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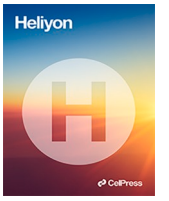

Research article

Efficacy and safety of warm needle acupuncture for allergic rhinitis: A systematic review and meta-analysis with trial sequential analysis

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A R T I C L E I N F O

Keywords:
Acupuncture
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Systematic review
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Evidence Gaps

A B S T R A C T

Backgrounds: Warm needle acupuncture is a distinct form of acupuncture therapy in which, after the needle is inserted into the acupoint, a lit moxa stick is placed on the needle's handle.
Objective: This research aims to provide evidence for efficacy and safety of warm needle acupuncture for allergic rhinitis.
Search strategies: Seven online databases were searched for study collection, which were published up to March 15th, 2022. Keywords of searching included "AR", "allergic rhinitis", "anaphylactic rhinitis", "warming needle", "warming needle acupuncture", "needle warming moxibustion", "warm needle", "warm needling method" and "warmed needle". The quality of the included trials was assessed using the Cochrane risk of bias tool.
Interventions: Among the included trials, warm needle acupuncture—either alone or in combination with Western medicine or other acupoint-based therapies—served as the primary intervention for the experimental groups. In contrast, the control groups received treatments such as Western medicine alone, manual acupuncture alone, or a combination of electro and manual acupuncture. Systematic reviews and meta-analyses were conducted using RevMan 5.3, following the Cochrane systematic review methodology, while trial sequential analysis was performed with TSA 0.9. The quality of the findings was assessed using GRADEpro.
Results: Finally, 23 studies involving 2230 participants were covered. Results of this study revealed that warm needle acupuncture only, or with western medicine, or with other acupoint-based interventions were significantly superior to western medicine alone, manual acupuncture alone, or electro plus manual acupuncture for allergic rhinitis. Adverse events associated with warm needle acupuncture included sensations of chest tightness, throat itching, and allergic reactions to moxa smoke; however, these occurrences were not more frequent than those observed

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with Western medicine. There is need for RCTs of high quality with placebo or waitlist controls of the intervention for allergic rhinitis.
Conclusion: Warm needle acupuncture is with potential efficacy and is safe for patients with allergic rhinitis, but more trials are need for further confirmation of the evidence.

Abbreviations:

AR	Allergic rhinitis
WNA	Warm needle acupuncture
MA	Manual acupuncture
EA	Electro-acupuncture
GM	Ginger moxibustion
WM	Western medicine (Oral administration of antihistamines and/or nasal hormone spray)
TCM	Traditional Chinese medicine
RR	Risk ratio
MD	Mean difference
CI	Confidence interval

1. Introduction

Allergic rhinitis (AR), an inflammatory disorder of the nasal mucosa, is triggered by IgE-mediated inflammatory mediators, along with various immune-active cells and cytokines, following exposure to allergens in susceptible individuals [1]. AR is characterized by key symptoms such as nasal discharge, congestion, itching, and sneezing. Patients with AR may experience reduced sleep quality, impaired work productivity, and diminished overall functioning, often leading to feelings of anxiety and depression [2].

It was estimated that approximate 10 %–41 % of the adults in the Europe, varying from different countries, and about 11 % (physician diagnosed) to 33 % (self-reported) individuals in the US were suffering from AR, with about 30 % of the patients were complicated by asthma [2,3]. Conventional interventions for AR include allergy preventions, allergen exposure restriction, pharmacologic treatment, including oral or intranasal administration of H1-antihistamines, leukotriene receptor antagonists and glucocorticosteroids mainly [4]. In addition, some complementary and alternative methods, with definite curative effect and fewer adverse events induced, are gradually favored by the patients with AR [5–7].

Warm needle acupuncture (WNA) is a distinct form of acupuncture therapy in which, after inserting the needle into an acupoint, an ignited moxa stick is placed on the needle's handle. It is now widely used in China, particularly for conditions like primary osteoporosis and functional dyspepsia, supported by substantial evidence [8,9]. As for AR, some researches favored WNA with higher efficacy, lower recurrence rate and fewer medication intake compared with acupuncture or moxibustion alone [10,11].

However, the clinical efficacy and safety of WNA for treating AR remain uncertain. This systematic review aims to determine the clinical efficacy and safety of WNA in managing AR, compare its efficacy and adverse effects against control groups through various comparisons, and further validate the findings using trial sequential analysis (TSA) and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) evidence profiles.

2. Material and methods

2.1. Registration

This study was registered in PROSPERO under the registration number CRD42018109362 (accessible at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=109362).

2.2. Search strategy

A comprehensive search was conducted across seven online databases—Cochrane Library, PubMed, Embase, Technology Periodical Database (VIP), China National Knowledge Infrastructure (CNKI), SinoMed (CBM), and Wanfang Data Information Site—from their inception until March 15th, 2023. The PRISMA guidelines were adhered to in formulating the search strategy and inclusion criteria. The search employed two sets of English terms: (1) "AR", "allergic rhinitis", and "anaphylactic rhinitis", connected with "OR"; and (2) "warming needle", "warming needle acupuncture", "needle warming moxibustion", "warm needle", "warm needling method", and "warmed needle", also connected with "OR". These two groups were then combined using "AND" (File S1). The searches were independently conducted by two authors, with corresponding search terms also used in Chinese.

2.3. Inclusion criteria

We searched for and included studies based on the following criteria.

(1) Trials in which patients were clinically diagnosed with AR according to specific published guidelines.
(2) Prospective randomized controlled trials (RCTs).
(3) Trials in which WNA, either alone or in combination with other interventions, was administered to experimental groups. Participants in control groups received placebo regimens, conventional treatments, or other traditional Chinese medicine (TCM) interventions. Studies were excluded if they involved conditions other than AR, such as cough, conjunctivitis, or asthma.
(4) Primary outcomes included clinical effective rate, reduction of RQLQ scores, and improvement of main nasal symptom (nasal congestion, itching, runny nose and sneezing).
(5) Trials in English or Chinese.

2.4. Study selection and data extraction

Two authors conducted database searches and documented the titles and abstracts of the identified trials. Eligibility assessment was independently performed by two authors, who made inclusion or exclusion decisions on a trial-by-trial basis. In cases of disagreement, the articles in question were reviewed and discussed with a third reviewer. Data extraction from each study was carried out independently by two reviewers, and any discrepancies were resolved through discussion with a third reviewer.

