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REVIEW

Acupuncture Dosage and Its Correlation with Effectiveness in Patients with Chronic Stable Angina: A Systematic Review and Meta-Analysis of Randomized Controlled Trial

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Objective: This systematic review aimed to compare the efficacy of various acupuncture dosages for Chronic Stable Angina (CSA) using randomized controlled trials (RCTs), addressing the unclear relationship between dosage and effectiveness despite acupuncture's potential.

Methods: We searched eight bibliographic databases from inception to October 31, 2024, evaluating RCTs comparing acupuncture to placebo or standard care for CSA patients, focusing on angina attack frequency as the primary outcome. Studies were categorized into high (HDG), moderate (MDG), and low (LDG) dosage groups based on acupuncture characteristics: the number of acupoints, total sessions, frequency per week, and the need for "Deqi".

Results: Of the 807 citations screened, 16 studies (1240 patients) were included: 3 studies in LDG, 10 in MDG, and 3 in HDG. Acupuncture significantly reduced angina attacks compared to placebo (SMD, −0.51; 95% CI [−0.77, −0.25], $P = 0.0001$, I^2=62%), and standard care (SMD, −1.25, 95% CI [−1.89, −0.61], $P = 0.00001$, I^2=92%) without increasing adverse events. MDG showed a notable difference in reducing angina attacks (SMD, −0.60, 95% CI [−0.91, −0.29], $P = 0.001$, I^2=60%) while LDG and HDG did not. There is no difference in adverse events between groups. The evidence quality ranged from very low to moderate, and the results should be cautiously applied.

Conclusion: Acupuncture therapy effectively and safely alleviates CSA symptoms. Moderate dosage demonstrated the potential for better effects in reducing symptoms, suggesting optimal dosage considerations for future treatments.

Prospero Registration Number: CRD42022321547.

Keywords: acupuncture, chronic stable angina, dose-related, effectiveness, meta-analysis

Introduction

Coronary heart disease represents a chronic, systemic ailment that encompasses a broad spectrum of symptoms, and significant healthcare expenditures.[1] According to the report of the American Association, nearly 5% of the United States population from 25 to 64 years old have been evaluated for suspected angina pectoris.[2,3] Chronic stable angina (CSA) occurs due to an imbalance in myocardial oxygen supply,[4] leading to distress, pain, and even feelings of suffocation in the chest. Notably, roughly 52.3% of CSA outpatient experience varying frequencies of angina attacks, significantly impacting their quality of life.[5] Evidence shows that cardiovascular disease is closely related to the disturbance of

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autonomic consciousness. For CSA, research[6] has found that the lower the parasympathetic activity level of patients with stable angina pectoris by 24 h dynamic electrocardiogram, the more severe their symptoms.

Acupuncture, a nonpharmacological treatment, has been widely practiced for decades to regulate the autonomic nervous system, possess anti-inflammatory properties, enhance endothelial function, alleviate oxidative stress, and adjust neurotransmitter levels to alleviate myocardial ischemia pain.[7,8] Previous systematic research indicates that acupuncture is effective and safe for cardiovascular diseases,[8] particularly stable angina pectoris.[9–11] However, the existence of a possible dose-response of acupuncture has not been investigated.

The significance of acupuncture characteristics on treatment efficacy is paramount, as evidenced by research,[12] with the dosage serving as a pivotal area of investigation.[13] Studies indicate that augmenting the quantity of needles and treatment sessions in acupuncture interventions for chronic pain may correlate with enhanced therapeutic outcomes.[14] Furthermore, a prior study comparing various modulated acupuncture stimulation doses, including needle manipulation, needle size, and needle count, discovered that high-dose acupuncture stimulation (involving bilateral stimulation at Hegu plus four additional needles) elicited a greater increase in sympathetic nerve activity compared to low-dose stimulation (bilateral stimulation at Hegu with a single needle).[13] In current clinical randomized controlled trials (RCTs) evaluating acupuncture's efficacy for CSA, there is significant variability in treatment characteristics. The acupuncture sessions range from 1 to 90,[15–17] the acupuncture frequency varies from daily[18] to twice weekly,[19] and the number of acupoints varies from 4[17] to 23.[19]

Given the disparate outcomes of acupuncture on CSA across studies, this systematic meta-review aims to synthesize eligible trials to determine the optimal acupuncture dosage for reducing angina attack frequency and alleviating other symptoms, thereby informing clinical practice.

Materials and Methods

Database Selection and Search Strategy

The pre-established review protocol has been officially documented and registered within the PROSPERO database (registration number is CRD42022321547), which was by the guidance of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement,[20] as shown in PRISMA checklist (Supplementary Materials, sTable 1). DJH and YWL conducted a comprehensive literature search from inception to October 31, 2024, encompassing databases such as Chinese National Knowledge Infrastructure (CNKI), Embase, China Biomedical Literature Database, Cochrane Library, PubMed, Web of Science, Wanfang Data, China Science Journal Database, and Chinese Clinical Trial Registry (ChiCTR). The search strategies are shown in (sTable 2 Supplementary Materials). In addition, to avoid missing studies, we also searched study registries for ongoing or yet-to-be-published trials that met our inclusion criteria. No limitations were imposed on the language of the publications.

Eligibility Criteria

Study Participants

RCTs were eligible for inclusion in our study if they involved patients who had been diagnosed with CSA following the criteria established by the American College of Cardiology and the American Heart Association.[21] We excluded observational studies.

Study Interventions

We imposed no restrictions on the types of acupuncture utilized in the studies, encompassing manual acupuncture, electro-acupuncture, auricular acupuncture, laser acupuncture, and transcutaneous electrical acupoint stimulation (TEAS). We screened studies compared with placebo acupuncture (placebo device, shallow acupuncture, non-acupoints, or mock electrical stimulation), or standard care only.

Study Outcomes

The primary endpoint of our analysis focused on the frequency of angina attacks. The second outcomes were the visual analog scale (VAS) after treatment (a higher score indicates greater pain), the Seattle Angina Questionnaire (SAQ) to

assess the overall quality of life and symptoms related to angina. Additionally, the 6-minute walk distance test (6-MWT) during treatment to evaluate the functional capacity and exercise tolerance of the patients; Furthermore, the Zung self-rating anxiety scale (SAS) and the Zung self-rating depression scale (SDS) were utilized to monitor and quantify changes in anxiety and depression levels, respectively. Also, total efficacy and adverse events (AEs) were extracted.

Data Collection and Analysis

Reviewers XYZ and LQK searched and imported the results into Endnote to remove duplicates. They then independently screened the titles and abstracts against the inclusion/exclusion criteria. Relevant full texts were retrieved and further evaluated. Disagreements were resolved by consulting the third reviewer, ZW.

Data were extracted onto a predevelopment sheet to display the study characteristics, such as author, published year, and sample size; the patient characteristics, including mean age, the intervention methods, and the comparisons; and details of the interventions, including number of acupoints, whether "Deqi" was needed, average frequency of acupuncture, acupuncture duration, and the total sessions of acupuncture.

Risk of Bias

To evaluate the potential risks of bias, we employed the Cochrane Collaboration tool.[22] Additionally, we utilized the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) framework[23] to assess the quality of the evidence, categorizing it into four levels: high, moderate, low, or very low. This assessment encompassed considerations such as the risk of bias, consistency of results, indirectness of evidence, imprecision, and potential publication bias.

Subgroup Analysis

According to the STRICTA (Standards for Reporting Interventions in Controlled Trials of Acupuncture) recommendations,[24] acupuncture parameters involve different perspectives (acupoints number, mode of acupuncture stimulation, number and frequency of treatment course, etc.).

Based on the recommendations of Smith et al,[25] Baker et al,[13] and Liu et al,[26] we performed a subgroup analysis that was grounded on four key acupuncture parameters to elicit the dose-dependent effectiveness of acupuncture: (1) the amount of chosen acupoints (more than 9 acupoints); (2) the "Deqi" response ("Deqi" sense is needed); (3) frequency of administrated acupuncture treatment (more than 2 sessions per week); (4) total treatment sessions (more than 8 sessions). To further clarify for the quantitative evaluation of the acupuncture dosage, for each parameter, a score of +1 was assigned if it met or exceeded the predefined level, while a score of −1 was given if it fell below that level. Above all, we defined the high dosage with sum scores more than 2 (HDG), the moderate dosage with scores from 0 to 2 (MDG), and the low dosage with scores less than 0 (LDG). Two acupuncturists (LQK, YJY) independently grouped the eligible studies.

