; THI, Tinnitus Handicap Inventory.

of TENS on tinnitus severity as measured by the THI, including two studies[21,22] in which electrodes were placed on C2 cervical nerves (MD = −9.60; 95% CI = −13.99, −5.21; I^2 = 0%; $p < 0.0001$) and two studies[19,28] in which electrodes were placed on the auricular branch of the vagus nerve (MD = −3.56; 95% CI = −6.92, −0.19; I^2 = 74%; $p = 0.04$) (Figure 8). To compare tDCS with sham stimulation for changes in the THI scores, we included six studies[20,23–27]with a total of 188 participants; this set of studies included two studies[25,26] in which electrodes were placed on the left temporoparietal area (LTA) (MD = −4.34; 95% CI = −15.18, 6.50; I^2 = 0%) which indicated that this stimulation method may be less effective than others due to the nonsignificant result in this group ($p = 0.43$) and four studies[20,23,24,27] in which electrodes were placed on the prefrontal cortex (PFC) or on both the PFC and LTA, denoted as PFC + LTA (MD = −15.51; 95% CI = −19.61, −11.41; I^2 = 9%; $p < 0.00001$) (Figure 9). The heterogeneity in these subgroups was markedly reduced, which indicated that different positions of the electrodes placed may be a source of the heterogeneity.

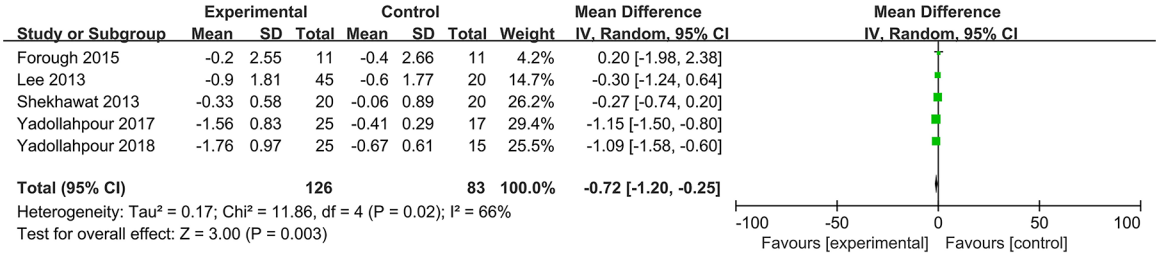

Figure 10. Analysis comparing electrical stimulation *versus* sham stimulation for the VAS loudness change scale score in tinnitus patients.
CI, confidence interval; IV, inverse variance; VAS, visual analogue scale.

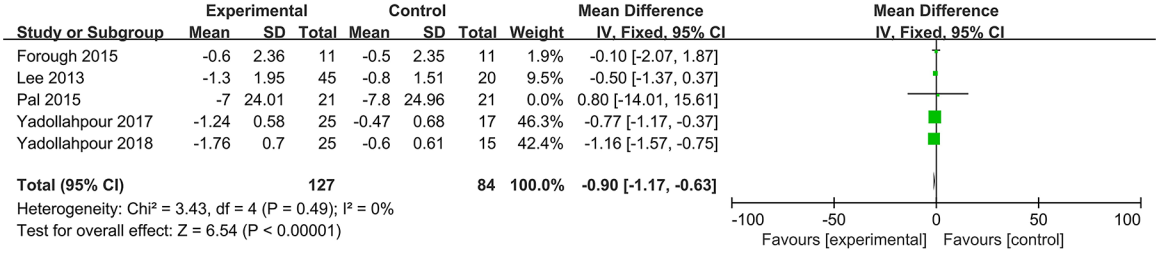

Figure 11. Analysis comparing electrical stimulation *versus* sham stimulation for the VAS distress change scale score in tinnitus patients.
CI, confidence interval; IV, inverse variance; VAS, visual analogue scale.