2.5. Quality assessment

The quality assessment of all trials included in this review was independently conducted by three reviewers using the Cochrane Collaboration risk of bias tool through RevMan 5.3 software. Any disagreements were resolved through discussions with a fourth reviewer.

2.6. Statistical analysis

Statistical analyses were performed using RevMan V.5.3 and TSA 0.9 software. Effect sizes were pooled and presented as mean difference (MD) or risk ratio (RR), with 95 % confidence intervals (CI). $P < 0.05$ indicates significant differences for effect sizes. In our meta-analysis, to handle three-arm trials without double-counting patients in the control arm, we split the control group into two equal parts. For example, if the control group had 100 participants, it was divided into two groups of 50. The sample sizes and variances were adjusted accordingly. For binary categorical outcomes, we just spited the number of events and non-events in the control group proportionally. For continuous outcomes with standard deviation (SD), we used the formula with standard error (SE) calculated without the *Mean* values adjusted: $SE_{original} = SD_{original}/\sqrt{n}_{original}$, and $SE_{new} = SE_{original} \times \sqrt{2}$. The adjusted was calculated as $SD_{new} = SE_{new} \times \sqrt{n}_{new}$. Sensitivity analyses were conducted to ensure the robustness of our results by comparing analyses with and without the split trials. This approach follows the Cochrane Handbook guidelines and maintains the accuracy of our meta-analytic effects [12].

The Q and I^2 tests were employed to assess the heterogeneity of results, with an I^2 value greater than 50 % indicating significant heterogeneity. Statistical analyses were conducted using either a fixed or random-effects model, depending on the variability in the inclusion/exclusion criteria of the included trials [12]. If at least ten trials were included, publication bias was explored using Egger's tests, accompanied by a trim-and-fill test to further verify the stability of results [12].

Trial sequential analysis (TSA) was performed using TSA 0.9 software, with a type I error (α) set at 0.05 and type II error (β) at 0.1, to minimize the risk of type I errors caused by sparse data and repeated significance testing with the addition of new trials [13]. Additionally, a penalized test was conducted using TSA 0.9 for further validation of our findings. A two-sided P value of less than 0.05 was considered statistically significant [13].

2.7. Evidence certainty assessment

The certainty of the evidence for each comparison was assessed using the GRADE methodology as detailed in the GRADE Handbook, utilizing the GRADEpro GDT online tool [14,15]. The evaluation process comprised five distinct steps: Risk of bias was categorized as "not serious", "serious", or "very serious", based on the outcomes of the quality assessment. Inconsistency was deemed "not serious" if the I^2 value was below 50 %, "serious" if the I^2 value ranged from 50 % to 75 %, and "very serious" if the I^2 value exceeded 75 %. Indirectness was classified as "not serious", "serious", or "very serious", contingent upon the degree of indirectness present in the available evidence and its impact on the overall quality. Imprecision was labeled as "serious" if the number of included studies or participants was insufficient (i.e., only one study or fewer than 200 participants), otherwise, it was considered "not serious". Publication bias was evaluated based on the results of Egger's test and was also suspected in cases where only one study was included.

2.8. Patient and public involvement

This study is a systematic review and meta-analysis, so patient and public involvement is not applicable.

3. Results

3.1. Study inclusion

Initially, 304 studies were identified through online searches, with no references to grey literature found. After removing duplicates, the number of studies was reduced to 79. Based on the titles and abstracts, 21 studies were excluded for reasons such as being case reports, animal experiments, non-randomized controlled designs, observational studies, reviews, studies unrelated to WNA for AR, and uncontrolled studies. The remaining 58 studies underwent further assessment, leading to the exclusion of 37 articles. Ultimately, 23 trials from 21 studies (with two three-arm studies recombined into four trials for comparison) were included, with 15 trials contributing to the qualitative synthesis and 18 to the quantitative synthesis (Fig. 1) [16–44].

3.2. Study characteristics

Among the 21 included studies, one was conducted in Switzerland and published in English, while the remaining studies were conducted in China and published in Chinese [35]. The trials were published between 2007 and 2020, involving a total of 2230 participants, aged 4 to 73, who had been diagnosed with AR for durations ranging from 0.5 to 14 years. Although some baseline characteristics were not reported in several studies, no significant differences between groups ($p < 0.05$) were noted. Regarding the interventions in the experimental groups, WNA was applied either alone or in combination with manual acupuncture (MA), electroacupuncture (EA), grain moxibustion (GM), or Western medicine (WM) (oral administration of H1-antihistamines and/or intranasal administration of glucocorticosteroids). Additionally, one trial utilized WNA combined with oral TCM [26]. Despite some variations in specific acupoint prescriptions among the studies, they followed similar principles and theories of TCM, focusing on relieving nasal congestion with local acupoints and regulating lung qi, as well as warming and tonifying healthy qi with remote acupoints. In the control groups, 14 trials employed WM (oral and/or intranasal) alone [21–33], five trials used a combination of EA and MA [16–20], and four trials used MA alone [23,34–36] (Table S1).