To explicit the applicable dosage of acupuncture treatment, an exploring subgroup analysis was conducted based on the average dosage parameters of acupuncture. The average number of careened acupoints was 5.8, the average screened frequency of acupuncture was 4 times per week, and the average total sessions of acupuncture was 16. For the acupuncture techniques, different characteristics between manual acupuncture and electroacupuncture.[25] Electroacupuncture involves the retention of electrical stimulation within the body, applied either comprehensively or selectively to the needle handle, utilizing pulsed current to serve dual functions of acupuncture and electrotherapeutic pulsation.[27] Thus, we explored the mode of acupuncture (electroacupuncture or manual acupuncture) in the subgroup analysis.

Sensitivity Analysis

A sensitivity analysis was conducted utilizing the method, in which studies were excluded individually. For instance, Ballegaard et al[28] was excluded from the analysis, and any resulting discrepancies in the outcomes were meticulously noted.[29]

Data Synthesis

We utilized RevMan5.4.1, a software tool provided by the Cochrane Collaboration, for data analysis. For continuous variables (eg, angina attack frequency, VAS scores, SAQ, SAS, SDS totals), we presented our findings in terms of the difference or standardized mean difference (SMD) alongside a 95% confidence interval (CI). In contrast, for dichotomous outcomes (such as overall efficacy and adverse event rates), we reported the results as odds ratios (OR) with a 95% CI. To assess the degree of heterogeneity among studies, we employed I-square (I^2) statistics and the Cochran Q-test.[22] Based on these assessments, we opted for a fixed-effects model in cases of low heterogeneity ($I^2 < 50\%$ or Cochran Q-test $P > 0.05$), and a random-effects model otherwise. Furthermore, we conducted publication bias evaluations using funnel plots, Egger's test, and Begg's test.

Patient and Public Involvement

No patient is involved.

Results

Literature results

Literature results identified through our search strategies, including 802 from databases and registers, and 10 through other sources like reference lists of published reviews. After excluding 159 duplicates, we screened the titles and abstracts of the remaining studies, eliminating 383 due to various reasons such as reviews, meta-analyses, protocols, animal studies, not involving acupuncture or TESA, or having irrelevant content. Upon reading the full texts of the remaining 245 studies (21 were without full text, 14 were not RCT, 30 were without outcomes for interest, and 180 were of too low quality). Additionally, 3 studies from other sources were not retrieved, and 6 were excluded for poor quality. Consequently, 16 studies were included in our analysis. The entire screening process and its outcomes are depicted in Figure 1.

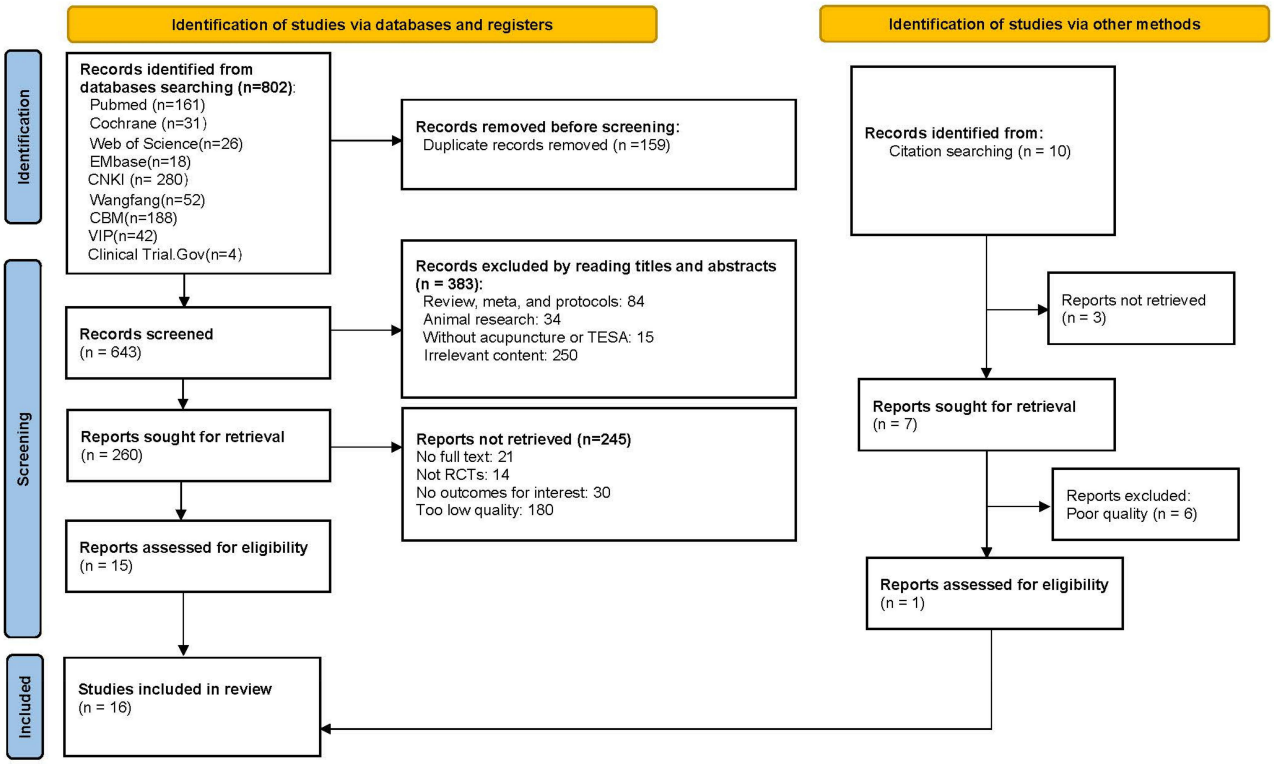

Figure 1 The PRISMA flow diagram of the study screening process.
Abbreviations: CNKI, China National Knowledge Infrastructure; CBM, China Biomedical Literature Database; VIP, China Science Journal Database; RCT, randomized controlled trial.

Eligible and Study Characteristics

The characteristics of RCTs included are presented in Table 1. One study came from Denmark,[28] one came from the United States,[19] and the other 14 studies came from China,[11,15–19,30–38] which were published between 1986 and 2022. The treatment group of each study administered true acupuncture (10 with manual acupuncture, and six with electro-acupuncture). Among all, six studies compared placebo acupuncture,[11,28,32,35,36,38] five studies compared standard medication,[15,16,18,31,33] one study compared an attention control,[19] and other four studies compared with two groups (placebo acupuncture group and standard medication group).[17,30,34,37] For intervention parameters values, all acupuncture needed to be "Deqi"; three studies[18,19,38] needed more than nine acupoints; all studies were conducted more than twice (≥2) per week except for one trial[15] which conducted only one session; 13 studies[11,16–19,30–32,34–38] received more than eight sessions in total (≥8). All studies reported the frequency of angina attacks except for one trial.[19] Besides, only five studies[17,18,30,32,38] reported the adverse effects.

Risk Bias

The risk of bias assessment for the 16 included studies is summarized in Figure 2 and (sTable 3 Supplementary Materials). Notably, two studies[28,33] exhibited an unclear risk of bias related to the random sequence generation process, as specific details regarding its implementation were lacking. Only five studies[17,30,31,34,38] mentioned the concealment with opaque sealed envelopes or an independent researcher. For performance bias, four studies[17,30,34,37] conducted a three-arm trial. For acupuncture compared with the placebo group, the performance bias is low; for acupuncture compared with the standard care group, the performance bias is high. Upon further evaluation, it was determined that there was a minimal risk of attribution bias and reporting bias within this systematic review. Overall, the level of bias in this study ranged from low to moderate.

Dose-Related Effects of Intervention

Table 2 shows the scoring system and dose-related group distribution based on the sum of each intervention parameter's scores. Three studies[18,19,38] were evaluated in HDG with a sum of four; 10 studies[11,16,17,30–32,34–37] were in the MDG with a sum of 0–2, and in three studies[15,28,33] were in the LDG with a sum of −2. The distribution of different outcomes and control groups in the three dose-related groups is shown in Figures 3–5.

