



Systematic review

Non-traditional acupuncture therapies for smoking cessation: a systematic review of randomized controlled trials

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ABSTRACT

Introduction: Non-traditional acupuncture (NTA), defined as the stimulation of certain parts of the body includes; acupressure, transcutaneous electrical acupoint stimulation (TEAS), laser acupuncture, intradermal needles, and acupoint catgut embedding (ACE). This systematic review evaluated their efficacy and safety for smoking cessation.

Methods: Randomized controlled trials (RCTs) comparing NTA with sham NTA or conventional therapy for smoking cessation were included. Ten databases were searched from their inception to March 2021. Data were synthesized using risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI). The primary outcome was abstinence rate defined as abstinence between date of quitting and follow-up.

Results: Acupressure was more effective than sham acupressure or conventional therapy in the short-term (RR 1.41, 95% CI [1.04 to 1.91]; low certainty; 8 trials, n=637) and for mid-term smoking cessation (RR 1.63, 95% CI [1.27 to 2.09]; low certainty; 8 trials, n=749). TEAS appeared more beneficial for mid-term abstinence (RR 1.58, 95% CI [1.10 to 2.27]; moderate certainty; 3 trials, n=325). Laser acupuncture was superior to sham control for long-term abstinence (RR 2.25, 95% CI [1.23 to 4.11]; moderate certainty; 2 trials, n=160). ACE was comparable to Bupropion for mid-term smoking cessation (RR 0.99, 95% CI [0.70 to 1.40]; low certainty; 2 trials, n=177). No serious adverse events were reported.

Conclusions: Low certainty evidence suggests that NTA was effective for short-term, middle-term or long-term smoking cessation. Further long-term follow-up RCTs are warranted to verify these benefits.

Registration: INPLASY 202120054.

1. Introduction

Cigarette smoking is one of major public health issues worldwide, which is closely related to the onset and progression of many diseases. Reports suggest that about 480,000 people die prematurely every year, and one-fifth of the deaths are related to smoking [1]. The Global Burden of Diseases, Injuries, and Risk Factors Study reported that in 2019, out of 87 risk factors, the leading risk factor for attributable deaths globally was high systolic blood pressure, and that smoking was the second leading risk factor and accounted for nearly 8.71 million deaths [2]. There were as many as 40 million adult smokers in the United States in 2017 and the number of smokers has continued to grow, with more than

50.6 million US adults in 2019 who smoked (accounting for 20.8% of the adult population) [3]. Responses from the National Health Interview Survey in 2015 indicated that 68% smokers (a total of 33,672 adult smokers) wanted to quit smoking [4]. Currently, smoking cessation therapies are recommended in guidelines and the US Food and Drug Administration have approved the use of pharmacological therapy, behavioral therapy, and complementary and alternative therapies [5]. However, studies have found that pharmacological therapy including nicotine replacement therapy (NRT), Varenicline and Bupropion have limited use in smoking cessation due to their high cost, side effects, tendency to relapse [6–8] as well as low popularity and being difficult access (particularly in China) [9]. To our knowledge, the latest Chinese

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guideline on smoking cessation focuses on medication and behavioral counseling [10]. Additionally, withdrawal symptoms are hard to control with psychological and behavioral interventions alone. Acupuncture has been used in different countries for smoking cessation since 1977 [11]. Clinical and experimental studies have found that acupuncture was effective for withdrawal symptoms through promoting the release of endogenous opioids [12–13] or suppressing the craving for cigarettes [14]. Acupuncture was recommended as a complementary therapy for smoking cessation in guidelines issued by National Comprehensive Cancer Network, however, further high-quality evidence was needed [5]. Traditional acupuncture generally uses filiform needles which penetrate the skin and are manipulated to stimulate acupoints to prevent and treat disease. However, traditional acupuncture may induce some pain when the filiform needle penetrates the acupoint. Quitting smoking is a process that requires long-term adherence to treatment if there are to be any beneficial effects to health. An in-depth interview study explored factors influencing participant compliance in acupuncture trials suggested that patient's fear of traditional acupuncture pain may reduce treatment compliance [15], hence improved or more convenient acupuncture related techniques maybe more appropriate for smoking cessation.

As acupuncture techniques have developed, various non-traditional acupuncture (NTA) techniques have been used to stop smoking. Non-traditional acupuncture (NTA), defined as the stimulation of certain parts of the body includes; acupressure, transcutaneous electrical acupoint stimulation (TEAS), laser acupuncture, intradermal needle, and acupoint catgut embedding (ACE). NTA therapies have been widely used for nicotine dependence in several trials worldwide due to convenience and acceptability. For example, acupressure is fairly painless, convenient and may be a self-administered within a smoking cessation procedure (every 2 or 3 days treatment cycle). Non-invasive of NTA therapies should be evaluated to assess their safety and effectiveness for smoking cessation.

Previous systematic reviews [16–17] have aimed to evaluate the effectiveness of traditional body acupuncture for smoking cessation, though one Cochrane systematic review [18] focused on the effectiveness of both traditional body acupuncture and selected NTA therapies on smoking cessation.

So far, we have not found any systematic reviews that comprehensively and individually evaluate common NTA therapies. Therefore, this systematic review aimed to collect all randomized controlled trials (RCTs) on NTA therapies for smoking cessation and to evaluate their therapeutic effect and safety.

2. Materials and methods

This systematic review was reported following PRISMA 2020 [19] statement, and the protocol of this systematic review was registered on INPLASY (INPLASY 202120054) [20]. There was no deviation from the registered protocol in conducting this systematic review.

2.1. Eligibility criteria

Parallel group RCTs regardless of blinding were included. The study population comprised of smokers of any age who had no serious diseases or who were not pregnant and wanted to quit smoking. The study interventions included were NTA therapies used alone or in combination with conventional therapy (medications or behavioral counseling). NTA therapies included; acupressure, transcutaneous electrical acupoint stimulation (TEAS), laser acupuncture, intradermal needle, and acupoint catgut embedding (ACE). Interventions with any traditional filiform needles penetrating through the skin at acupoints were excluded. The controls were medications (NRT, Bupropion or Varenicline), behavioral counseling, sham NTA or non-specific acupoint stimulation, or no treatment. The primary outcome was continuous abstinence rate defined as smoking cessation between quit day and a follow-up period

[21], and smoking cessation could be self-reported or biochemically validated. The secondary outcomes were nicotine withdrawal symptoms measured by Minnesota Nicotine Withdrawal Scale Score, daily cigarette consumption, the Fagerström test for nicotine dependence (FTND), the level of exhaled carbon monoxide (CO), relapse rate, craving for cigarettes and adverse events. Three follow-up periods were employed to report the outcomes in the short-term (1-3months), mid-term (3-6months), and long-term (≥ 6 months). Trials that failed to report at least one required outcome were excluded.