Meta-analysis of VAS in patients with tinnitus after electrical stimulation

VAS loudness assessment. Three trials with 209 participants reported a change in tinnitus loudness after treatment using the VAS. Pooled analysis demonstrated a statistically significant difference in the change in tinnitus loudness assessed by the VAS between the electrical stimulation and sham stimulation groups (MD = −0.90; 95% CI = −1.17, −0.63; I^2 = 66%; $p < 0.00001$) with moderate heterogeneity (Figure 10).

VAS distress assessment. When comparing the change of tinnitus distress using the VAS between the electrical stimulation group and sham stimulation group, a fixed-effects model was used because of the lack of important heterogeneity ($p = 0.49$; $I^2 = 0\%$). The pooled MD was −0.90 (95% CI = −1.17, 0.63; $p < 0.00001$) (Figure 11), indicating a statistically significant difference in the change in score between the two groups.

Other indicators for outcome evaluation. Various included studies attempted to use other patient-reported symptom severity questionnaires to assess the effectiveness of electrical stimulation; nevertheless, significant heterogeneity in reporting outcomes and the limited data included precluded further assessment using these measures. However, the baseline score, posttreatment score, MD of scores and statistical significance of the differences for each were extracted for these studies. A detailed summary is shown in Table 3. Notably, there were statistically significant improvements in most outcome measures. Shekhwat used TFI, and the result illustrated that there was a marginal, but not statistically significant, difference between sham tDCS and real tDCS groups for the overall change in the TFI score with the sham tDCS group showing more change, $F(1, 52.3) = 3.14$, $p = 0.08$, compared with the tDCS group at the 3- and 6-month follow-up after hearing aid fitting. Li reported TQ, and the results demonstrated that the patients undergoing verum TENS showed statistically significant efficacy of symptoms relief, as measured TQ ($p < 0.01$), compared with patients receiving sham TENS.

Adverse effects associated with treatment were reported in five studies[22,23,25,26,28] In three of these studies,[22,24,25] the absence of side effects in either group was also reported. However, Pal and colleagues[26] reported that all patients experienced