Primary outcomes

Thirteen studies[11,16–18,28,30–32,34–38] reported the frequency of angina attacks. Figure 3 displayed the merged data that acupuncture declined the frequency of angina attacks than the control groups (SMD, −0.82; 95% CI [−1.16, −0.48], $P<0.00001$, $I^2=88\%$). More favorable outcomes were observed with acupuncture in comparison to the placebo group (SMD, −0.51; 95% CI [−0.77, −0.25], $P = 0.0001$, $I^2=62\%$) and the standard care group (SMD, −1.25, 95% CI [−1.89, −0.61], $P = 0.00001$, $I^2=92\%$).

In the subgroup analysis, one study was[38] in HDG, eight studies[11,17,30,32,34–37] in MDG, and one[28] in LDG evaluated the frequency of angina attacks. Compared with the placebo group, LDG showed no difference (SMD, −0.23, 95% CI [−1.00, 0.55], $P=0.005$, $I^2=62\%$), while MDG is significantly effective (SMD, −0.60, 95% CI [−0.91, −0.29], $P=0.01$, $I^2=60\%$). However, in HDG, no significant reduction in angina attacks was shown, which may indicate that disease-related acupoints (low-sensitive acupoints of CSA) in the control might not be inert. Compared with the standard care group, a relatively higher dosage of acupuncture was more effective. In MDG, acupuncture can significantly decrease the frequency of the attacks (SMD, −1.44, 95% CI [−2.10, −0.79], $P<0.00001$, $I^2=91\%$) while in LDG, acupuncture showed no difference (SMD, −0.12, 95% CI [−0.62, 0.39], $P = 0.45$, I^2=not applicable).

Second outcomes

VAS

Compared with the placebo acupuncture group, only six studies[17,30,32,34,36,37] in MDG reported the VAS, while compared with the standard care group, six studies[16,17,30,31,34,37] in MDG, and one study[15] in LDG evaluated the VAS. Acupuncture might reduce the patients' performance on the VAS in overall analysis with low heterogeneity (MD, −0.47, 95% CI

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Table 1 Characteristics of the Eligible Studies

Study ID	Setting	N[a]	Age of Participants (Mean [SD]/ Median [Range])	Intervention Group						Control Group	Outcomes
				Intervention Method	No. of Needling Points	"De qi" Response	Average Frequency (per Week)	Duration (Week)	Total Sessions		
Ballegaard 1986[28]	Denmark	T:13 C:13	T: 54 (40–70)[b] C: 58 (38–66)[b]	MA	6 (PC6, ST36, BL14)	Yes	2.3	3	7	SA (non-acupoint with the same spinal segments)	Exercise tolerance; anginal attacks;
Chen 2015[30] [c]	China	T:11 C1:11 C2:12	T: 67.8±9.2 C1: 67.1±8.9 C2: 67.4±6.1	EA with medication	4 (PC6, HT5)	Yes	3	4	12	C1: SA with medication (non-meridian and non-acupoint group) C2: WL with medication	The frequency of angina attacks, VAS, SAQ,6-MWT, SAS, SDS, total effect, AEs
Wang 2015[31]	China	T: 15 C: 15	T: 59 (55–66)[b] C: 57 (53–68)[b]	EA with medication	2 (PC6)	Yes	3	4	12	Medication	Frequency of angina attacks, VAS, SAQ, 6-MWT, SAS, SDS
Jing 2016[32]	China	T:18 C:18	T: 66.67±6.28 C: 67.11±5.97	MA with medication	4 (PC6, HT5)	Yes	5	2	10	MA with medication (non-disease-related acupoints)	The frequency of angina attacks; VAS; AEs
Wu 2016[18]	China	T:56 C:56	T:68.56±7.68 C:69.93±9.21	MA with medication	18 (BL23, BL17, BL15, PC6, ST36, SP6, KI3, ST40, CV12; CV6)	Yes	7	4	28	Medication	6-MWT, total effect, AEs
Xie 2016[15]	China	T: 40 C: 40	T: 54.8±4.8 C: 55.3 ±4.8	MA with medication	2 (Xiongtong xue)[d]	Yes	1	1	1	Medication	VAS, total effect
Yao 2016[33]	China	T: 30 C: 30	T: 70.2±6.11 C: 69.2±7.3	MA with medication	5 (PC6, ST36, CV5)	Yes	7	1	7	Medication	VAS, SAQ, total effect
Zhang 2016[34] [c]	China	T: 96 C1:101 C2:100	T: 62.24 ± 9.85 C1: 62.56±8.89 C2: 63.42±10.29	EA with medication	4 (PC6; HT5)	Yes	3	4	12	C1: SA with medication (non-meridian and non-acupoint group) C2: WL with medication	The frequency of angina attacks; VAS, SAQ, total effect
Chen 2017[35]	China	T:9 C:11	T: 68±8.5 C:56±7.7	EA with medication	4 (PC6; HT5)	Yes	3	4	12	SA with medication (non-disease-related acupoints)	The frequency of angina attacks; VAS; 6MWT; SAS; SDS

Yin 2018[36]	China	T:15C:11	T: 65.27±5.97 C: 62.73±6.79	MA with medication	4 (PC6, HT5)	Yes	5	2	10	SA with medication (non-disease-related acupoints)	The frequency of angina attacks; SAQ; SAS; SDS
Zhang 2018[37] [c]	China	T: 30 C: 30	68.12 ± 7.45[e]	EA with medication	4 (PC6; HT5)	Yes	3	4	12	SA with medication (non-disease-related acupoints)	The frequency of angina attacks; VAS
Zhao 2019[17] [c]	China	T: 99 C1:101 C2:99	T: 62.52 ± 9.86 C1: 62.56 ± 8.89 C2:63.36 ± 10.33	EA with medication	4 (PC6, HT5)	Yes	3	4	12	C1: SA with medication (non-meridian and non-acupoint group) C2: WL with medication	The frequency of angina attacks, VAS, SAQ, 6-WMT, SAS, SDS, AEs
Ye 2020[16]	China	T:58C:58	T:67±6 C:67±7	MA with medication	8 (PC6, HT5, BL17, HT15)	Yes	7	12	90	Medication	The frequency of angina attacks; VAS; total effect
Huang 2021[38] [f]	China	T:109 C: 93	HSG: 66.06 ± 9.11 LSG: 66.22± 10.02	MA	HSG: 9 (HT3, HT7, PC6, HT6, RN17)	Yes	3	4	12	LSG: 9 (BL15, BL16, BL14, HT1, RN14)	Frequency of angina attacks; nitroglycerin consumption, CCS, SAQ, AEs
DeVon 2022[19]	USA	T:11 C:13	Average age 59 ± 12	MA	23 (LR4, LU7, PC4, PC6, HT7, LI4, ST36, ST40, KI6, SP3, LR3, CV6,)	Yes	2	5	10	Attention control (watch the health videos from the NOVA Science NOW™ series on PBS)	MPQ; SAQ–7
Lan 2022[11]	China	T: 15 C:14	T: 66.2±5.97 C: 65.86±7.96	MA with medication	4 (PC6, HT5)	Yes	5	2	10	MA with medication (non-disease-related acupoints)	The frequency of angina attacks; MPQ; SAS; SDS

Notes: [a]Number of randomized participants; [b]Median age (years) and range; [c]Two control groups were set in the trial. Control group 1 (C1) is a placebo group, two fixed sham acupoints were used, and control group 2 (C2) is a waitlist group without acupuncture. [d]Xiongtong Xue is an experimental acupoint located between the ulna and radius on 4 cun above the dorsocarpal transverse crease. the mean (standard deviation) of all participants; [f]Acupoints were selected by pressure-pain thresholds of 12 disease-related acupoints, and five acupoints with the highest thresholds were selected to be used in the low-sensitivity group (LSG). The five acupoints with the lowest thresholds were selected to be used in the high-sensitivity group (HSG).

Abbreviations: MA, manual acupuncture, SA, sham acupuncture; EA, electroacupuncture; WL, waitlist; MPQ, McGill Pain Questionnaire; SAQ, the Seattle Angina Questionnaire; HSG, high sensitivity group; LSG, low sensitivity group; CCS, Canadian cardiovascular society classification; VAS, visual analog scale; 6-MWT, 6-minute walk distance test; SAS, self-anxiety scale; SDS, self-depression scale; AEs, adverse events.