2.2. Search strategy

We systematically searched RCTs from PubMed, the Cochrane Library, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Sino-Med and Wanfang databases from their inception to March 10, 2021. Ongoing trials from ClinicalTrials.gov and Chinese Clinical Trial Registry were also retrieved. The search strategy for each database is presented in the Supplementary material. Additionally, relevant reference lists from systematic reviews were also checked.

2.3. Study selection and data extraction

After removing duplicates, two authors (ZYY and HDL) independently screened studies by title and abstract, uncertainty was determined for eligibility through checking full texts. Reasons for excluding trials were recorded at the full-text screening stage, and any discrepancies were discussed by two review authors or arbitrated by third party (JPL). In the data extraction process, data were extracted by two authors (ZYY and HDL) independently using a pre-defined electronic data extraction form which included basic information on the study design (study ID, setting, sample size, centers, and funding); participants characteristics; details of NTA therapies and controls; outcome measures at various timepoints; follow ups; dropouts and adverse events.

2.4. Quality assessment

The methodological quality of each included trial was evaluated independently by two review authors (ZYY and HDL). Cochrane Risk of Bias tool (ROB) [22] was employed to assess the risk of bias of each trial based on its seven domains (the adequacy of sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias). Grading of Recommendations Assessment, Development and Evaluation (GRADE) [23] was applied to evaluate the certainty of the body of evidence based on risk of bias, directness, precision, consistencies, and publication bias.

2.5. Data synthesis

For dichotomous data, data were presented as risk ratio (RR) with 95% confidence interval (CI). For continuous data, mean difference (MD) with 95% CI was estimated. Meta-analysis was conducted by Cochrane Review Manager 5.4 software when the trials have similarities in study design and clinical characteristics. Otherwise, data were synthesized qualitatively. The Cochrane Q test and I^2 statistic was utilized to test the statistical heterogeneity [22]. The fixed effects model was used when $I^2 \leq 30\%$, otherwise the random effects model was applied in meta-analysis. Comparisons groups for meta-analysis were medication and/or behavioral counseling, sham NTA, non-specific acupoint stimulation, or no treatment. To explain heterogeneity, subgroup analysis was predefined by the comparisons (active control and inactive control). Active controls referred to conventional therapy alone or conventional therapy plus sham NTA, active controls were known to be effective for smoking cessation; inactive controls referred to sham NTA or no treatment, inactive controls were considered ineffective for smoking

cessation. Sensitivity analysis was employed to explore the influence of the randomization concealment (clear or not) and blinding (blinded or not). Funnel plots were generated to detect possible publication bias if 10 or more trials were included in a meta-analysis.

3. Results

3.1. Screening

Initially 660 records were retrieved and 191 duplicates were removed. A total of 423 records were excluded in title and abstract screening process, leaving 46 records for full text screening. In the full-text screening process, 21 trials were excluded because: ineligible study type (5 trials), studies with only abstracts (4 trials), interventions were combined with traditional acupuncture (6 trials), ineligible controls (2 trials), and ineligible or incomplete outcomes (4 trials). The list of

excluded studies is presented in (Supplementary material: Table 6). Finally, 25 trials were identified and were all quantitatively synthesized. The flow chart of study selection is shown in (Fig. 1).

3.2. Characteristics of included trials

The identified 25 [24–48] trials were conducted in several countries, 11 [27,30–34,37,39,44,47–48] in China, five [28,36,41,43,45] in UK, two [38,40] in USA, three [24–26] in Korea, and one each in Canada [35], Australia [29], Turkey [42], and Singapore [46]. There were only two [33–34] multi-center trials, the rest were single center trials. Twelve trials [24–25, 27–28, 31–33, 39–40, 43, 46, 48] reported their funding source. The sample sizes varied from 18 to 500 and the ratio of males varied from 40% to 100%. The study population reported were adults or adolescents who smoked more than 5 cigarettes a day for at least three months. The follow up ranged from 4 weeks to 18 months and the