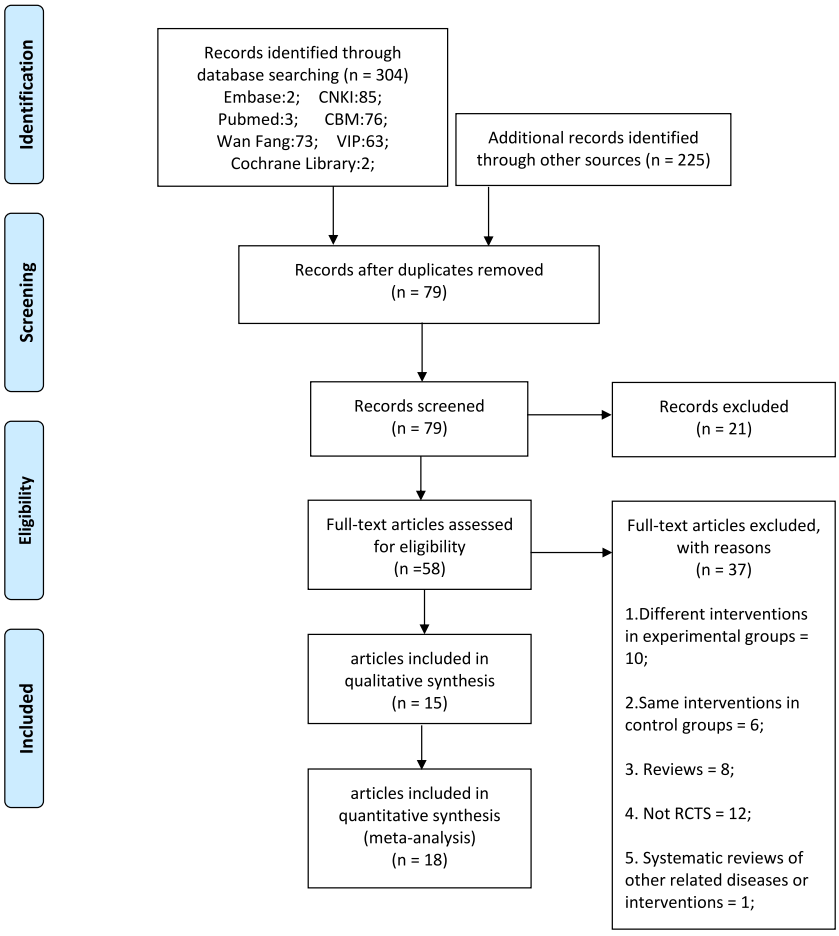

Fig. 1. The PRISMA flow diagram of the study selection process.

3.3. Assessment of quality and bias

According to the Cochrane Collaboration risk of bias tool [12], 15 trials clearly and appropriately described their method of randomization, with no trial classified as having a high risk of bias [17,21–25,27,28,30,32–34,36]. Allocation concealment was clearly described in nine trials [17,21–23,28,30,34], while the remaining trials were at high risk of bias for this aspect. None of the trials implemented blinding methods for participants and personnel; however, blinding specifically assigned for outcome assessment was conducted in four trials [23,28,34]. Dropouts were mentioned in five trials [21,28,32,33], and only one trial reported its protocol prior to the experiment [25] (Figs. S1 and S2).

3.4. Pooled results of WNA in AR patients

In our meta-analysis, we pre-specified the use of a random effects model due to the variability in the inclusion/exclusion criteria of the included trials. This approach accounts for both within-study and between-study variability, addressing the inherent heterogeneity. The choice of the random effects model aligns with the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions, given the clinical and methodological diversity among the included studies.

3.4.1. WNA versus WM alone

In this section, a total of 14 trials were included.

Compared with WM alone groups, results of WNA alone (RR = 1.25; P for RR = 0.001; 95%CI:1.09–1.43; $I^2 = 0$ %) or plus MA (RR = 1.08; P for RR = 0.12; 95%CI:0.98–1.18; $I^2 = 0$ %), oral TCM (RR = 1.38; P for RR = 0.007; 95%CI:1.09–1.73; $I^2 = 0$ %), WM (RR = 1.14; P for RR = 0.003; 95%CI:1.04–1.24; $I^2 = 0$ %) or GM groups (RR = 1.29; P for RR = 0.02; 95%CI:1.05–1.59; $I^2 = 0$ %) favored higher clinical effective rate [21,24–26,30–33]. However, higher rate was reported in WM alone group compared with WNA plus EA group [22] (Table 1; Fig. S3).

As for WNA alone groups versus WM alone groups, more reduction on RQLQ scores (the overall score and 7-items score in detail, including activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function) and serum IgE were reported [21,30]. In addition, evidence favored WNA plus oral TCM, compared with WM alone group, with better improvement on nasal congestion, itching, runny nose, sneezing, and higher reduction on serum IgE [21,28,29] (Table 1; Figs. S4–12).

Compared with WM alone groups, studies included favored WNA plus MA for AR on higher reduction on overall RQLQ score (and follow-up for 3/6 months of it), and better improvement on nasal congestion, itching, runny nose and sneezing (and follow-up for 3/6 months of them) [27–29]. As for signs of the AR patients, significantly higher reduction on overall score of signs in nasal cavity (MD = 0.48; P for MD < 0.001; 95%CI:0.33–0.63; $I^2 = 0$ %), and with 1 month follow-up, were reported [32,33]. Some laboratory findings also favored the experimental group with significantly higher reduction on serum IgE and serum IL-4, and significantly better improvement on serum IFN-γ (and with 1 month follow-up) (Table 1; Figs. S5–13).

In addition, evidence shows that WNA plus GM could reduce overall RQLQ score (and with 6 months follow-up), and improve nasal congestion, itching, runny nose and sneezing better [23,24] (Table 1; Figs. S5–9).

3.4.2. WNA versus MA alone

In this section, a total of four trials were included.

As for WNA alone groups versus MA alone groups, significantly higher clinical effective rate was reported in the experimental group [35]. In addition, evidence favored WNA alone for AR on higher reduction on overall RQLQ score (and follow-up for 1/3/6 months of it), and better improvement on nasal congestion, itching, runny nose and sneezing (and follow-up for 1/2 months of them) [34]. Laboratory findings also favored the experimental group with higher reduction on serum IgE and serum IL-10 (Table 2; Figs. S14–20).

In addition, evidence favored WNA plus GM, compared with MA alone group, with higher reduction on overall RQLQ score, and better improvement on nasal congestion, itching, runny nose and sneezing [23] (Table 2; Figs. S15–19).

3.4.3. WNA + MA versus EA + MA

In this section, a total of five trials were included.

Other evidence also evaluated efficacy of WNA indirectly [16–20]. Trials included favored WNA + MA for AR on higher clinical effective rate (RR = 1.16; P for RR < 0.001; 95%CI:1.07–1.26; $I^2 = 24$ %), and follow-up for 1/3/6 months of it. Evidence shows that WNA + MA could significantly better reduce overall score of signs and main symptoms, and overall score of main symptoms after one and three months of the treatment (Table 3; Figs. S21 and S22).

Compared with EA + MA groups, laboratory findings of WNA + MA groups favored more reduction on serum IL-4, serum IL-5, nasal eosinophil count, and better improvement on nasal mucociliary transport (MD = 1.48; P for MD < 0.001; 95%CI:0.90–2.05; $I^2 = 43$ %). However, higher reductions on IgE and nasal eosinophil percentage were reported in the control group (Table 3; Fig. S23).