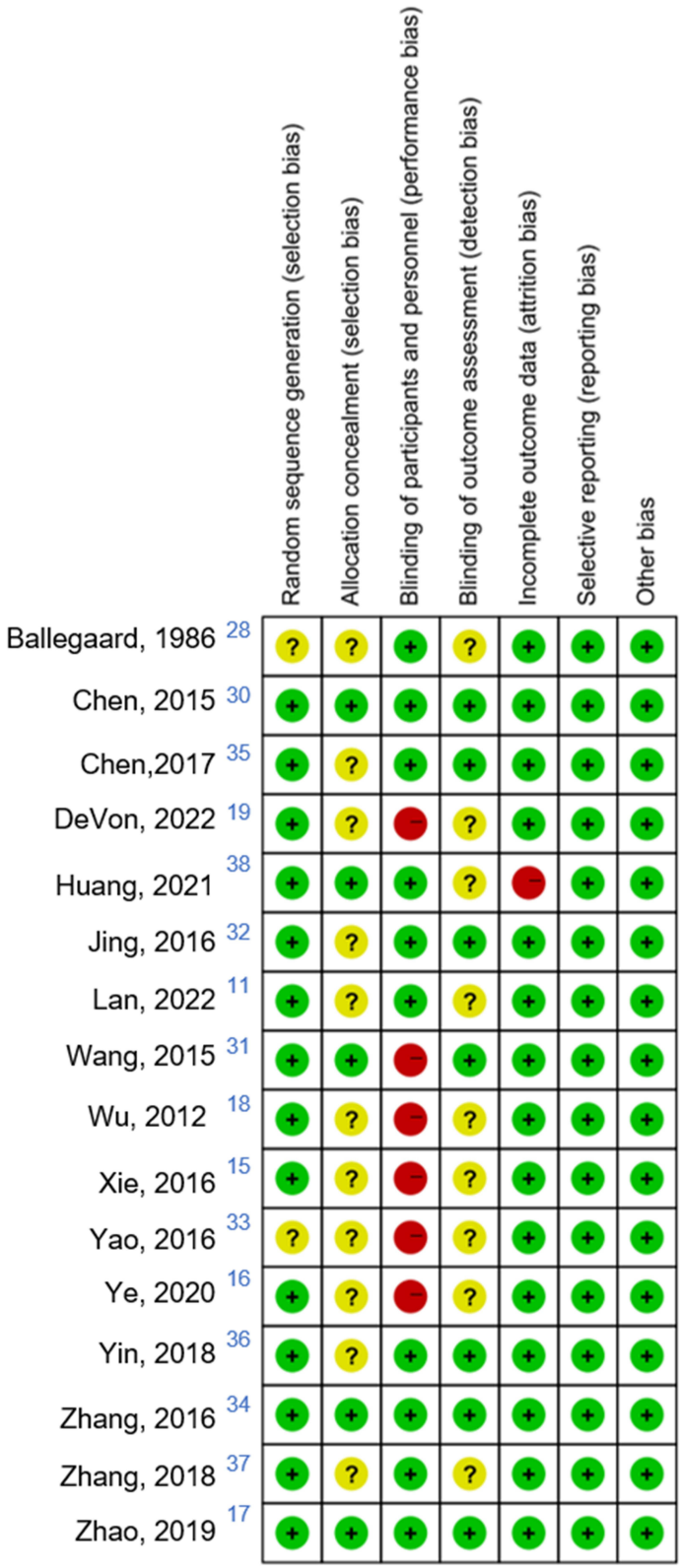

Figure 2 Risk of bias.

Table 2 Acupuncture Dose Scores and Distribution[19]

Study ID	Parameters values*				Sum Scores	Dose Group
	Points Needed	*De qi* Response	Frequency of Treatment	Sessions of Treatment		
Ballegaard, 1986[28]	−1	1	1	−1	0	LDG
Chen, 2015[30]	−1	1	1	1	2	MDG
Wang, 2015[31]	−1	1	1	1	2	MDG
Jing, 2016[32]	−1	1	1	1	2	MDG
Wu, 2016[18]	1	1	1	1	4	HDG
Xie, 2016[15]	−1	1	−1	−1	−2	LDG
Yao, 2016[33]	−1	1	1	−1	0	LDG
Zhang, 2016[34]	−1	1	1	1	2	MDG
Chen, 2017[35]	−1	1	1	1	2	MDG
Yin, 2018[36]	−1	1	1	1	2	MDG
Zhang, 2018[37]	−1	1	1	1	2	MDG
Zhao, 2019[17]	−1	1	1	1	2	MDG
Ye, 2020[16]	−1	1	1	1	2	MDG
Huang, 2021[38]	1	1	1	1	4	HDG
DeVon, 2022[17]	1	1	1	1	4	HDG
Lan, 2022[11]	−1	1	1	1	2	MDG

Notes: *Parameters value based on the four acupuncture parameters: A parameter was defined as a high dose if: (1) the number of points needed was ⩾9, or (2) there was a de qi response; (3) the frequency of treatment was ⩾2 sessions a week; or (4) the total number of treatment sessions was ⩾ 8. A parameter was defined as a low dose if the numbers were below the abovementioned levels. Based on the high/low dose categorization of the four parameters, a scoring system was built to determine the dose of the overall acupuncture treatment. Each high-dose parameter attracted a score of +1 and each low-dose parameter attracted a score of −1. Based on the sum of the scores, we defined three doses of acupuncture treatment, namely high dosage (HD, score >2), medium dosage (MD, score >0 and ≤ 2), and low dosage (LD, score ≤ −2 and ≤ 0).

Abbreviations: HDG, high dosage group; MDG, moderate dosage group; LDG, low dosage group.

[−0.56, −0.39], P<0.00001, I^2=26%). Moreover, acupuncture was more effective relative to placebo acupuncture with moderate dosage (MD, −0.30, 95% CI [−0.48, −0.12], P=0.001, I^2=45%) or standard care alone (MD, −0.52, 95% CI [−0.61, −0.42], P<0.00001, I^2=0%). In the subgroup analysis, compared with the standard care, MDG can significantly improve the VAS (MD, −0.52, 95% CI [−0.61, −0.42], P<0.00001, I^2=0%), while LDG has no significance in reducing the VAS (MD, −0.60, 95% CI [−1.26, 0.06], P = 0.08, I^2= not applicable) (Figure 4).

SAQ

Two studies[17,34] in MDG reported the SAQ when compared with the placebo group, one study[19] in HDG, and three studies[31,34,37] in MDG reported the SAQ when compared with the standard care group. The results showed a significant improvement in the patient's performance on the SAQ in overall effect analysis with moderate heterogeneity (MD, 0.73, 95% CI [0.43, 1.04], P<0.00001, I^2=65%). Subgroup analysis was performed, and the heterogeneity decreased. Compared with placebo acupuncture, the heterogeneity was 0%. Further analysis in the standard care, different dosages of acupuncture were the main heterogeneity cause. One study was in HDG, and three in MDG with small heterogeneity (I^2= 26%) (Figure 5A).