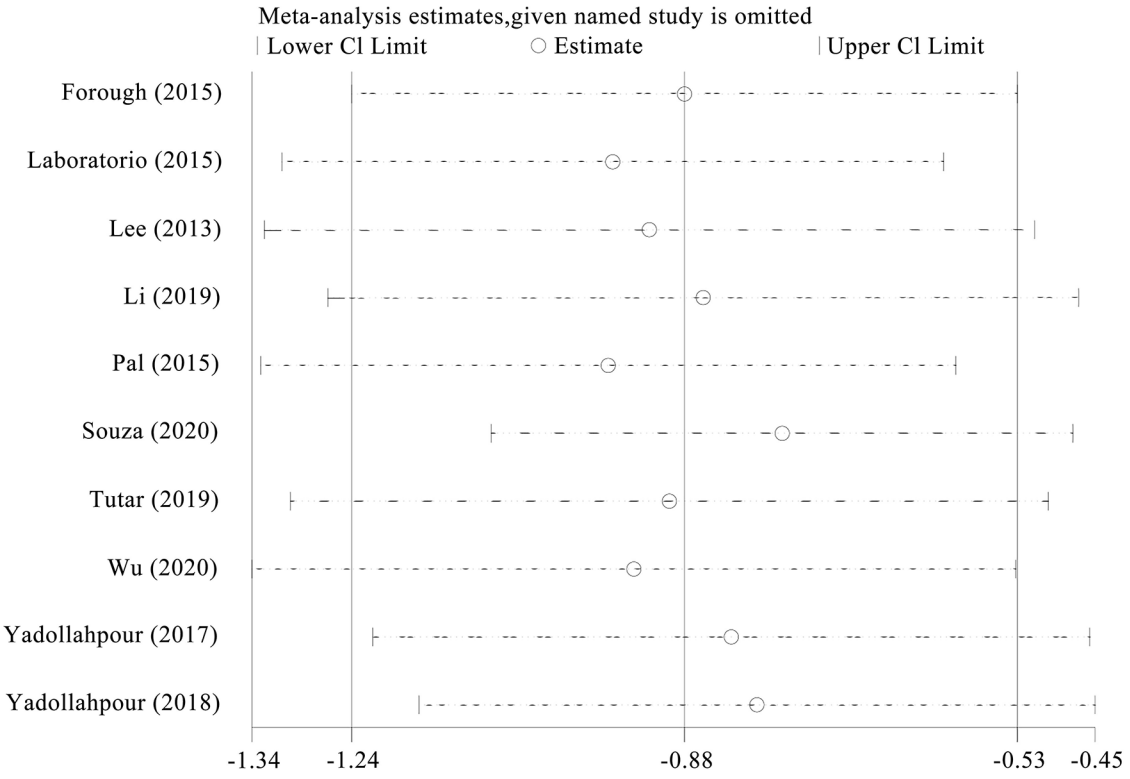

Figure 12. Sensitivity analysis of included studies for THI change scores.
CI, confidence interval; THI, Tinnitus Handicap Inventory.

occasional 'tingling', although it was most often of short duration. Lee and colleagues[28] reported mild side effects in eight patients including four patients who experienced dizziness, two who experienced a headache and one with facial numbness. Yadollahpour and colleagues reported some symptoms during treatment such as itching, tingling, scalp pain, burning, pinching, fatigue, headache, skin irritation and discomfort in both the real and sham stimulation groups. Nevertheless, all the side effects were transient and dissipated after cessation of treatment. In terms of tolerability for the treatment, only one study[23] used a 5-point Likert-type scale, which demonstrated that most had a very high tolerance for the treatment (92% in the real stimulation group and 93.3% in the sham stimulation group).

Sensitivity analyses. Sensitivity analyses were performed for the selected studies on the changes of THI scores to identify outliers that affected the overall results (Figure 12). We also excluded studies with a high risk of bias, and the results did not change substantially.

Publication bias. Potential meta-analysis biases of studies on the changes of THI scores were evaluated by funnel plots, as shown in Figure 13. The results revealed general symmetry, and Egger's test results ($p = 0.249 > 0$) (Figure 14) indicated no significant publication bias among the articles included in the meta-analysis.

Discussion

Tinnitus can adversely impact patients' quality of life.[30] Owing to its unknown pathogenesis, the treatment of tinnitus is varied and cured rate is not ideal. Electrical stimulation may represent a promising treatment approach for tinnitus and widely used. However, the treatment still lacks sufficient evidence to make related recommendations. In this study, we have developed detailed search strategies and strict inclusion criteria to obtain data for the comprehensive meta-analysis and conclusion first, showing that electrical stimulation could effectively ameliorate tinnitus. Nevertheless, the therapeutic effect varies in some ways.

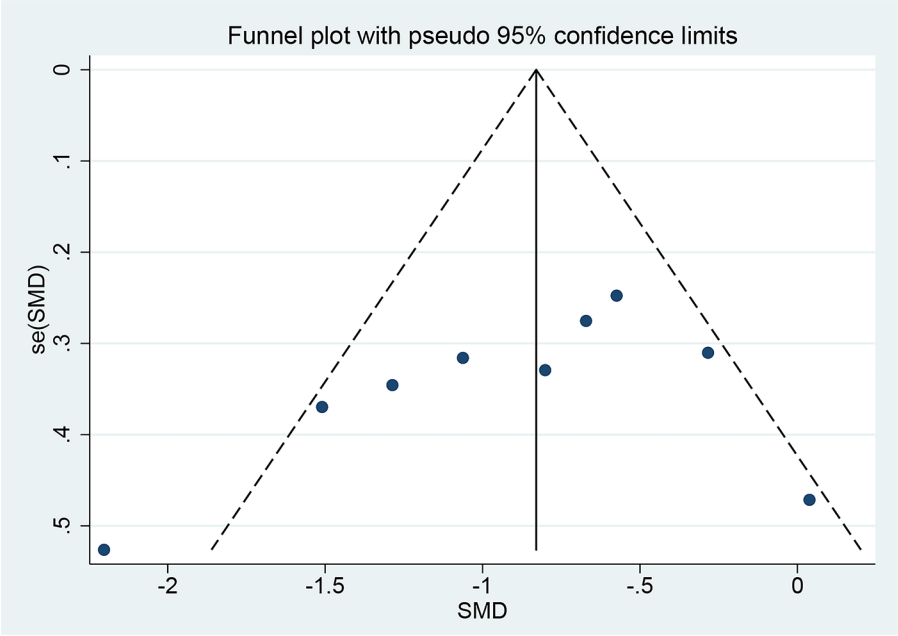

Figure 13. Funnel plot of included studies for THI change scores.
THI, Tinnitus Handicap Inventory.