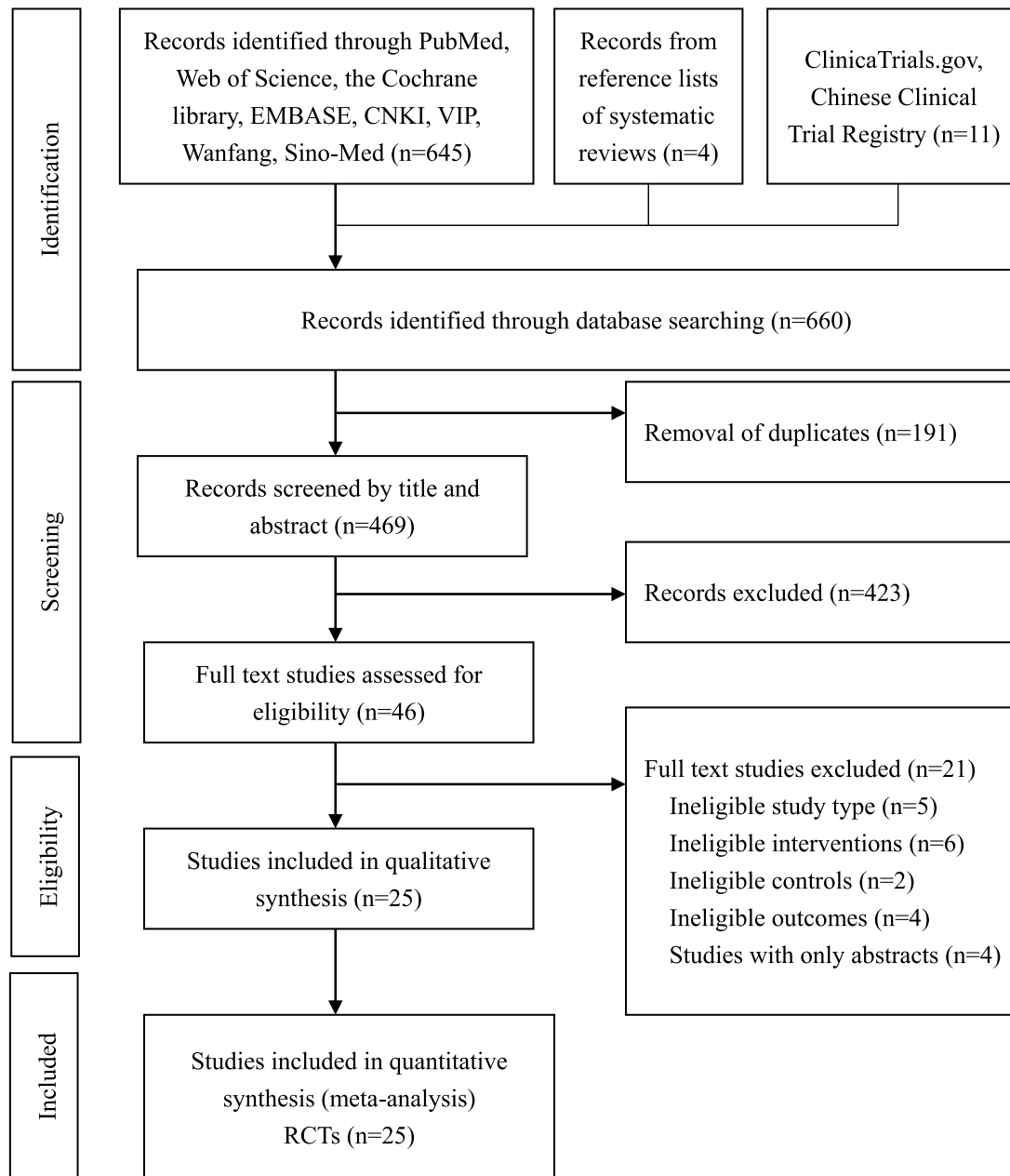


Fig. 1. PRISMA flow diagram of study selection.
Notes: RCT: randomized controlled trials.

duration of treatment ranged from one week to 12 weeks. The dropout rates varied from 0 to 68.4%. Almost all treatment sites were in the ears except for 2 trials [47–48], the most commonly used auricular acupoints were “ear Lung (CO₁₄)”, “ear Shenmen (TF₄)”, and “ear Mouth (CO₁)”. Auricular acupressure was used alone or in combination with behavioral counseling or medication for smoking cessation in 11 trials [24–34]. Auricular point sticking was used to produce continuous acupressure and was changed alternatively on right and left sides every 2 or 3 days, and the treatment duration ranged from 3 weeks to 2 months. Auricular intradermal needles were utilized alone or in combination with counseling in 5 trials [35–39]. Intradermal needles were imbedded in the ear to provide continuous stimulation and changed alternately to right and left sides once a week, and the course of treatment ranged from 1 week to 8 weeks. TEAS was used in 6 trials [34, 40–44]. TEAS was given once a week, 20 minutes each time, and the treatment duration ranged from 1 week to 6 weeks, the frequency of stimulation varied from 4 Hz to 100 Hz. Two trials [45–46] focused on laser acupuncture and 2 trials [47–48] on ACE. The dose of laser acupuncture was 2.5 mw to 3 mw, three times a week and 4 minutes each time during 2 or 4-week treatment period. ACE therapy was given once every 2 weeks and lasted for 8 or 12 weeks. There were two types of sham stimulation which used controls, one was non-acupoint stimulation [26–27, 36, 38, 44], and the other was the use of real acupoints stimulation [24–25, 29, 31, 35, 38–39] (which were considered not specific acupoints for smoking cessation). Other controls included medications [28, 34, 47–48], behavioral counseling [24–25, 28, 30, 32, 36, 40–41], and no treatment [33, 37]. The outcomes reported at time-points varied from 4 weeks to 18 months. The smoking cessation was measured by biochemically verified abstinence rate in 6 trials, including cotinine test [24–25, 44] and exhaled carbon monoxide [27, 29, 47]. Smoking cessation was self-reported in the remaining trials. Secondary outcomes were not fully reported in the identified trials, and we combined all available outcomes. The details are shown in (Table 1).

3.3. Risk of Bias assessment

The detailed methods of random sequence generation were reported in 14 trials [24–26, 28–30, 34, 36, 39–41, 45–47], including random number tables [24–25, 28–29, 36, 39–41, 45–47], drawing lots [26], and the central randomization system [30, 34]. In terms of allocation concealment, ten trials [24–25, 28–30, 34–35, 40–41, 47] were judged as low risk of bias since the random number was kept in opaque envelopes. The blinding of the participants were reported and sham or placebo acupuncture was used in 13 trials [24, 26, 29, 35–36, 38, 40–46], hence these trials were assessed as low risk of performance bias. Blinding of the intervention was not successful in one trial [25] as the participants were aware of treatments. The blinded outcome assessment was clearly reported in 7 trials [24, 29–30, 40–41, 45–46] and were rated as low risk of detection bias. In terms of attrition bias, 14 trials [24–26, 30, 32, 34, 36, 38–40, 42–43, 47–48] were assessed as low risk of bias due to conducting an intention-to-treat analysis, and the dropouts rate was <10%. Eight trials [27–29, 33, 41, 44–46] were rated as high risk of attrition bias due to higher dropouts rates (>20%). Of the included 25 trials, only one trial [34] was assessed as low risk of reporting bias since the protocol was registered and there was consistency between the outcomes described in protocol and actual outcomes in the results. One trial [29] was rated as ‘high’ due to the inconsistent outcomes between protocol and actual results. The protocols were not reported in the rest of the trials and were considered as unclear risk of reporting bias. In terms of the “other bias” domain, the funding was reported and the baseline data were comparable in 11 trials [24–25, 27, 29, 31–32, 34–35, 37, 40, 48]. There was a potential conflicts of interest in one trial [43] and this was considered as high risk of bias. The remaining 13 trials were assessed as ‘unclear’ since either the funding or the baseline data was not reported. The risk of bias summary is shown in the Supplementary material: Fig. 1.

3.4. Effects of interventions

Three time periods were employed to report each outcome to evaluate the therapeutic effects of interventions in the short-term (1–3 months), mid-term (3–6 months), and long-term (≥ 6 months), when there was sufficient data for each outcome.