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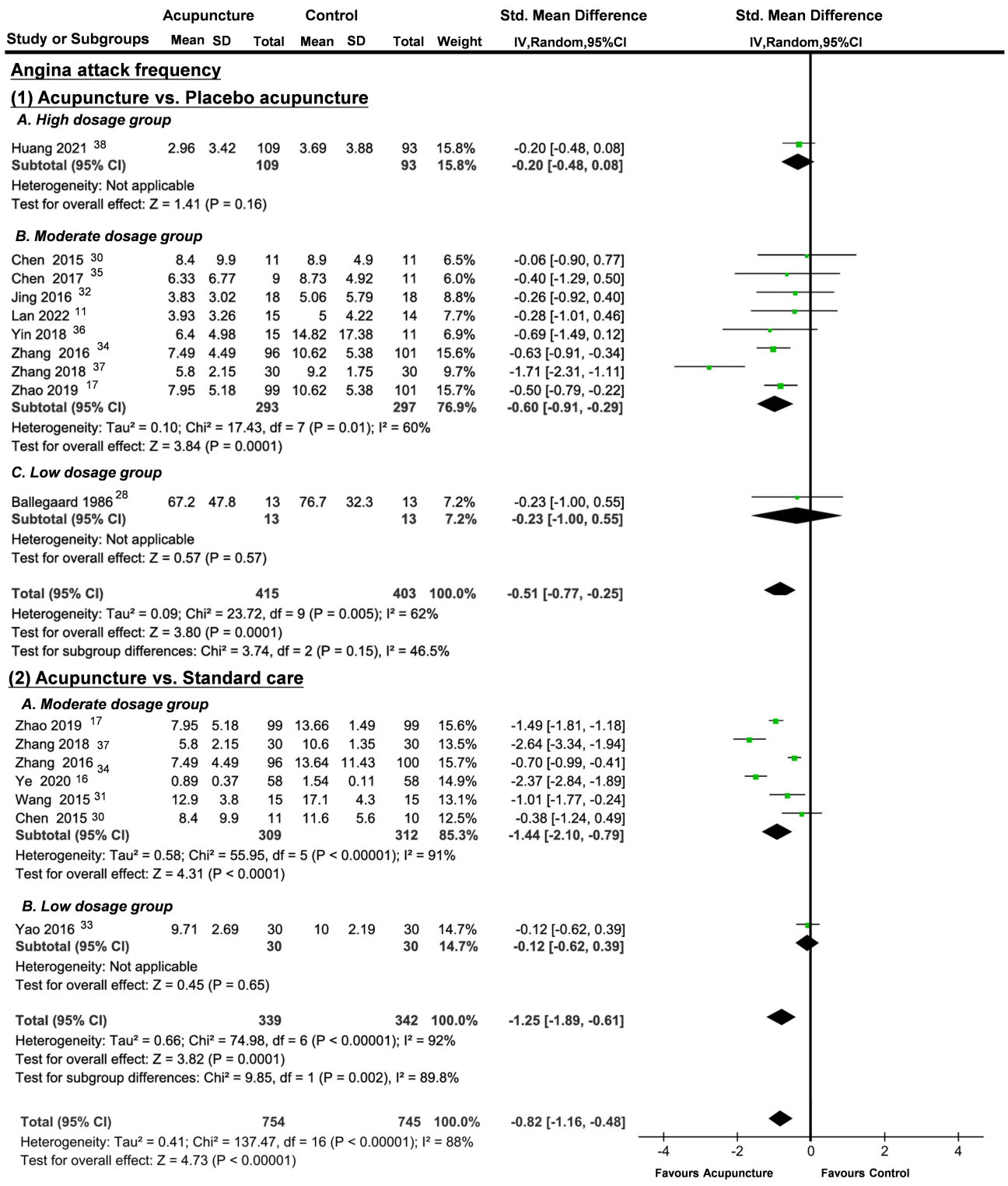

Figure 3 Forest plot of compassion between acupuncture and control in angina attack frequency.

6-MWT

Compared with the placebo acupuncture group, only MDG (3 studies[17,30,35]) reported the 6-MWT; and compared with the standard care group, HDG (one study[18]) and MDG (3 studies[17,30,31]) reported the outcomes. Figure 5B showed that when the combined data is analyzed, acupuncture is significantly associated with improved patient performance on the

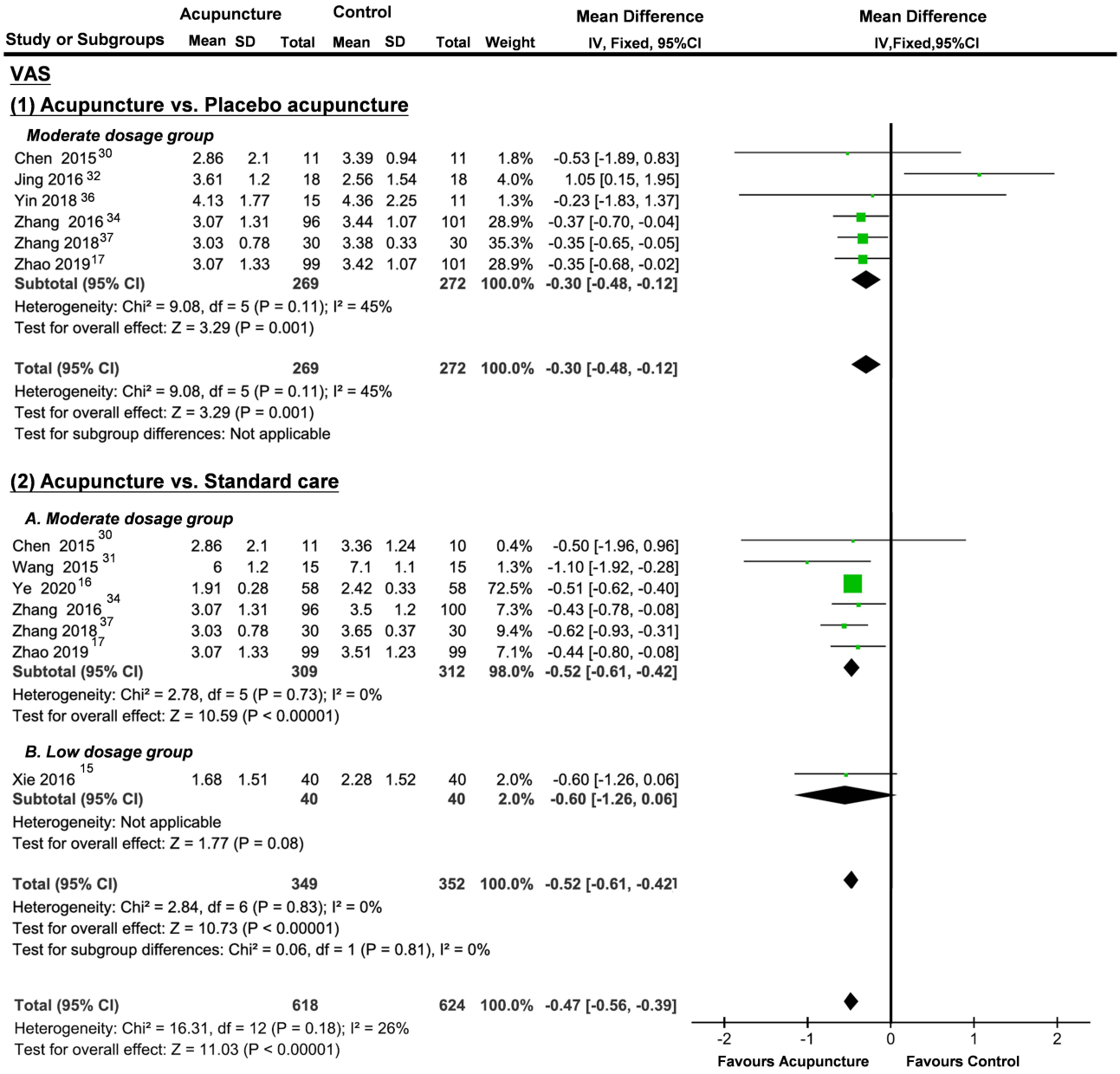

Figure 4 Forest plot of compassion between acupuncture and control in VAS. VAS = visual analog scale.

6-Minute Walk Test (6-MWT), compared to either placebo treatment or standard care alone, in the overall effect analysis (MD, 31.60, 95% CI [1.83, 61.37], P= 0.04, I^2=85%). The subgroup analysis revealed that acupuncture exhibited a more pronounced effectiveness compared to the placebo group, and importantly, this finding was consistent across subgroups, indicating no heterogeneity in the observed effect (MD, 25.56, 95% CI [7.97, 43.15], P= 0.004, I^2=0%), while acupuncture has no significant difference with substantial heterogeneity (I^2=91%) compared with standard care. However, subgroup analysis indicated that, in HDG, acupuncture was more effective than in standard care (MD, 91.92, 95% CI [73.03, 110.81], P<0.00001), while in MDG, no significant difference was found without heterogeneity.