3.5. Sensitive analyses based on the influence analyses

Meta-influence analyses were conducted on the comparisons with high heterogeneity ($I^2 > 50$ %) to scan, analyze, and potentially exclude outlier trials. Several outlier trials were identified, revealing differences among various variables related to the design, participants, and interventions of the trials. However, none of these differences exceeded the inclusion or exclusion criteria, nor could they

Table 1
Summary of Findings for WNA vs. WM

Outcome	Sub-group consideration	No. of trials	Partici-pants	Effect size (RR/MD)	95 % CI	P value of effect size	I^2 value
Clinical effective rate	WNA vs. WM	3	290	RR = 1.25	1.09 to 1.43	0.001	0 %
	WNA + EA vs. WM	1	147	RR = 0.94	0.70 to 1.26	0.94	NA
	WNA + WM vs. WM	2	284	RR = 1.14	1.04 to 1.24	0.003	0 %
	WNA + GM vs. WM	1	63	RR = 1.29	1.05 to 1.59	0.02	NA
	WNA + OTCM vs. WM	1	100	RR = 1.38	1.09 to 1.73	0.007	NA
	WNA + MA vs. WM	2	300	RR = 1.08	0.98 to 1.18	0.12	0 %
RQLQ scores reduction (WNA vs. WM)	Activity limitation	3	290	MD = 0.56	0.34 to 0.79	<0.001	0 %
	Sleep problems	3	290	MD = 0.48	−0.07 to 1.03	0.09	87 %
	Nose symptoms	3	290	MD = 0.60	0.17 to 1.03	0.007	76 %
	Eye symptoms	3	290	MD = 0.52	0.06 to 0.98	0.03	80 %
	Non-nose/eye symptoms	3	290	MD = 0.39	−0.20 to 0.99	0.20	88 %
	Practical problems	3	290	MD = 0.66	0.40 to 0.92	<0.001	32 %
	Emotional function	3	290	MD = 0.57	0.22 to 0.92	0.001	64 %
Overall RQLQ score reduction	WNA vs. WM	3	290	MD = 4.04	1.50 to 6.57	0.002	92 %
	WNA + MA vs. WM	2	168	MD = 16.84	16.08 to 17.60	<0.001	0 %
	WNA + MA vs. WM (3 months follow-up)	1	64	MD = 26.85	25.92 to 27.78	<0.001	NA
	WNA + MA vs. WM (6 months follow-up)	1	64	MD = 16.84	15.97 to 17.71	<0.001	NA
	WNA + GM vs. WM	1	39	MD = 3.17	0.93 to 5.41	0.006	NA
	WNA + GM vs. WM (6 months follow-up)	1	39	MD = 23.15	2.11 to 44.19	0.03	NA
Nasal congestion improvement	WNA + MA vs. WM	2	154	MD = 0.15	−0.10 to 0.41	0.24	0 %
	WNA + GM vs. WM	1	29	MD = 0.30	−0.36 to 0.96	0.37	NA
	WNA + OTCM vs. WM	1	100	MD = 0.54	0.47 to 0.61	<0.001	NA
Itching improvement	WNA + MA vs. WM	2	154	MD = 0.25	−0.03 to 0.54	0.08	0 %
	WNA + GM vs. WM	1	29	MD = 0.50	−0.01 to 1.01	0.05	NA
	WNA + OTCM vs. WM	1	100	MD = 0.17	0.03, 0.31	0.02	NA
Runny nose improvement	WNA + MA vs. WM	2	154	MD = 0.05	−0.78 to 0.88	0.90	89 %
	WNA + GM vs. WM	1	29	MD = 0.18	−0.55 to 0.91	0.63	NA
	WNA + OTCM vs. WM	1	100	MD = 0.72	0.60 to 0.84	<0.001	NA
Sneezing improvement	WNA + MA vs. WM	2	154	MD = −0.05	−0.33 to 0.22	0.71	9 %
	WNA + GM vs. WM	1	29	MD = 0.54	−0.03 to 1.11	0.07	NA
	WNA + OTCM vs. WM	1	100	MD = 0.83	0.73 to 0.93	<0.001	NA
Nasal congestion improvement (follow-up)	WNA + MA vs. WM (for 3 months)	1	85	MD = 0.63	0.19 to 1.07	0.005	NA
	WNA + MA vs. WM (for 6 months)	1	66	MD = 0.38	−0.11 to 0.87	0.13	NA
Itching improvement (follow-up)	WNA + MA vs. WM (for 3 months)	1	85	MD = 0.53	0.06 to 1.00	0.03	NA
	WNA + MA vs. WM (for 6 months)	1	66	MD = 0.59	0.08 to 1.10	0.02	NA
Runny nose improvement (follow-up)	WNA + MA vs. WM (for 3 months)	1	85	MD = 0.57	0.11 to 1.03	0.01	NA
	WNA + MA vs. WM (for 6 months)	1	66	MD = 0.37	−0.16 to 0.90	0.17	NA
Sneezing improvement (follow-up)	WNA + MA vs. WM (for 3 months)	1	85	MD = 0.55	0.06 to 1.04	0.03	NA
	WNA + MA vs. WM (for 6 months)	1	66	MD = 0.44	−0.10 to 0.98	0.11	NA
Reduction on overall score of signs in nasal cavity	WNA + MA vs. WM	2	300	MD = 0.48	0.33 to 0.63	<0.001	0 %
	WNA + MA vs. WM (1 month follow-up)	2	300	MD = 0.51	0.26 to 0.77	<0.001	59 %
Serum IgE reduction	WNA vs. WM	3	290	MD = 51.66	11.83 to 91.49	0.01	86 %

(*continued on next page*)

Table 1 (*continued*)

Outcome	Sub-group consideration	No. of trials	Partici-pants	Effect size (RR/MD)	95 % CI	P value of effect size	I^2 value
	WNA + WM vs. WM	1	200	MD = 34.53	12.93 to 56.13	0.002	NA
	WNA + MA vs. WM	1	200	MD = 86.14	65.54 to 106.74	<0.001	NA
	WNA + MA vs. WM (1 month follow-up)	1	200	MD = 112.75	91.53 to 133.97	<0.001	NA
Other laboratory findings (WNA + MA vs. WM)	Serum IL-4 reduction	1	200	MD = 4.76	3.31 to 6.21	<0.001	NA
	Serum IL-4 reduction (1 month follow-up)	1	200	MD = 5.21	3.76 to 6.66	<0.001	NA
	Serum IFN-γimprovement	1	200	MD = 6.07	4.31 to 7.83	<0.001	NA
	Serum IFN-γimprovement (1 month follow-up)	1	200	MD = 9.44	7.68 to 11.20	<0.001	NA

WNA: Warm needle acupuncture; MA: Manual acupuncture; EA: Electro-acupuncture; GM: Ginger moxibustion; WM: Western medicine (Oral administration of antihistamines and/or nasal hormone spray); TCM: Traditional Chinese medicine; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; RR: Risk ratio; MD: Mean difference; CI: Confidence interval; NA: Not applicable.