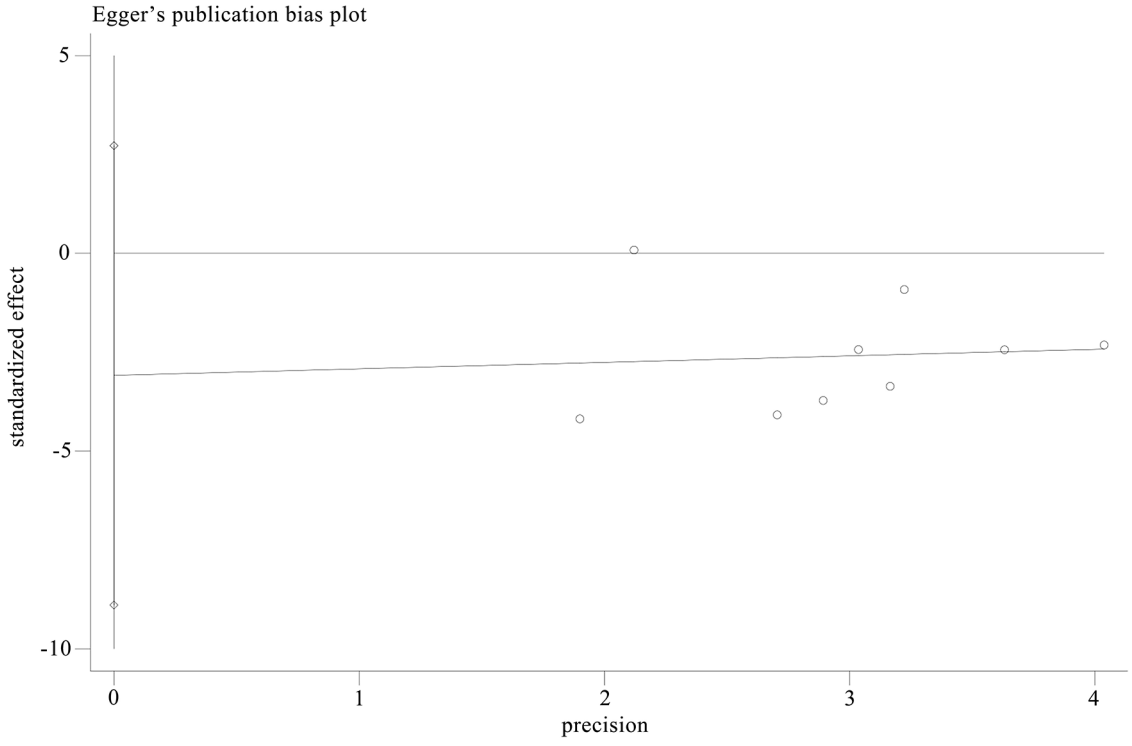

Figure 14. Egger's test of included studies.

THI is widely used in clinical practice and trials.[5,6] For assessing a change in THI, 10 studies were included, and the pooled result showed that electrical stimulation is more likely to relieve. We also conducted subgroups based on studies on the changes of THI scores for several factors.