3.4.1. Acupressure versus sham acupressure or conventional therapy (counseling or NRT)

3.4.1.1. Primary outcome. Eight trials [24–25, 27–28, 30–32, 34] reported the short-term abstinence rate, with 126 of 328 (38.4%) smokers achieving smoking cessation in acupressure group versus 82 of 309 (26.5%) in the control group, suggesting that acupressure was more effective (RR 1.41, 95% CI [1.04 to 1.91]; $I^2 = 31\%$; low certainty; 8 trials, $n=637$). Subgroup analysis by controls suggested that acupressure was still superior to inactive controls in improving short-term abstinence rate (RR 2.01, 95% CI [1.10 to 3.67]; low certainty; 2 trials, $n=210$), but this effect was not observed in active controls (RR 1.30, 95% CI [0.93 to 1.82]; $I^2 = 33\%$; low certainty; 6 trials, $n=427$) (Fig. 2, Table 2). The mid-term abstinence rate was 29.9% in acupressure group and 18.9% in control group, suggesting that acupressure was still more effective in improving mid-term abstinence rate (RR 1.63, 95% CI [1.27 to 2.09]; low certainty; 8 trials [25, 34, 27, 29–33], $n=749$). This effect was still observed regardless of the active controls (RR 1.52, 95% CI [1.17 to 1.98]; $I^2 = 18\%$; low certainty; 6 trials, $n=539$) and inactive controls (RR 2.44, 95% CI [1.13 to 5.25]; low certainty; 2 trials, $n=210$) (Fig. 3, Table 2). However, the long-term abstinence effect was not significant between acupressure group and control group (RR 1.85, 95% CI [0.59 to 5.82]; $I^2 = 14\%$; moderate certainty; 2 trials [24–25], $n=74$) (Table 2, Supplementary material: Table 1).

3.4.1.2. Secondary outcomes. Acupressure was found to be more effective than sham acupressure or counseling in relieving short-term withdrawal symptoms (MD -2.68, 95% CI [-5.34 to -0.03]; $I^2 = 83\%$; 4 trials [25, 27–28, 30], $n=180$). Subgroup analysis suggested that acupressure was still more effective than active control (MD -4.44, 95% CI [-5.40 to -3.48]; 3 trials, $n=115$) (Fig. 4). In terms of daily cigarettes consumption, there was no significant difference between acupressure and sham acupressure in short-term (MD 1.27, 95% CI [-1.30 to 3.85]; 2 trials [24–25], $n=111$) and long-term effect (MD -0.19, 95% CI [-2.84 to 2.46]; 2 trials [24–25], $n=111$) (Supplementary material: Table 1). Acupressure was also not superior to sham acupressure in decreasing nicotine dependence score (FTND) in short-term (MD -0.32, 95% CI [-1.72 to 1.08]; $I^2 = 93\%$; 4 trials [26, 30–31, 34], $n=373$), and mid-term FTND (MD -0.85, 95% CI [-4.00 to 2.29]; $I^2 = 97\%$; 2 trials [30, 34], $n=250$). Subgroup analysis by controls did not change the result. The pooled data from 2 trials [26, 30] suggested that acupressure was more effective than sham acupressure in decreasing the level of short-term exhaled CO (MD -3.84, 95% CI [-5.03 to -2.66]; 2 trials, $n=103$) (Supplementary material: Table 1). However, acupressure failed to demonstrate a better effect than sham control in suppressing the short-term cravings for cigarettes (MD -0.13, 95% CI [-0.85 to 0.59]; 1 trial [27], $n=70$).

3.4.2. Intradermal needle versus sham intradermal needle or counseling

3.4.2.1. Primary outcome. Short-term abstinence rate was reported in 5 trials [35–39], with 66 of 172 (38.4%) smokers achieving smoking cessation in the intradermal needle group versus 40 of 174 (23%) smokers in the control group. This suggests that intradermal needle was not superior to sham control in improving abstinence rate (RR 1.62, 95% CI [0.85 to 3.08]; $I^2 = 64\%$; low certainty; 5 trials, $n=346$) (Supplementary material: Table 1–2). Subgroup analysis did not change the result, neither for active controls (RR 1.12, 95% CI [0.72 to 1.73];

Table 1

Characteristics of the included randomized controlled trials.

Study ID	Study population	Sample size T/C	Male (%)T/C	Intervention	Comparison	Treatment duration	Outcome measurement time	Outcome reported
Lee 2019 [24]	37 adults who have smoked for ≥ 6 months and wanted to quit smoking	18/19	94.4/84.2	auricular ACP+behavioral counseling	placebo ACP+behavioral counseling.	6w	6w, 6m-1y, 1y	1, 2
Lee 2019 [25]	74 adults who have smoked for ≥ 6 months and wanted to quit smoking	42/32	97.6/96.9	auricular ACP +group counseling	placebo ACP+group counseling	6w	6w, 6m-1y,1y	1, 2, 3
Lee 2016 [26]	53 male smoking college students	27/26	100/100	auricular ACP	non-specific auricular acupoints ACP	6w	3w, 6w	4, 5
Wing 2010 [27]	70 adults who wanted to quit smoking	38/32	68.4/71.9	auricular ACP+ACP (Hegu L14, Neiguan PC6)	non-acupoints ACP	3w	1w, 2w, 3w, 4w, 3m	1,3,5,6
White 2007 [28]	19 adults who smoked ≥ 10 cigarettes a day and wanted to quit smoking	12/7	66.7/16.7	auricular ACP+NRT+group counseling	NRT+group counseling	5w	5w	1,3,7
Zhang 2013 [29]	43 adults who smoked ≥ 10 cigarettes a day and wanted to quit smoking	20/23	40/43.5	auricular acupoints ACP+counseling	non-specific auricular acupoints ACP +counseling	8w	8w,3m	1,2
Zhao 2017 [30]	50 adult smokers	25/25	92/84	auricular acupoints ACP+behavioral counseling	behavioral counseling	8w	4w,8w, 12w, 24w	1,3,4,5
Li 2009 [31]	140 adults who smoked ≥ 10 cigarettes a day and wanted to quit smoking	70/70	74.3/78.6	auricular acupoints ACP	non-specific auricular acupoints ACP	3w	3m	1
Jiang 2011 [32]	47 soldiers who volunteered to quit smoking	23/24	100/100	auricular acupoints ACP+behavioral counseling	behavioral counseling	1m	1m, 3m, 6m, 1y	1
Li 2011 [33]	150 adults who have smoked for ≥ 1 year and want to quit smoking	75/75	98.4/96.5/98.4/98.2	auricular ACP+behavioral counseling	behavioral counseling	2m	6m	1,2
Chai 2019 [34]	300 adults who smoked ≥ 10 cigarettes a day and wanted to quit smoking	100/100/100	92/95/95	T1.auricular acupoints ACP T2.auricular acupoints TEAS	NRT	8w	8w, 6m	1,5
Gilbey 1977 [35]	92 subjects who smoked >15 cigarettes/day for 3 years	44/48	NR	auricular acupoints intradermal needling	inactive auricular point ("Kidney") stimulation	1w	1m,3m	1
Gillams 1984 [36]	55 adults smoking >50 cigarettes/week for 5 years	28/27	NR	auricular acupoints intradermal needling	non-specific acupoints stimulation	4w	4w, 3m, 6m	1
Leung 1991 [37]	64 subjects who had smoked ≥ 1 year and were motivated to stop	32/32	NR	auricular acupoints intradermal needling+counseling	counseling	2w	1m, 3m, 6m	1
Parker 1977 [38]	41 smokers, other characteristics unspecified	T1/C1:9/9;T2/C2:11/12	NR	T1:auricular acupoints intradermal needling; T2: auricular acupoints TEAS	C1:non-specific acupoints stimulation; C2: non-specific auricular acupoints TEAS	3w	6w	1
Wu 2007 [39]	131 subjects who smoked >10 cigarettes/day for 1 years	64/67	81.4/88.1	auricular acupoints intradermal needling+ counseling	non-specific acupoints stimulation+ counseling	8w	8w,6M	1,2,3
Fritz 2013 [40]	125 subjects who smoked >10 cigarettes/day	64/61	75.0/77.0	auricular acupoints TEAS (80Hz) +counseling	sham TEAS (0Hz)+ counseling	5w	3w,6w	1,3
White 1998 [41]	76 adults who smoked >10 cigarettes/day	38/38	44.7/52.6	TEAS+counseling	sham TEAS+counseling	1w	3d, 2w,9m	1
Dinn 2011 [42]	47 smokers who had a score of Fagerstrom ≥ 5	24/23	66.7/60.9	auricular acupoints TEAS	sham TEAS	3w	3w,7w, 3m, 6m	1,2,3,4,5
Waite 1998 [43]	79 subjects who had smoked for ≥ 1 year	39/40	NR	auricular acupoints TEAS+Tianmei acupoint TEAS	sham auricular acupoints TEAS+sham Tianmei acupoint TEAS	6w	6w	1,2,4
Yeh 2009 [44]	78 adults who smoked >10 cigarettes/day	40/38	55/55.3	auricular acupoints TEAS+ACP	inactive TEAS +ACP	2w	2w,2m,4m,6m	1,7
		130/89		laser acupuncture	sham laser acupuncture	2w	3m,6m,18m	1