Table 2
Summary of Findings for WNA vs. MA

Outcome	Sub-group consideration	No. of trials	Participants	Effect size (RR/MD)	95 % CI	P value of effect size	I^2 value
Clinical effective rate	WNA vs. MA	1	180	1.12	1.01 to 1.23	0.02	NA
	WNA + MA vs. MA	1	48	1.14	0.88 to 1.49	0.32	NA
Overall RQLQ score reduction	WNA vs. MA	1	30	10.10	−4.85 to 25.05	0.19	NA
	WNA vs. MA (1 month follow-up)	1	30	13.95	−0.51 to 28.41	0.06	NA
	WNA vs. MA (2 months follow-up)	1	30	14.65	0.91 to 28.39	0.04	NA
	WNA vs. MA (6 months follow-up)	1	30	18.95	−3.85 to 41.75	0.10	NA
	WNA + GM vs. MA	1	30	8.73	−14.13 to 31.59	0.45	NA
Nasal congestion improvement	WNA vs. MA	1	30	1.50	0.05 to 2.95	0.04	NA
	WNA vs. MA (1 month follow-up)	1	30	1.59	0.23 to 2.95	0.02	NA
	WNA vs. MA (2 months follow-up)	1	30	1.92	0.57 to 3.27	0.005	NA
	WNA + GM vs. MA	1	30	−0.06	−0.66 to 0.54	0.85	NA
Itching improvement	WNA vs. MA	1	30	1.52	−0.39 to 3.43	0.12	NA
	WNA vs. MA (1 month follow-up)	1	30	2.19	0.39 to 3.99	0.02	NA
	WNA vs. MA (2 months follow-up)	1	30	2.52	0.73 to 4.31	0.006	NA
	WNA + GM vs. MA	1	30	0.50	−0.17 to 1.17	0.14	NA
Runny nose improvement	WNA vs. MA	1	30	1.50	0.05 to 2.95	0.04	NA
	WNA vs. MA (1 month follow-up)	1	30	1.59	0.23 to 2.95	0.02	NA
	WNA vs. MA (2 months follow-up)	1	30	1.92	0.57 to 3.27	0.005	NA
	WNA + GM vs. MA	1	30	0.24	−0.44 to 0.92	0.49	NA
Sneezing improvement	WNA vs. MA	1	30	1.50	0.05 to 2.95	0.04	NA
	WNA vs. MA (1 month follow-up)	1	30	1.59	0.23 to 2.95	0.02	NA
	WNA vs. MA (2 months follow-up)	1	30	1.92	0.57 to 3.27	0.005	NA
	WNA + GM vs. MA	1	30	0.36	−0.20 to 0.92	0.21	NA
Laboratory findings (WNA vs. MA)	Serum IgE reduction	1	9	55.03	−37.23 to 147.29	0.24	NA
	Serum IL-10 reduction	1	9	53.25	−332.80 to 439.30	0.79	NA

WNA: Warm needle acupuncture; MA: Manual acupuncture; EA: Electro-acupuncture; GM: Ginger moxibustion; WM: Western medicine (Oral administration of antihistamines and/or nasal hormone spray); TCM: Traditional Chinese medicine; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; RR: Risk ratio; MD: Mean difference; CI: Confidence interval; NA: Not applicable.

Table 3
Summary of Findings for WNA + MA vs. EA + MA.

Outcome	Sub-group consideration	No. of trials	Participants	Effect size (RR/MD)	95 % CI	P value of effect size	I^2 value
Clinical effective rate	After treatment	5	398	1.16	1.07 to 1.26	<0.001	24 %
	1 month follow-up	1	60	1.00	0.84 to 1.18	1.00	NA
	3 month follow-up	1	36	1.02	0.76 to 1.37	0.88	NA
	6 month follow-up	1	60	1.29	0.99 to 1.67	0.06	NA
Reduction on overall score of signs and main symptoms	After treatment	1	60	1.30	1.07 to 1.53	<0.001	NA
Reduction on overall score of main symptoms	1 month follow-up	1	60	1.06	0.87 to 1.25	<0.001	NA
	3 month follow-up	1	60	0.26	0.03 to 0.49	0.03	NA
Laboratory findings	Serum IgE reduction	1	60	−3.19	−20.77 to 14.39	0.72	NA
	Serum IL-4 reduction	2	186	10.85	6.45 to 15.24	<0.001	89 %
	Serum IL-5 reduction	2	186	8.61	3.21 to 14.02	0.002	92 %
	Nasal mucociliary transport improvement	3	252	1.48	0.90 to 2.05	<0.001	43 %
	Nasal eosinophil count reduction	1	100	4.59	3.64 to 5.54	<0.001	NA
	Nasal eosinophil percentage reduction	1	60	−0.17	−0.42 to 0.08	0.19	NA

WNA: Warm needle acupuncture; MA: Manual acupuncture; EA: Electro-acupuncture; RR: Risk ratio; MD: Mean difference; CI: Confidence interval; NA: Not applicable.

be interpreted rationally. Consequently, no trial was excluded.

3.6. Trial sequential analysis (TAS) and penalized test

TAS and penalized test was conducted for each comparison with no less than three trials included.

As for more reductions on serum IgE, RQLQ nose symptoms, RQLQ emotional function score, and overall RQLQ score in WNA alone groups, compared with WM alone group, though the number of included trials with patients was small and therefore the quality of evidence is not high, TSA led us to upgrade the overall assessment, and the upgrading of the last two outcomes were also supported by penalized test (Fig. 2a and b). However, more inclusion was needed to meet the required information size (RIS) for the first three outcomes.