SAS

Only MDG reported SAS in the placebo group (five studies[11,17,30,35,36]) and the standard care group (three studies[17,30,31]). Acupuncture was found to be more effective in alleviating the patient's anxiety level in the overall effect analysis, demonstrating no heterogeneity in the observed effect (MD, −1.51, 95% CI, [−2.69, −0.32], P=0.01; I^2=0%). However,

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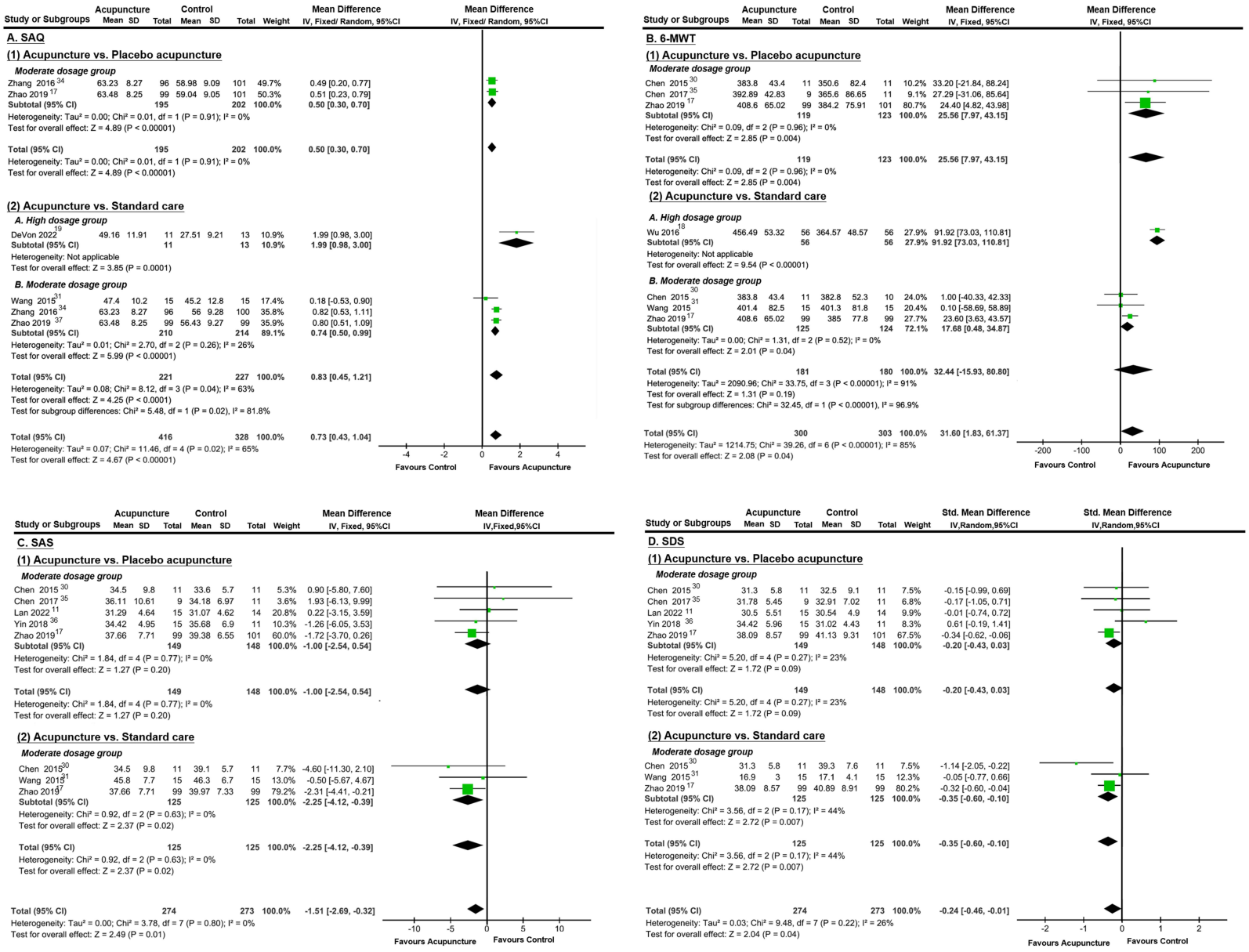

Figure 5 Forest plot of compassion between acupuncture and control in SAQ (**A**), 6-MWT (**B**), SAS (**C**), and SDS (**D**).
Abbreviations: SAQ, Seattle Angina Questionnaire; 6-MWT, Six-Minute Walk Test; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

subgroup analysis showed different outcomes. Compared with the placebo acupuncture, no significant difference was found without heterogeneity (MD, –1.00, 95% CI, [−2.54, 0.54], P= 0.20; I^2 = 0%); compared with the standard care, acupuncture can significantly improve the SAS (MD, –2.25, 95% CI, [−4.12, −0.39], P= 0.02; I^2=0%) (Figure 5C).

SDS

Acupuncture was associated with a notable improvement in depression levels among patients (MD, −0.24, 95% CI [−0.46, −0.01], P= 0.04; I^2= 26%). Subgroup analysis indicated that SDS showed no significant difference compared with the placebo acupuncture (MD, −0.20, 95% CI [−0.43, 0.03], P= 0.09; I^2 = 23%). A significant difference was observed between acupuncture and standard care, despite a moderate level of heterogeneity among the results. (MD, −0.35, 95% CI [−0.60, −0.10], P= 0.007; I^2 = 44%) (Figure 5D).

Adverse Events

In one study of HDG[38] and two studies[32,34] of MDG reported the occurrence of adverse events when compared to the placebo group. One study[18] of HDG and two studies[15,33] of LDG reported adverse events compared with standard care. There was no statistically significant difference observed between the acupuncture group and the control groups, including the placebo group (OR, −0.28, 95% CI [0.01, 7.0], P = 0.44) and the standard care group (OR, 1.89, 95% CI [0.35, 10.16], P= 0.46, I^2 = 53%) (sFigure 1 Supplementary Material).

Total Effectiveness

For the total effectiveness of acupuncture, only two studies[30,34] of MDG were reported when compared with the placebo group; one study[18] of HDG, three[16,30,34] studies of MDG, and two studies[15,33] of the LDG compared with the standard care. Acupuncture can improve the overall effectiveness of CSA compared with the placebo group (OR, 7.74, 95% CI [3.68, 16.25], P<0.00001, I^2=0%) and the standard group (OR, 7.84, 95% CI [5.09 12.07], P<0.00001, I^2=46%) (sFigure 2 Supplementary Materials).

Subgroup Analysis

To find a suitable dosage for CSA, we conducted a subgroup analysis of the angina attack frequency (details shown in sTable 4 Supplementary Materials). In this review, the average number of acupoints was 5.8 (median [min-max], 4 [1–23]). When restricted to acupoints ≤5.8, acupuncture can improve the angina attack frequency compared both in the placebo-controlled group (SMD, −0.60, 95% CI [−0.91, −0.29, P<0.00001, I^2=60%) and the standard care-controlled group (SMD, −1.05, 95% CI [−1.67, −0.44, P=0.008, I^2=90%); when restricting to acupoints >5.8, no significant difference was found in combining all trials or compared with the placebo group (SMD, −0.07, 95% CI [−0.51, 0.38, P=0.77, I^2=36%) or the standard care group (SMD, −2.37, 95% CI [−2.84, −1.89, P<0.00001, I^2=not applicable). For the frequency of acupuncture, one study was once per week,[15] 7 trials were twice or three times per week,[17,19,28,30,31,35,38] three studies were 5 times per week,[11,32,36] and two studies were once a day.[16,33] The average acupuncture frequency was 4 times per week (median [min-max], 3.5 [1–7]), and the average total sessions of acupuncture were 16 (median [min-max], 11.5 [1–90]). There is a significant difference was found in the ≤4 times per week group when restricted to the placebo group (SMD −0.49, 95% CI [−0.85, −0.13], P=0.008, I^2=77%) and the standard care group (SMD −1.05, 95% CI [−1.67, −0.44], P=0.0008, I^2=90%; while no difference was found in the >4 times per week compared with the placebo group (SMD −0.22, 95% CI [−0.61, 0.16], P=0.26, I^2=8%). In addition, a significant difference was found in the >16 sessions in the total frequency of angina attacks (SMD −2.37, 95% CI [−2.84, −1.89], P<0.00001, I^2=not applicable). In comparison, no difference was found in the ≤16 sessions in total (SMD −0.68, 95% CI [−0.99, 0.38], P<0.00001, I^2=85%). Furthermore, we found electroacupuncture can significantly reduce the frequency of angina attacks (SMD −0.88, 95% CI [−1.31, −0.46], P<0.00001, I^2=85%), while no difference was found applying manual acupuncture (SMD −0.58, 95% CI [−1.22, 0.05], P<0.00001, I^2=90%) (sTable 4 Supplementary Material).

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Sensitivity Analysis

The sensitivity analysis showed consistency in some studies upon individual exclusion, with minimal impact on overall results and conclusions. Notable reductions in heterogeneity were achieved excluding Zhang et al[37] decreased angina attack heterogeneity from 67% to 22% compared to placebo acupuncture, Jing's exclusion[32] eliminated VAS heterogeneity (from 45% to 0%) versus placebo, DeVon's exclusion[19] within the HDG reduced SAQ heterogeneity from 63% to 26% compared to the standard group, and Wu's exclusion[18] decreased 6-MWT heterogeneity from 91% relative to the standard group.