(continued on next page)

Table 1 (continued)

Study ID	Study population	Sample size T/C	Male (%)T/C	Intervention	Comparison	Treatment duration	Outcome measurement time	Outcome reported
Kerr 2008 [45]	219 smokers who motivated to quit smoking		56.5% (192/340)					
Cai 2000 [46]	330 adolescents who smoked >5 cigarettes/day for 3 months	160/170	NR	laser acupuncture	sham laser acupuncture	4w	4w, 3m, 36m	1
Li 2019 [47]	100 subjects who smoked >10 cigarettes/day for 1 year.	50/50	83.7/83.3	acupoint catgut embedding	Bupropion	8w	8w	1
Zeng 2019 [48]	80 subjects who smoked >10 cigarettes/day and wanted to quit smoking	40/40	75/77.5	acupoint catgut embedding	Varenicline	12w	4w, 8w, 12w	1

Notes: ACP, Acupressure; TEAS, Transcutaneous electrical acupoint stimulation; NR, Not reported; NRT, Nicotine replacement treatment; w, weeks; m, months; y, years. Outcomes: 1, Abstinence rate; 2, Daily cigarettes consumption; 3, Withdrawal symptoms; 4, The level of exhaled CO; 5, Nicotine dependence; 6, Craving for cigarettes; 7, Relapse rate.

moderate certainty; 3 trials, n=165) nor for inactive controls (RR 3.49, 95% CI [0.40 to 30.59]; $I^2 = 88\%$; very low certainty; 2 trials, n=181). The mid-term effect of quitting smoking was also not significant between two groups (RR 1.49, 95% CI [0.68 to 3.27]; low certainty; 3 trials [36-37, 39], n=187) (Supplementary material: Table 1-2).

3.4.3. TEAS versus sham TEAS or counseling

3.4.3.1. Primary outcome. The short-term and mid-term abstinence rates were reported in five [34, 38, 40, 43-44] and three trials [34, 42-43] respectively. The pooled data indicated that TEAS failed to demonstrate a better effect than controls in achieving short-term smoking cessation (RR 1.27, 95% CI [0.96 to 1.67]; moderate certainty; 5 trials, n=485) (Supplementary material: Table 1, Table 3). However, TEAS maybe more beneficial for mid-term smoking cessation (RR 1.58, 95% CI [1.10 to 2.27]; $I^2 = 51\%$; moderate certainty; 3 trials, n=325). TEAS failed to show a better effect on long-term abstinence rate (RR 0.50, 95% CI [0.05 to 5.28]; moderate certainty; 1 trial [41], n=76)

(Supplementary material: Table 1, Table 3).

3.4.3.2. Secondary outcomes. Two trials [42, 44] reported the daily cigarettes consumption and the exhaled CO level in short-term. The pooled data showed that TEAS was not superior to sham TEAS in decreasing daily cigarettes consumption (MD -0.91, 95% CI [-3.55 to 1.73]; 2 trials, n=126) and exhaled CO level (ppm) (MD -0.64, 95% CI [-6.59 to 5.31]; $I^2 = 66\%$; 2 trials, n=124) (Supplementary material: Table 1). The pooled data of FTND indicated that there was no significant difference between TEAS and controls in relieving nicotine dependence at mid-term follow-up (MD -0.30, 95% CI [-0.90 to 1.49]; $I^2 = 51\%$; 2 trials [34, 42], n=247) (Supplementary material: Table 1). Only one trial [43] reported the short-term relapse rate and suggested that TEAS was not superior to sham TEAS in reducing relapse rate (RR 0.82, 95% CI [0.64 to 1.06]; 1 trial, n=51) (Supplementary material: Table 1).