Results of TAS and penalized test of other comparisons are listed in Figs. S24–43.

3.7. Adverse event reported in trials

Adverse events were reported for the experimental groups of four trials [26,31,33,35], and for the control groups of three trials [26,31,33], with no adverse event reported in four trials (neither in experimental groups nor in control groups) [17,28,30,34]. Among them, WNA related events with tangible evidence included stuffy sensation in the chest (1 case, 1.37 %), itching in the throat (1 case, 1.37 %) and allergic to moxa smoke (1 case, 1 %). WM induced events with tangible evidence included hyperthermia (2 case, 4 %), dizziness (3 case, 6 %), stomach discomfort (4 case, 2.82 %), dry mouth (3 case, 2.11 %) and headache (1 case, 0.7 %). As for the events reported in the experimental groups of other trials, including rash (5 case, 10 %), hyperthermia (4 case, 8 %), dizziness (4 case, 8 %), sore throat (3 case, 6 %), headache (1 case, 2.38 %) and stomach discomfort (1 case, 2.38 %), it's difficult to clarify the reason of specific intervention as more than one therapy (plus WM, oral TCM or MA) was applied [17,28,30].

Adverse events were not reported in the other 14 trials [16,18–25,27,29,32,36].

3.8. Certainties of evidence by the GRADE

Firstly, the levels of evidence for WNA versus WM were determined as moderate (in 3 comparisons, 6.12 %), low (in 5 comparisons, 10.20 %) and very low (in 41 comparisons, 83.68 %) through the GRADE-pro (Table S4). Secondly, as for the WNA versus MA, which were more positive, the levels of evidence were determined as low (in 23 comparisons, 92.00 %) and very low (in two comparisons, 8.00 %) through the GRADE-pro (Table S5). However, in the WNA + MA versus EA + MA comparisons, the levels of evidence were rated as high (in one comparison, 7.69 %) and very low (in 12 comparisons, 92.31 %) (Table S6).

4. Discussion

This is the first systematic review and meta-analysis concerning efficacy and safety WNA for AR. As an allergic disease with increasing incidence rates, AR affects the quality of life of the world population [2]. In theory of TCM, AR falls into four syndromes,

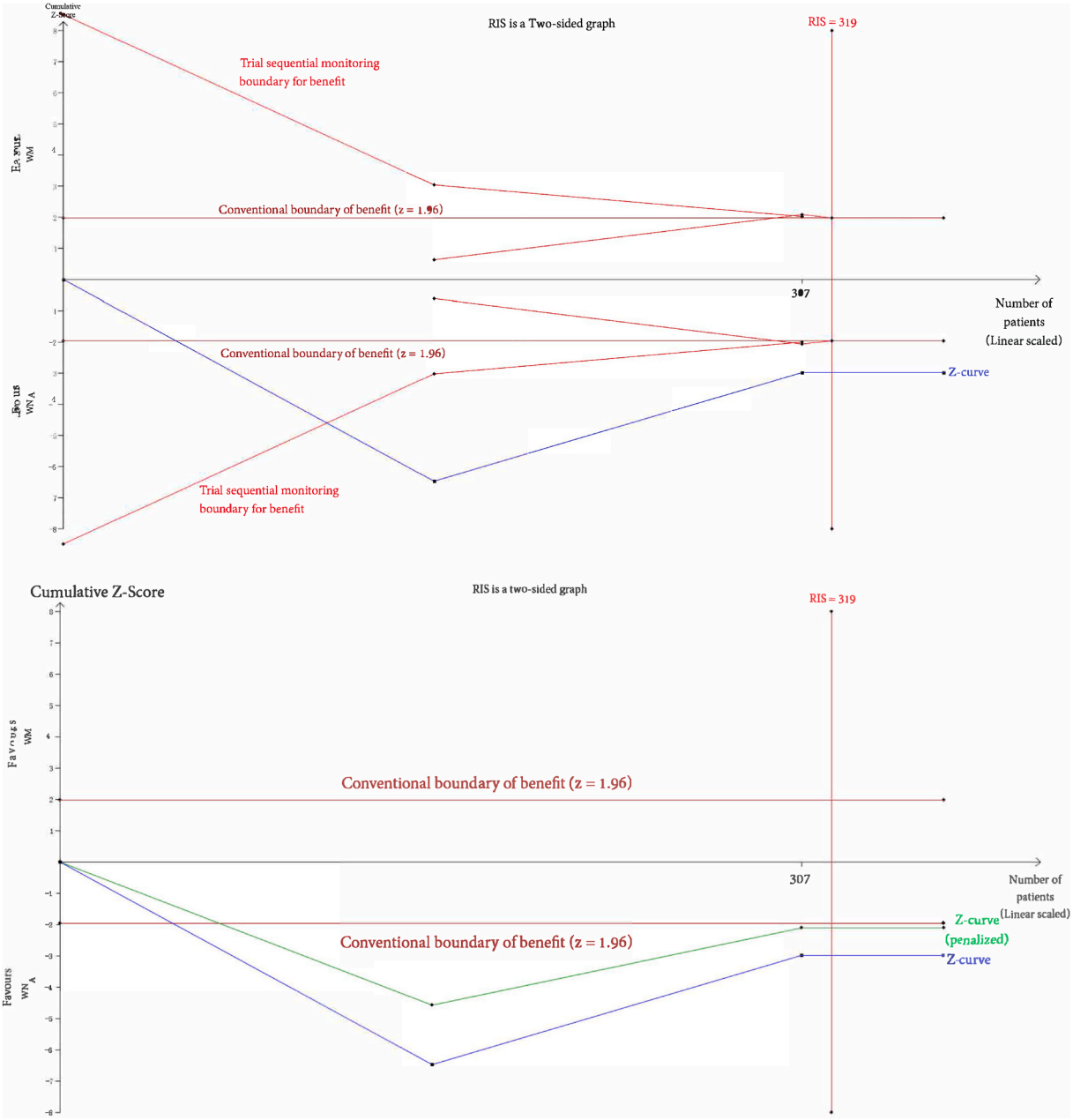

Fig. 2a. Trial sequential analysis of WNA versus WM on RQLQ emotional function reduction

WNA: Warm needle acupuncture; WM: Western medicine (Oral administration of antihistamines and/or nasal hormone spray); RQLQ: Rhino-conjunctivitis Quality of Life Questionnaire; RIS: required information size.