Reporting Bias

Given the limited number of studies reporting on the outcomes, excluding angina attack frequency, a single funnel plot was generated for the analysis (sFigure 3 Supplementary Material). Egger's test ($P = 0.753$) and Begg's test ($P = 0.68$) suggest that no publication bias was found in the analysis of the primary outcomes.

GRADE for Quality of Each Evidence

Table 3 summarizes the comparison results and GRADE analyses, encompassing 20 outcomes about the efficacy of acupuncture in CSA. The quality of evidence ranged from very low to moderate, primarily due to concerns regarding the overall risk of bias stemming from methodological flaws in the randomization process, including issues with randomization, concealment, and incomplete reporting. However, by conducting subgroup analyses based on different control groups and dosages, heterogeneity was mitigated. Furthermore, publication bias emerged as a potentially significant factor contributing to the diminished evidence quality.

Table 3 Quality of Evidence Based on GRADE

Outcome Indicators	No	No. of participants		Effect [95% CI]	I^2	Quality of Evidence
		Intervention Group	Control Group			
Angina attacks Frequency						
Acupuncture* vs *Placebo acupuncture						
High dosage group	1	109	93	−0.2[−0.48,0.08]	/	⊕⊕◯◯ Low (a, b)
Moderate dosage group	8	293	297	−0.6[−0.91, −0.29]	60%	⊕◯◯◯ Very low (a, b, d, e)
Low dosage group	1	13	13	−0.23[−1.00,0.55]	/	⊕⊕⊕◯ Moderate (a)
Total	**10**	**415**	**403**	**−0.47[−0.75, −0.19]**	**67%**	⊕◯◯◯ Very low (a, b, e)
Acupuncture* vs *Standard care						
Moderate dosage group	**5**	309	312	−1.44[−2.1, −0.79]	91%	⊕◯◯◯ Very low (a, b, d, e)
Low dosage group	**1**	30	30	−0.12[−0.62, 0.39]	/	⊕⊕◯◯ Low (a, c)
Total	**6**	**339**	**342**	**−1.25[−1.89, −0.61]**	**92%**	⊕◯◯◯ Very low (a, b, d, e)
Overall effect	**16**	**754**	**745**	**−0.82[−1.16, −0.48]**	**89%**	⊕◯◯◯ Very low (a, b, d, e)

(*Continued*)

Table 3 (Continued).

Outcome Indicators	No	No. of participants		Effect [95% CI]	I^2	Quality of Evidence
		Intervention Group	Control Group			
VAS						
Acupuncture* vs *Placebo acupuncture						
Moderate dosage group	6	269	272	−0.30[−0.48, −0.12]	45%	⊕⊕⊕◯ Moderate (a)
Acupuncture* vs *Standard care						
Moderate dosage group	6	309	312	−0.52[−0.61, −0.42]	0%	⊕⊕⊕◯ Moderate (a)
Low dosage group	1	40	40	−0.6[−1.26, 0.06]	/	⊕⊕⊕◯ Moderate (a)
Total	**7**	**349**	**352**	**−0.52[−0.61, −0.42]**	**0%**	⊕⊕⊕◯ Moderate (a)
Overall effect	**13**	**618**	**624**	**−0.47[−0.56, −0.39]**	**26%**	⊕⊕⊕◯ Moderate (a)
SAQ						
Acupuncture* vs *Placebo acupuncture						
Moderate dosage group	2	195	202	0.50[0.30, 0.70]	0%	⊕⊕◯◯ Moderate (c, e)
Acupuncture* vs *Standard care						
High dosage group	1	11	13	1.99[0.98, 3.00]	/	⊕⊕⊕◯ Moderate (a)
Moderate dosage group	3	210	214	0.74[0.50, 0.99]	26%	⊕⊕⊕◯ Moderate (a)
Total	**4**	**221**	**227**	**0.83[0.45, 1.21]**	**63%**	⊕⊕◯◯ Low (a, b)
Overall effect	**6**	**416**	**328**	**0.73[0.43, 1.04]**	**65%**	⊕⊕◯◯ Low (a, b)
6-MWT						
Acupuncture* vs *Placebo acupuncture						
Moderate dosage group	3	119	123	25.56[7.97, 43.15]	81%	⊕⊕◯◯ Moderate (b, e)
Acupuncture* vs *Standard care						
High dosage group	1	56	56	91.92[73.03, 110.81]	/	⊕⊕◯◯ Low (a, b)
Moderate dosage group	3	125	124	17.68 [0.48, 34.87]	0%	⊕⊕◯◯ Low (a, b)
Total	**4**	**181**	**180**	**32.44[−15.93, 80.80]**	**97.1%**	⊕◯◯◯ Very low (a, b, e)
Overall effect	**7**	**300**	**303**	**31.60[1.83, 61.37]**	**84%**	⊕◯◯◯ Very low (a, b, e)

(*Continued*)

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Table 3 (Continued).

Outcome Indicators	No	No. of participants		Effect [95% CI]	I^2	Quality of Evidence
		Intervention Group	Control Group			
SAS						
Acupuncture* vs *Placebo acupuncture						
Moderate dosage group	5	149	148	−1.00[−2.54, 0.54]	23%	⊕⊕⊕◯ Moderate (e)
Acupuncture* vs *Standard care						
Moderate dosage group	3	125	125	−2.25[−4.12, −0.39]	44%	⊕⊕◯◯ Moderate (b, e)
Overall effect	**8**	**274**	**273**	**−1.51[−2.69, −0.32]**	**26%**	⊕⊕⊕◯ Moderate (e)
SDS						
Acupuncture* vs *Placebo acupuncture						
Moderate dosage group	5	149	148	−0.2[−0.43, 0.03]	23%	⊕⊕◯◯ Low (a, c)
Acupuncture* vs *Standard care						
Moderate dosage group	3	125	125	−0.35[−0.6, −0.10]	44%	⊕⊕◯◯ Low (a, c)
Overall effect	**8**	**274**	**273**	**−0.24[−0.46, −0.01]**	**26%**	⊕⊕◯◯ Low (a, c)
Adverse effects						
Acupuncture* vs *Placebo acupuncture						
High dosage group	1	109	93	0.28 [0.01, 7.00]	NA	⊕◯◯◯ Very low (a, b, d, e)
Moderate dosage group	2	114	118	Not estimate	NA	⊕◯◯◯ Very low (a, b, d, e)
Total	**3**	**223**	**211**	**0.28 [0.01, 7.00]**	NA	⊕◯◯◯ Very low (a, b, d, e)
Acupuncture* vs *Standard care						
High dosage group	1	56	56	7.39 [0.37, 146.52]	**NA**	⊕◯◯◯ Very low (a, b, d, e)
Low dosage group	2	70	70	Not estimate	NA	⊕⊕◯◯ Low (a, c)
Total	**3**	**126**	**126**	**7.39 [0.37, 146.52]**	**NA**	⊕⊕◯◯ Low (a, c)
Overall effect	**6**	**349**	**337**	**1.89 [0.35, 10.16]**	**53%**	⊕◯◯◯ Very low (a, b, d, e)
Overall effectiveness						
Acupuncture* vs *Placebo acupuncture						
Moderate dosage group	2	107	112	7.74 [3.68, 16.25]	**0%**	⊕⊕◯◯ Low (a, c)

(*Continued*)

Table 3 (Continued).