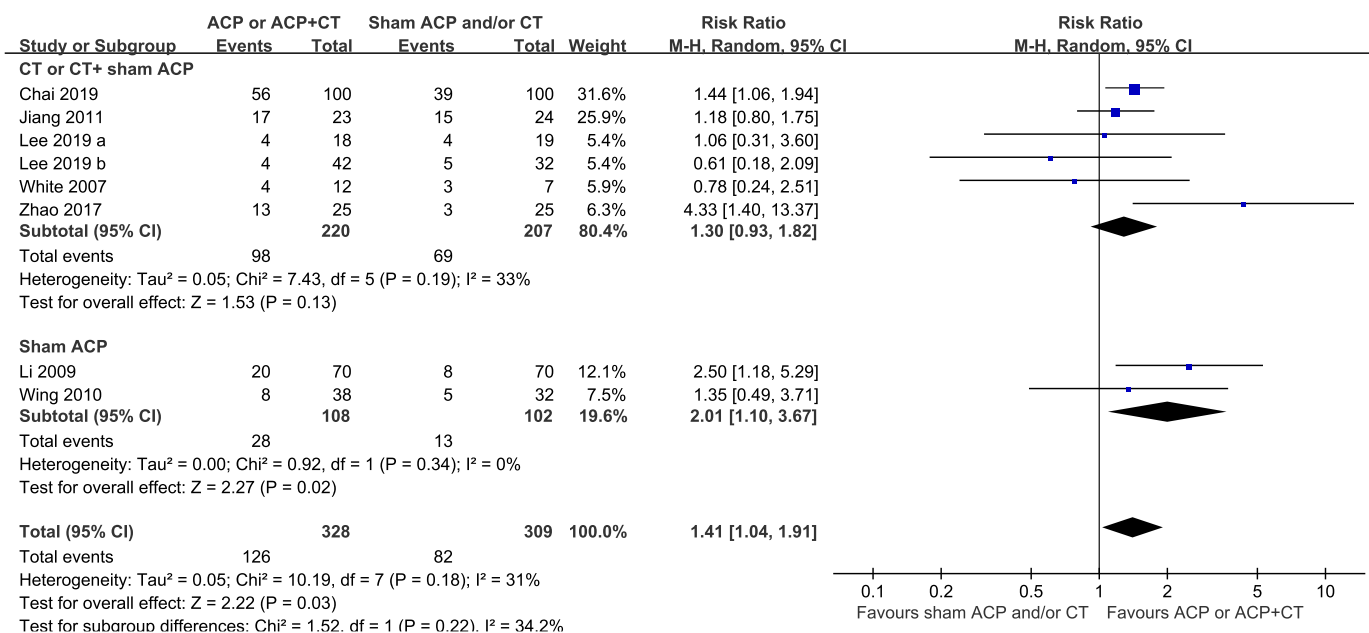


Fig. 2. Acupressure for short-term smoking cessation.

Notes: ACP: acupressure; CT: conventional therapy; CT or CT +sham ACP was active comparison; sham ACP was inactive comparison.

Table 2

Evidence summary of smoking cessation: Acupressure versus sham acupressure or conventional therapy.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACP	Control	Relative (95% CI)	Absolute (95% CI)		
Short-term abstinence rate												
8	randomized trials	serious ^a	not serious	not serious	serious ^b	undetected	126/328 (38.4%)	82/309 (26.5%)	RR 1.40 (1.04 to 1.91)	106 more per 1,000 (from 11 more to 241 more)	⊕⊕○○ LOW	CRITICAL
Short-term abstinence rate in active controls												
6	randomized trials	serious ^a	not serious	not serious	serious ^b	undetected	98/220 (44.5%)	69/207 (33.3%)	RR 1.30 (0.93 to 1.82)	100 more per 1,000 (from 23 fewer to 273 more)	⊕⊕○○ LOW	IMPORTANT
Short-term abstinence rate in inactive controls												
2	randomized trials	serious ^a	not serious	not serious	serious ^b	undetected	28/108 (25.9%)	13/102 (12.7%)	RR 2.01 (1.10 to 3.67)	129 more per 1,000 (from 13 more to 340 more)	⊕⊕○○ LOW	IMPORTANT
Mid-term abstinence rate												
8	randomized trials	serious ^a	not serious	not serious	serious ^b	undetected	114/381 (29.9%)	69/368 (18.8%)	RR 1.63 (1.27 to 2.09)	118 more per 1,000 (from 51 more to 204 more)	⊕⊕○○ LOW	CRITICAL
Mid-term abstinence rate in active controls												
6	randomized trials	serious ^a	not serious	not serious	serious ^b	undetected	94/273 (34.4%)	61/266 (22.9%)	RR 1.52 (1.17 to 1.98)	119 more per 1,000 (from 39 more to 225 more)	⊕⊕○○ LOW	IMPORTANT
Mid-term abstinence rate in inactive controls												
2	randomized trials	serious ^a	not serious	not serious	serious ^b	undetected	20/108 (18.5%)	8/102 (7.8%)	RR 2.44 (1.13 to 5.25)	113 more per 1,000 (from 10 more to 333 more)	⊕⊕○○ LOW	IMPORTANT
Long-term abstinence rate												
2	randomized trials	not serious	not serious	not serious	serious ^b	undetected	7/36 (19.4%)	4/38 (10.5%)	RR 1.85 (0.59 to 5.82)	89 more per 1,000 (from 43 fewer to 507 more)	⊕⊕⊕○ MODERATE	IMPORTANT

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence. Moderate certainty (⊕⊕⊕○): We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty (⊕⊕○○): Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. **Notes:** ACP, Acupressure; CI, Confidence interval; RR, Risk ratio; a, The blinding method was not used; b, A small number of events of less than 300.

3.4.4. Laser acupuncture versus sham laser acupuncture

3.4.4.1. Primary outcome. Only 2 trials [45–46] on laser acupuncture were identified, and which reported the mid-term and long-term abstinence rate. The pooled data suggested that laser acupuncture was not superior to sham laser acupuncture at mid-term follow-up (RR 2.98, 95% CI [0.24 to 37.81]; $I^2 = 96\%$; low certainty; 2 trials, $n=427$) (Supplementary material: Table 1, Table 4). However, laser acupuncture may be more effective in achieving long-term smoking cessation (RR 2.25, 95% CI [1.23 to 4.11]; moderate certainty; $n=160$, 2 trials) (Supplementary material: Table 1, Table 4).

3.4.5. ACE versus Bupropion or Varenicline

3.4.5.1. Primary outcome. Absorbable catgut was embedded in specific acupoints for continuous stimulation, usually one treatment every two weeks, this is a more recently developed form of acupuncture. Two trials [47–48] comparing the effect of ACE with Bupropion or Varenicline on smoking cessation were identified. The pooled data suggested that ACE was comparable to medication in improving abstinence rate at mid-term follow-up (RR 0.99, 95% CI [0.70 to 1.40]; low certainty; 2 trials, $n=177$) (Supplementary material: Table 1, Table 5).