Upper: Trial sequential analysis of WNA versus WM on RQLQ emotional function reduction. 1) Z-cure crossed the RIS between the second and third studies, indicating that the number of included studies has reached the amount required for meta-analysis; 2) Z-cure crossed the conventional boundary of benefit (z = 1.96), indicating that the difference of RQLQ emotional function reduction between WNA group versus WM group was statistically significant, excluding the possibility of false positive; 3) Z-cure crossed trial sequential monitoring boundary for benefit, which indicated that WNA was superior to WM.

Lower: Penalized test of WNA versus WM on RQLQ emotional function reduction. In penalized test of the result above, the z-cure crossed the conventional boundary of benefit (z = 1.96), which further consolidated the reliability of WNA for patients with allergic rhinitis.

lung *yang(Qi)* deficiency, spleen *Qi* deficiency, kidney *yang* deficiency, and stagnant heat of lung meridian, mainly [37]. In China, five researches involving 3137 participants showed that lung *yang(Qi)* deficiency and spleen *Qi* deficiency are the two most common syndromes in AR [38–42]. Additionally, one trial with 1216 minors aged 2–18 years also revealed higher distributions on lung *yang (Qi)* deficiency (536, 44.1 %) and spleen *Qi* deficiency (457, 37.6 %), compared with stagnant heat of lung meridian (188, 15.5 %) and

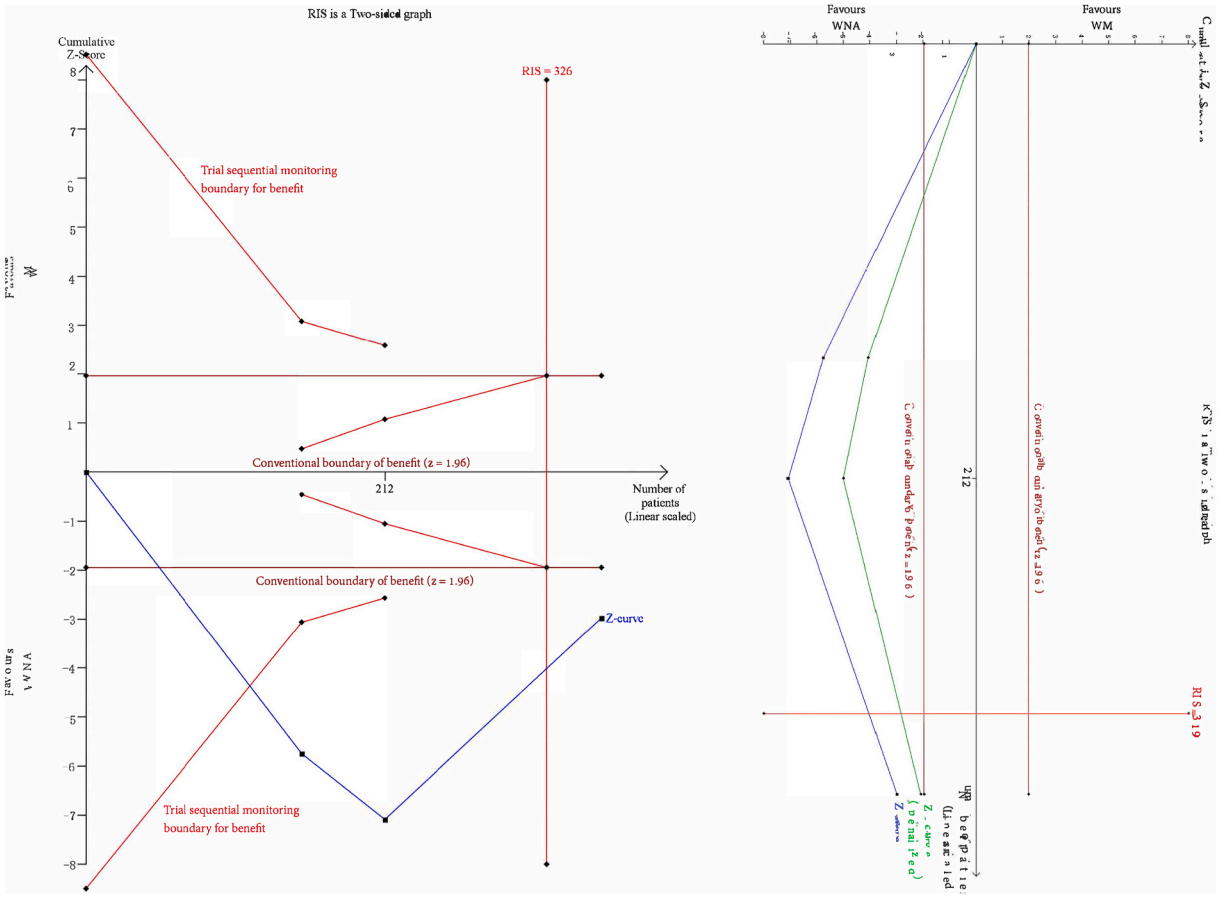

Fig. 2b. Trial sequential analysis of WNA versus WM on overall RQLQ score reduction

WNA: Warm needle acupuncture; WM: Western medicine (Oral administration of antihistamines and/or nasal hormone spray); RQLQ: Rhino-conjunctivitis Quality of Life Questionnaire; RIS: required information size.

Left: Trial sequential analysis of WNA versus WM on overall RQLQ score reduction. 1) Z-cure crossed the RIS between the second and third studies, indicating that the number of included studies has reached the amount required for meta-analysis; 2) Z-cure crossed the conventional boundary of benefit (z = 1.96), indicating that the difference of overall RQLQ score reduction between WNA group versus WM group was statistically significant, excluding the possibility of false positive; 3) Z-cure crossed trial sequential monitoring boundary for benefit, which indicated that WNA was superior to WM.