First, the follow-up time was subjected to subgroup analysis, with the results suggesting that electrical stimulation might be effective in both the short and the long term. However, compared with the MD in the short-term (−10.77) and medium-term (−11.36) groups, the MD was reduced to −2.38, which suggested that the treatment effect may continue for a short term, and several stimulations are required for better therapeutic effects. The second subgroup was defined according to the course of the disease, and the results showed that the treatment effect may not be obvious in acute or subacute tinnitus patients. Electrical stimulation may be more suitable for chronic tinnitus. Third, some researchers have reported that electrical stimulation for a longer duration and elevated current resulted in significant suppression.[16] However, our results demonstrated that a higher current intensity may not improve the treatment effect. Finally, tDCS and TENS, the most common methods of electrical stimulation, were analysed based on different stimulation areas, and the results indicated that the stimulation method in which electrodes were placed on the LTA may be less effective than others which suggested that tDCS may require multipoint stimulation for better efficacy. However, the validity and sensitivity of the THI have been previously challenged. THI questionnaire uses a three-label category scale and involves the assignment of numbers that can lead to more difficulties in deciphering differences based on the use of this restrictive scale.[12,16]

Since Adamchic and colleagues[16] demonstrated that a change in loudness and distress was a valid and reliable measure for changes in response to treatment in patients with chronic tinnitus, five studies were included respectively as for a change in loudness and distress. Furthermore, there was significant difference in VAS. Nevertheless, when we use VAS scale to assess the condition of tinnitus, it is necessary to state the length of the line and the markings and labels on the line, and the resolution which could be used to convert the subjects marking into number. This is so that other researchers can replicate the work and facilitate more effective cooperation and comparisons of outcomes.[31]

Adverse effects of electrical stimulation are relevant to any use of the technique as safety and tolerability may affect the feasibility of its clinical application.[32] Although we did not find any serious or persistent side effects, temporary discomfort was reported to occur frequently during treatment which is usually tolerable,[23] and disappeared after stimulation. Loo indicated that adding saline could usually reduce any pain experienced, and skin burns which is considered as the most common adverse reaction to the treatment,[23,26,28] and thus, it was rarely necessary to cease stimulation midsession.[33]

Conditions of relevant existing studies

A number of systematic reviews and meta-analyses have been conducted on electrical stimulation in tinnitus treatment; of those, one[34] compared the effects of TENS *versus* sham stimulation, and the results indicated that TENS showed a significant overall reduction in the THI (MD = −7.55; 95% CI = −10.93, −4.18; $p < 0.0001$) and VAS scores (MD = −0.65; 95% CI = −0.99, −0.30; $p < 0.0002$). However, the study included controlled before-and-after trials of low quality. Meanwhile, two meta-analysis[12,35]studies compared the effects of tDCS in tinnitus therapy. Song and colleagues[35] performed a meta-analysis and reported that the percentage reduction in tinnitus intensity between active and sham tDCS was 0.77 ($Z = 2.81$; $p = 0.005$; 95% CI = 0.23, 1.31), indicating a significant medium to large effect size. Furthermore, the authors reported that the weighted mean percentage of tinnitus intensity reduction by active LTA and bifrontal tDCS were 14.6% and 13.1%, respectively, suggesting that these two locations of active electrodes were comparably effective for tinnitus treatment. However, Song and colleagues[35] also concluded that the efficacy of tDCS could not be verified because of the limited number of studies included in their study. Recently, Wang and colleagues[12] determined that compared with a sham treatment, tDCS did not have a beneficial effect on loudness (MD = 0.674; 95% CI = −0.089, 1.437; $p = 0.083$). They also did not observe a difference in the change in the THI scores between the two groups. However, in the study, the authors also included nonrandomized controlled trials which may consequently affect the accuracy of the analytical results. A recent network meta-analysis reported by Chen and colleagues[36] in 2020 showed that compared with a sham control procedure, the cathedral tDCS-F3 plus anomaly tDCS-F4 plus transcranial random noise stimulation (tRNS)-T3 combination

was associated with improvements in tinnitus severity and quality of life .