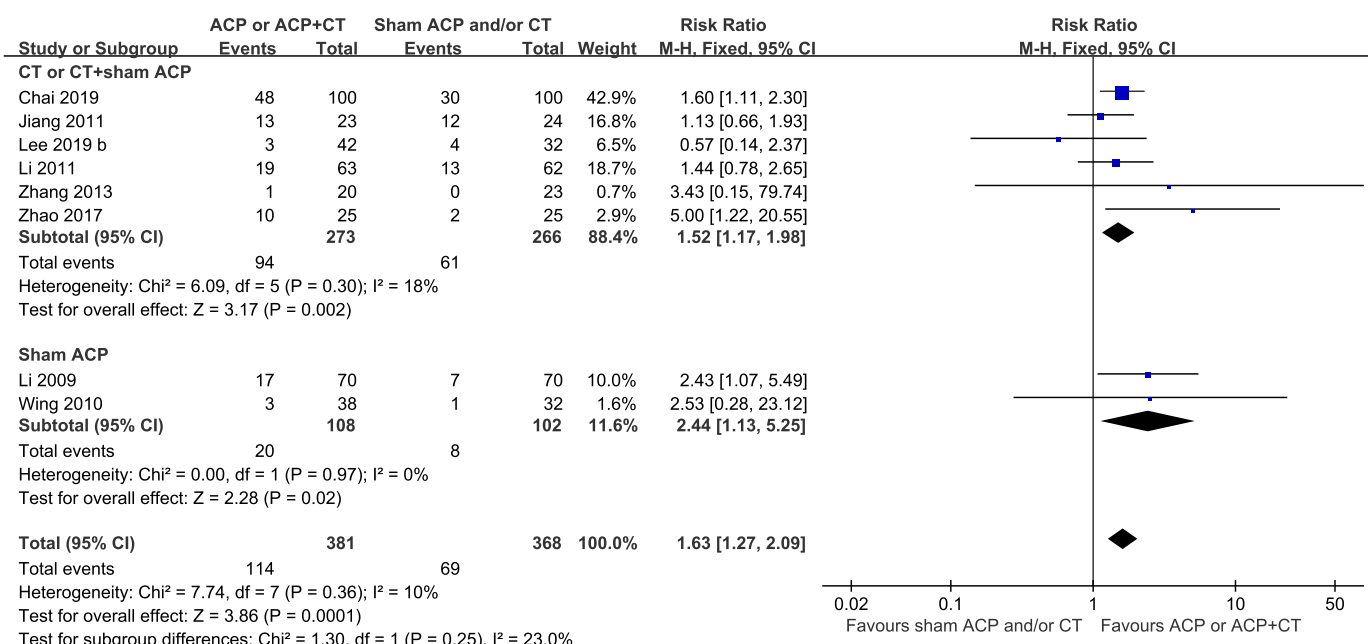


Fig. 3. Acupressure for mid-term smoking cessation.

Notes: ACP: acupressure; CT: conventional therapy; CT or CT +sham ACP was active comparison; sham ACP was inactive comparison.

3.4.6. Adverse events

Four trials [24-26, 29] reported the transient and minor auricular adverse events both in the acupressure group (itching in 12 cases, mild tenderness in 13 cases, feeling hot in 4 cases) and in the control group (uncomfortable feeling in 5 cases, dizziness in 1 case), the pooled data suggested that there was no significant difference between acupressure and controls (RR 2.51, 95% CI [0.24 to 26.59]; $I^2 = 70\%$; 4 trials, $n=240$) (Supplementary material: Table 1). One trial [43] reported adverse events both in TEAS group (pain in 2 cases, soreness in 3 cases) and sham TEAS (soreness in 2 cases, headache in 2 cases). One trial [47] reported adverse events both in ACE group (pain and soreness in 2 cases, minor swelling in 1 case) and bupropion group (nausea in 5 cases, insomnia in 2 cases). No serious adverse events were reported in the included trials.

3.4.7. Publication bias

Funnel plots were not performed to detect publication bias since there was no meta-analysis combining more than ten trials at one time.

3.4.8. Additional analysis

Predefined subgroup analysis via the controls (active control and inactive control) was conducted for 3 outcomes under acupressure, and one outcome under intradermal needle. We were unable to conduct other meaningful subgroup analysis due to limited trials. Sensitivity analysis for allocation concealment for short-term abstinence rates suggested that clear allocation concealment may influence the results (RR 1.51, 95% CI [0.95 to 2.41]; $I^2 = 44\%$; 5 trials [24-25, 28, 30, 34], $n=520$).

3.4.9. Certainty of evidence

GRADE approaches were employed to assess the certainty of evidence from primary outcomes. The quality of the evidence was downgraded to low or very low quality due to lack of blinding, imprecision, inconsistency or indirectness. The detailed evidence summary of outcomes is presented in (Table 2-3, Supplementary material: Table 2-5).

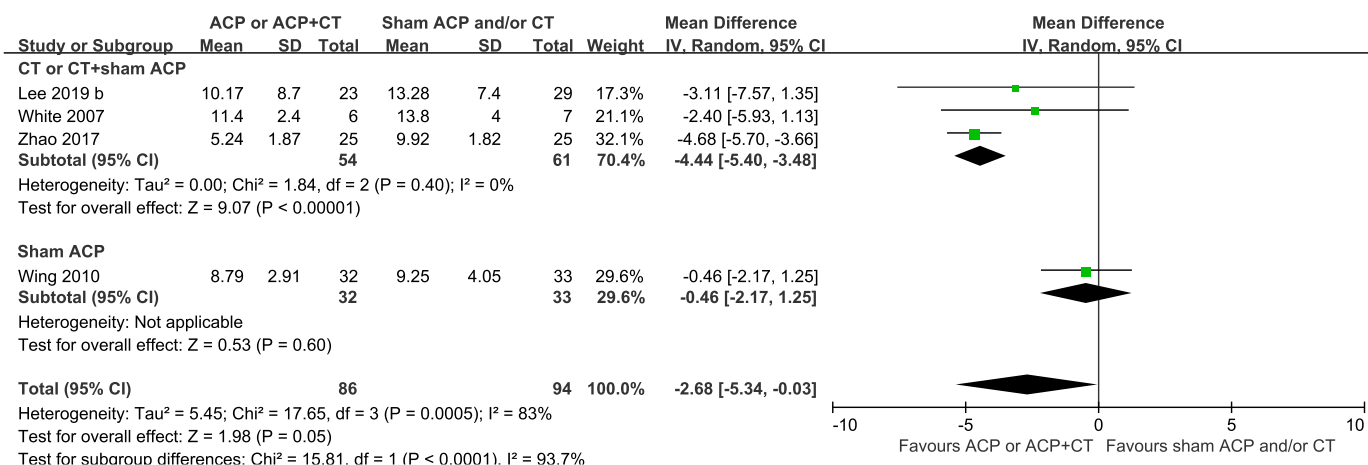


Fig. 4. Acupressure for short-term withdrawal symptoms.