Right: Penalized test of WNA versus WM on overall RQLQ score reduction. In penalized test of the result above, the z-cure crossed the conventional boundary of benefit (z = 1.96), which further consolidated the reliability of WNA for patients with allergic rhinitis.

kidney *yang* deficiency (35, 2.9 %) [43]. This is also similar as a study covering 192 aged adults from 60 to 80 years, with kidney *yang* deficiency reported as 83 cases (43.23 %), lung *yang(Qi)* deficiency as 56 cases (29.17 %), spleen *Qi* deficiency as 38 cases (19.79 %) and stagnant heat of lung meridian as 15 cases (7.81 %) [44].

WNA is a popular therapy especially in China, as a comprehensive method of acupuncture and moxibustion, it can exert the stimulation of acupuncture and the effect of moxibustion at the same time. Some studies presented that acupuncture and moxibustion could regulate the human immune function and lower the total IgE level [45,46], and reduce the expression of substance P, STAT6, NFκB, and iNOS in rat models [47]. In our study, the top three acupoints mostly applied included Zusanli (ST36, 12 times), Dazhui (GV14, 11 times), Yingxiang (LI20, 10 times) in WNA, Hegu (LI4, 10 times), Shangxing (GV23, 9 times), Yintang (GV29, 8 times) in MA, Zusanli (ST36, 4 times), Dazhui (GV14, 3 times), Lieque (LU7, 2 times) in GM, and Yintang (GV29, 1 time) in EA only. As for the most frequently selected meridians, they were large intestine meridian (LI, 22 times), governor vessel meridian (GV, 21 times), bladder meridian (BL, 17 times) in WNA, governor vessel meridian (GV, 19 times), large intestine meridian (LI, 17 times), gallbladder meridian (GB, 7 times) in MA, governor vessel meridian (GV, 4 times), stomach meridian (ST, 4 times), lung meridian (LU, 3 times) in GM, and governor vessel meridian (GV, 1 time) in EA only. Details of ranking of common acupoints and meridians frequently used are in Tables S5 and S6.

Results of our review show that compared with applying WM alone, MA alone, or plus other acupoint-based TCM therapies, better clinical effective rate, higher reductions on RQLQ scores, IgE, overall score of signs in nasal cavity, and more improvement on nasal congestion, itching, runny nose and sneezing were reported in experimental groups, including applying WNA alone, plus WM or plus

other acupoint-based therapies. Our study also favored the experimental groups with longer-term (1–6 months) effects.

In our study, WNA related adverse events, including stuffy sensation in the chest, itching in the throat and allergic to moxa smoke, were not more than those associated with WM application, such as hyperthermia, dizziness, stomach discomfort, dry mouth and headache. For some other events reported, it was difficult to clarify their reasons because more than one therapies were applied. However, a strict safety norm on moxa for local treatment places of patients and clinics is suggested [48].

Previously, many systematic reviews with meta-analyses have failed to achieve sufficient statistical power to detect or rule out even substantial intervention effects [49,50]. As meta-analyses are continuously updated, they should be considered interim analyses that progress toward achieving the required information size [13,51]. Evaluating meta-analyses should involve comparing the total number of randomized participants to the necessary meta-analytic information size, as well as the corresponding number of required trials, while accounting for statistical diversity [49,52]. If a meta-analysis contains fewer participants than required—based on a realistic and minimally important intervention effect—the constant use of a traditional 95 % confidence interval or a 5 % statistical significance threshold can result in false positive and negative conclusions [13,49]. The Lan-DeMets' sequential monitoring boundaries in trial sequential analysis (TSA) provide adjusted, widened confidence intervals and more restrictive thresholds for statistical significance when the diversity-adjusted required information size and the required number of trials have not yet been met [53–55]. TSA thus offers a more transparent assumption-based analysis compared to traditional meta-analyses that use unadjusted confidence intervals and unadjusted statistical significance thresholds [49,52].

As for risk of bias and study quality, all the 23 studies are RCTs while placebo control was employed in one trial only. 15 studies performed appropriate method for randomization with statement, while method for blinding and allocation concealment were of unclear risk of bias in most trials. 5 studies reported drop-out, but with no clear data processing measure reported. Registration or protocol before trial was only recoeded in one trial, an no trial conducted blinding method for participants or personnel. As a result, more randomized, prospective, blinded, placebo-controlled trials of WNA as a therapy for AR are need.

In terms of practical application and extrapolation in real-world situations, studies in recent years have suggested the use of pragmatic trials to obtain clinically relevant results [56,57]. In addition, there was no missing outcome data in this study, and we suggest to consider the statistical methods in the systematic review by Yagiz G et al. for calculation of missing data, if happened [58]. Given the complexity and flexibility of TCM treatments, this type of trial is particularly suitable for the study of efficacy and safety in TCM.

5. Limitations

This study had several limitations. Firstly, risk of bias among the included trials were between moderate to substantial, such as lack of reporting on the details of random sequence generation, concealment, and blindness to the quality of participants, people, and outcome assessments. Secondly, some of the experimental and control groups had multiple interventions, which made it impossible to identify some adverse reactions without clear evidence. Finally, assessment of publication bias and trial sequential analysis were inapplicable in many comparisons due to the small quantity of included trials. The GRADE evidence profiles (EP) (Tables S2–4) revealed that most of the evidence are in low or even very low quality.

6. Conclusion

This study proved that applying WNA alone, plus WM or plus other acupoint-based TCM interventions may be of higher efficacy for AR than having WM, MA or EA. However, several outcomes suggested that the experimental therapies were not superior to the controls. Adverse events of WNA included stuffy sensation in the chest, itching in the throat and allergic to moxa smoke, but were not more than those associated with the WMs. More RCTs of high quality are needed, e.g., larger sample size, with placebo or waitlist controls of WNA for AR.

CRediT authorship contribution statement

Shasha Yang: Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Qinwei Fu:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Jing Wu:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Qinxiu Zhang:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Hua Deng:** Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Data curation, Conceptualization. **Shucheng Chen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Huihui Yang:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Mingling Yan:** Writing – review & editing, Writing – original draft, Software, Resources, Investigation, Conceptualization. **Linjie Zhang:** Writing – review & editing, Writing – original draft, Validation, Resources, Conceptualization.

Ethical statement

This study is a systematic review and meta-analysis, with no human participant involved.

Data availability statement

This study is a systematic review and meta-analysis, and all the data available are in the manuscript and supplementary materials.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

7. Acknowledgement

No applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39058.

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