Limitation

Several potential limitations should be considered for this meta-analysis. First, different follow-up times, tinnitus durations and stimulation points may lead to heterogeneity in the results. To address this, we defined subgroups to explore sources of heterogeneity, and in some subgroups, heterogeneity was reduced slightly. However, some other probable contributors such as sex, types of tinnitus and stimulation settings were not analysed because of the small sample size and lack of detailed classification in the original literature. Pertinently, we found that when we excluded a study,[19] the heterogeneity was obviously reduced, which might be due to the larger number of acute tinnitus patients included in that study; moreover, the symptoms might disappear and improve significantly with or without treatment. Second, sleep disturbance has long been recognized as the single most important complaint among adults with tinnitus;[30] however, we could not assess the treatment efficacy using insomnia scale because of the limitation of the original studies assessing sleep condition. Third, bias may have arisen because most articles did not explain their specific methods of randomization and concealment, which reduced the quality of evidence of outcomes in this review. Fourth, the sample size of most included studies was relatively small, as sample sizes ranged from 18 to 68 patients, with recent clinical trials still underway. Fifth, the PFC, auditory cortices (ACs) and LTA have been the most commonly investigated areas because of their suggested roles in tDCS treatment. However, in our study, we combined PFC and PFC + LTA as a subgroup because of the limited number of included trials. Sixth, three studies[19,22,29] reported that some adjuvant therapies were combined with electrical stimulation including oral mecobalamin, vitamins and hearing aid treatment, although drug therapies are not recommended by some guidelines because of the potential side effects and dubious curative effect. However, hearing aid therapy is recommended in tinnitus guidelines and considered effective, especially in tinnitus patients combined with hearing loss which may potentially affect the outcomes and accuracy of analysis to some extent. Seventh, the sham electrical stimulation current setting in the control groups was different in the included studies and could not be analysed because of the limited number of included studies. Finally, as the limited number of high-quality original studies and the underlying mechanism of tinnitus and the electrical stimulation have largely remained elusive, we initially pooled the data of different stimulation points and then divided them into subgroups.

Research needs

From our study, we suggest that future studies need to focus on (1) advocating the utilization of multiple instruments to more accurately capture the functional impact of disease and treatment, such as the Tinnitus Primary Function Questionnaire (TPFQ),[37] which is focused on patients' four primary reactions to tinnitus, emotions, hearing, sleep and concentration, and it is considered responsive to treatment-related changes to scale the overall severity of tinnitus; (2) categorizing and grouping the tinnitus population according to the baseline data, such as the causes and severity of the disease and age; (3) comparing the efficacy among different stimulation points which may help us to determine the locations and mechanisms of tinnitus and developing the comparison between single site and multipoint stimulation for better therapeutic efficacy; (4) dividing patients with tinnitus into groups according to different causes such as idiopathic tinnitus, sudden hearing loss and Meniere disease, with corresponding standard treatment protocols; and (5) conducting experiments in animals showing that combining sound stimulation with electrical stimulation can drive extensive plasticity across the auditory system up to the midbrain and cortex that can potentially treat tinnitus, and showing that electrical stimulation can drive auditory plasticity.[31] Therefore, electrical stimulation combined with other treatments, such as sound therapy to improve therapeutic effects, may be a promising direction for future research. In addition, in future studies, (6) treatment should be administered to elderly individuals and patients with some underlying conditions such as stroke, and epileptic and cerebrospinal-cardiovascular disease, and should be evaluated with longer follow-up durations to elucidate the universal applicability and safety profile of the treatment.

Conclusion

We performed a meta-analysis of trials that confirmed the efficacy of electrical stimulation in which treatment outcomes were evaluated by the THI and VAS scores and showed satisfactory efficacy and safety as a tinnitus therapy for patients with tinnitus.

Nonetheless, although electrical stimulation is a promising treatment for chronic tinnitus, our conclusions are based on a relatively small number of trials, which should be interpreted with caution. However, larger well-designed multicenter trials with large samples and longer follow-up periods are suggested.

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We acknowledge all the contributing authors.

Author contributions

HL and TY designed the study. TY designed the search strategy. TY and HL performed the search. TY and JZ performed the abstract screening, full-text screening, data extraction and risk-of-bias assessment. BW and WZ helped in the revision process. All the authors drafted and revised the article.

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Conflict of interest statement

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Consent for publication

All the contributing authors have agreed to the publication of this article.

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Availability of data and materials

The datasets used in this study are available from the corresponding author upon request. All data generated or analysed in this study are included in the published articles or obtained from the authors who published the enrolled articles.

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