Notes: ACP: acupressure; CT: conventional therapy; CT or CT +sham ACP was active comparison; sham ACP was inactive comparison.

4. Discussion

4.1. Main findings

Twenty-five RCTs involving 2600 smokers were identified. In terms of the risk of bias assessment, the majority of trials were assessed as unclear risk of bias in reporting bias and other bias domain due to lack of registered protocols and funding information. Additionally, we downgraded the certainty of evidence to moderate or low due to imprecision or absence of blinding method. Therefore, the results should be interpreted with caution and our confidence in the effect estimates was limited. However, low to moderate evidence suggested that NTA therapies had different effects on smoking cessation at different time periods. Compared with sham acupressure or conventional therapy, acupressure improved the short-term and mid-term abstinence rate by 11.9% and 11.0% respectively. Additionally, acupressure was also favorable in decreasing the short-term withdrawal symptom score (-2.68) and reducing the level of exhaled CO (-3.84 ppm). Intradermal needles failed to demonstrate a better effect than sham control or counseling in achieving both short-term and mid-term smoking cessation. TEAS was found superior to sham TEAS or counseling in improving mid-term abstinence rate by 11.2%. However, TEAS failed to show a better effect in reducing daily cigarettes consumption, the level of exhaled CO, FTND, and relapse rate. Two double blinded trials suggested that compared with sham laser acupuncture, laser acupuncture successfully improved abstinence rate by 20.6% at long-term follow-up. Two trials involving 177 smokers compared the effect of ACE with Bupropion or Varenicline, with 41.6% and 42.0% smokers achieving smoking cessation in the ACE group and control group respectively at 8-12 weeks follow-up suggesting that ACE maybe comparable with Bupropion or Varenicline in assisting smoking cessation. We have not found evidence of serious adverse events associated with the use of NTA therapies.

4.2. Relation to previous research

A systematic review [49] published in 2019 evaluated the effect of traditional filiform needle acupuncture on smoking cessation. The eligible intervention was traditional acupuncture with filiform needles penetrating into acupoints, and any interventions without using traditional filiform acupuncture were excluded. However, in our systematic review, we identified NTA therapies using modified needles or non-needles to stimulate certain part of body. Such as acupressure, TEAS, intradermal needles, laser acupuncture or ACE, and any interventions with traditional filiform needles were ineligible. Another Cochrane systematic review published in 2014 [18] evaluated some NTA therapies (e.g. acupressure, TEAS, laser acupuncture) and consistently found that acupressure was superior to sham acupressure in achieving short-term smoking cessation. In addition, we also found that acupressure was beneficial for mid-term smoking cessation, relieving withdrawal symptoms, and decreasing the level of exhaled CO. TEAS, laser acupuncture, and ACE were also potentially effective for mid-term or long-term smoking cessation. The eligible ear acupuncture reported in this systematic review was a kind of intradermal needle imbedded in auricular acupoints for continuous stimulation, and therefore ear acupuncture was also classified as NTA therapies.

4.3. Strengths and limitations

Several systematic reviews have been conducted to evaluate the effect of traditional acupuncture on smoking cessation [16-18, 49-50]. However, very few systematic reviews have focused on the potential benefits of NTA therapies on smoking cessation. NTA therapies are widely used for smoking cessation due to convenience and good compliance [51]. Therefore, this systematic review was a comprehensive and individual evaluation of NTA therapies for smoking cessation.

Withdrawal symptoms, nicotine dependence, and other outcomes were also assessed. The protocol of this systematic review was registered on INPLASY. Predefined subgroup analysis via controls (active control and inactive control) was conducted. GRADE approaches were employed to assess the certainty of evidence. There were several limitations for this systematic review. Although, blinding of the participants was applied in more than 50% identified trials, it was difficult to confirm whether the participants were unaware of the interventions they received, since "sham acupuncture" can be easily identified. Additionally, the certainty of the evidence was downgraded to moderate or low certainty due to imprecision or high risk of bias in blinding domain.

4.4. Implications for practice

Although insufficient evidence suggested that traditional acupuncture was effective in smoking cessation, yet one study [15] indicated that patient's fear of pain from traditional acupuncture, and the frequent visit to hospitals may reduce treatment compliance. NTA therapies were characterized by less pain and convenience, since patients can visit hospital every 2 days or once a week. Therefore, NTA therapies may be more appropriate in clinical practice than traditional filiform needle acupuncture for smoking cessation since quitting smoking is a process that requires long-term adherence to treatment. Moreover, relapse usually occurs after quitting for about one month due to withdrawal symptoms [52], and we found that acupressure was effective in relieving withdrawal symptoms in short-term follow up. Hence, NTA therapies play an important role in enhancing smoking cessation at different stage and relieving withdrawal symptoms.

4.5. Implications for research

The smoking cessation was measured by biochemically verification of abstinence rates in 6 trials [24-25, 27, 29, 44, 47] the remaining trials were self-reports. Self-reported data of smoking behavior was found less accurate than objectively tested [53], which may influence the results. Therefore, cotinine or exhaled CO verifications of smoking cessation are warranted. Non-specific acupoints stimulation was used as sham or placebo acupuncture in many trials. However, it was uncertain whether this kind of sham control was really inactive for cessation, and participants may identify sham acupuncture easily. Hence, programmatic RCT may be more appropriate to evaluate the effect of NTA therapies for smoking cessation. Programmatic RCT differs from explanatory RCT and aims to evaluate the effect of complex interventions in real-world clinical practice [54]. Additionally, long-term follow up data was rarely reported in the included trials, and needs to be improved in future studies.

5. Conclusion

Low to moderate certainty evidence suggests that acupressure, TEAS, laser acupuncture and ACE maybe effective in achieving short-term, middle-term or long-term smoking cessation. Acupressure also appears to be beneficial to relieve withdrawal symptoms and decrease the level of exhaled CO. However, the use of an intradermal needle was found to be ineffective in aiding cessation at any time point. No serious adverse events were reported in the included trials. However, large sample size, fully reported and long-term follow up RCTs are warranted to confirm these effects.

Author contributions

YYZ and JPL were responsible for the conception and design of this study. YYZ contributed to analysis of data and drafted the manuscript. ZYY and HDL contributed to acquisition of data and quality assessment. SBL, MF, NR and JPL revised and commented on the manuscript. All authors approved the final manuscript.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest to declare. Prof Nicola Robinson is editor in chief and Prof Jianping Liu is an editorial board member of this journal.

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Data availability

All data generated or analyzed during this study are included in this manuscript and its supplementary material.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eujim.2021.101390.

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