Outcome Indicators	No	No. of participants		Effect [95% CI]	I^2	Quality of Evidence
		Intervention Group	Control Group			
Acupuncture* vs *Standard care						
High dosage group	1	56	56	38.55 [2.24, 664.59]	**NA**	⊕⊕◯◯ Low (a, c)
Moderate dosage group	3	165	168	9.08 [4.70, 17.56]	**77%**	⊕◯◯◯ Very low (a, b, d, e)
Low dosage group	2	70	70	3.14 [1.12, 8.75]	**0%**	⊕⊕◯◯ Low (a, c)
Total	6	291	294	7.89 [4.64, 13.40]	**61%**	⊕◯◯◯ Very low (a, b, d, e)
Overall effect	**8**	**398**	**406**	**7.84 [5.09, 12.07]**	**48%**	⊕◯◯◯ Very low (a, b, d, e)

Notes: a: Download one level for serious risk of bias: failure to develop and apply appropriate eligibility criteria (inclusion of control population), flawed measurement of both exposure and outcome, failure to adequately control confounding, or incomplete or inadequately short follow-up. b: Downgraded one level for serious inconsistent: inconsistency refers to an unexplained heterogeneity of results, which includes the wide variance of point estimates across studies, minimal or no overlap of confidence intervals (CI), and statistical criteria, including tests of heterogeneity which test the null hypothesis that all studies have the same underlying magnitude of effect, have a low p-value ($p < 0.05$), indicating to reject the null hypothesis. c: Downgraded one level for serious indirectness: including differences in the population (applicability), differences in interventions (applicability), differences in outcomes measures (surrogate outcomes), and indirect Comparisons. d: Downgraded one level for serious imprecision: dichotomous outcomes and continuous outcomes were considered separately, including that, the optimal information size criterion was not med, or 95% CI overlaps no effect. e: Downgraded one level when publication bias is suspected.

Discussion

This is the first review evaluating the efficacy of acupuncture across various dosage parameters in the treatment of CSA. We rigorously evaluated the quality of eligible studies using the GRADE. We identified statistically significant pooled benefits of acupuncture in alleviating symptoms of chronic angina attacks (specifically, reducing the frequency of attacks and lowering VAS scores) and enhancing quality of life (as measured by SAQ and 6-MWT results) when administered at moderate to high dosages. Nevertheless, acupuncture in anxiety and depression levels might be a placebo effect compared with the placebo group and the standard care. Acupuncture was a safe and effective intervention in the analysis of adverse effects and overall effects.

CSA arises from blood supply–demand imbalance, causing reversible ischemia/hypoxia-related myocardial events. Acupuncture alleviates CSA symptoms, acting through "Deqi" (soreness, numbness, and heaviness). Analgesic mechanisms of acupuncture involve transmitters like endogenous opioids, cholecystokinin octapeptide, 5-hydroxytryptamine, glutamate, γ-aminobutyric acid, acetylcholine, and orexin-A.[39] Acupuncture can also modulate the autonomic nervous system, orexinergic system, and abnormal calcarine activity,[40] and inhibit blood pressure surges via TRPV1,[41] impacting the cardiovascular system.

Questions regarding adequate doses are ongoing in acupuncture research. However, there is no consensus yet on the definition of "acupuncture dosage". Acupuncture treatment is a physical procedure utilizing one or multiple needles while considering the patient's subsequent perceptions (sensory, affective, and cognitive). Thus, the dose of acupuncture is determined by the amount of needling stimulus and the individual patients' perception (*Deqi* sensation, expectation, and muscle trigger points).[42]

Under the complexity and individualization of acupuncture doses, we classified the acupuncture parameters into four characteristics: the number of needles, the "Deqi" response, the frequency of treatment, and the total number of sessions. This classification was coincident with dose–response evaluations in chronic pain,[12] primary dysmenorrhoea,[25] and knee osteoarthritis.[26]

Studies have demonstrated that increasing the number of needles enhances treatment efficacy, with Backer and his team showing that four extra needles significantly elevate sympathetic nerve activity.[13] While stimulation intensity appears to be a more critical factor than needle count, given that each acupuncture point may not elicit an equivalent

clinical physiological response,[14] published research often lacks details on needle rotation and manipulation. For chronic pain relief, the number of needles, retention time, and mode of stimulation are associated with neurophysiological stimulation.[25] The total acupuncture sessions and frequency of treatments are the important components of the cumulative dose,[25] with evidence suggesting that six acupuncture sessions may be the minimum required to achieve clinical effects in treating chronic prostatitis/chronic pelvic pain syndrome.[43] Chinese acupuncturists typically administer treatments three times a week, a frequency found by Liu to improve symptoms and quality of life in patients with postprandial distress syndrome compared to once a week.[44] Furthermore, *Deqi*, an essential parameter in STRICTA evaluations,[24,45] is pivotal for therapeutic effects, particularly in analgesia.[46] Brain imaging studies have shown that *Deqi* triggers intrinsic changes in blood flow, tissue displacement, and hemodynamic signals across various brain areas.[47] highlighting its importance in dose–response selection. Thus, in determining acupuncture protocols, attention to needle count, frequency, total number of stimulations, and achievement of *Deqi* is vital for optimal outcomes.

Based on clinical experience and existing literature,[26,48,49] we employed a cut-off point for defining "adequate acupuncture" and summarized four parameters to quantify the acupuncture dosage in CSA according to the included RCTs: (1) ⩾9 points needed; or (2) *De qi* response; or (3) ⩾2 sessions frequency of treatment per week; or (4) ⩾8 sessions in total. Furthermore, a scoring system was built to classify the included RCTs.[26] Retrieved studies were categorized into HDG, MDG, and LDG. This review provides evidence suggesting that the effectiveness of acupuncture may be influenced by the dosage of the treatment, indicating a potential dose–response relationship. For the primary outcome, compared with the placebo group, MDG can reduce the frequency of angina attacks significantly, while LDG and HDG showed no significant difference. However, in HDG, low-sensitive acupoints (which are also disease-related acupoints) in the control group reduce the testing effect. Compared with standard care, acupuncture can decrease the frequency of angina attacks in MDG, while LDG has shown no significant difference.

To investigate the suitable dosage for CSA, we found that acupoints less than 5.8 may be significant in clinical treatment (SMD, −0.74, 95% CI [−1.11, −0.47], $P<0.00001$, $I^2=83\%$), intervention frequency is less than 4 times per week (SMD, −0.74, 95% CI [−1.09, −0.39], $P<0.00001$, $I^2=87\%$), and total sessions are less than 16 (SMD, −2.37, 95% CI [−2.84, −1.89], $P<0.00001$) may be a benefit in the clinical treatment. This finding contradicts previous research, suggesting that higher doses do not invariably lead to superior outcomes. Instead, an adequate dosage should be tailored to the specific pathology and disease stage.[14] Two studies, each examining three dosage levels, reported the largest effect sizes in the intermediate dosage group, with a decline at the highest dosage.[50,51] Specially, for chronic conditions, underlying diseases as well as complications should also be taken into consideration. Consequently, the determination of an "adequate dosage" should be appropriately set by thoroughly incorporating the characteristics of the disease.

Subgroup analyses confirmed the efficacy of electroacupuncture rather than manual acupuncture. Regarding dose classification, all electroacupuncture treatments commence with a manual stimulation to achieve *Deqi*. Electroacupuncture provides a higher dose of stimulation compared to manual acupuncture alone, due to its enhanced activation of endogenous opioid mechanisms (EOM).[52]

A bibliometric analysis highlights *Tongli* (HT5) and *Neiguan* (PC6) as acupoints particularly relevant to CSA based on Traditional Chinese Medicine's (TCM) syndrome differentiation theory. These paired points are also identified as highly responsive in CSA patients in Huang's research,[38] with *Neiguan* (PC6) stimulation specifically demonstrated to attenuate sympathoexcitatory cardiovascular reflex responses.[53]

In our review, the placebo group and the standard care group were conducted in the subgroup analysis. Evaluation of SAS and SDS indicated that the placebo acupuncture may not be entirely inert or without any effect (Figure 5C and D). As summarized in our previous review,[54] different placebo control methods (placebo device,[55,56] sham acupuncture,[57] and non-acupoints[58]) were reported, however, acupuncture-specific efficacy cannot avoid.[59] Moreover, the potential heterogeneities may be related to the different placebo interventions.[60] In addition, in the standard group, blinding is a ubiquitous challenge due to its intrinsic nature.[61] The lack of reliable blinding in studies can lead to a high level of performance bias and potentially exaggerate the effect size of acupuncture. This is a significant factor contributing to the degraded quality of evidence, as it can introduce bias and uncertainty into the results.

Throughout, acupuncture is safe and effective in improving symptoms of CSA, and adequate acupuncture dosage might benefit the clinical treatments. Additional research utilizing more objective methods and incorporating a valid

sham control group is essential to strengthen the reliability of the evidence and minimize the heterogeneity observed in current studies. Such efforts will help to provide a clearer understanding of the efficacy and mechanisms of acupuncture.

However, our study also has limitations. First, adequate heterogeneities remain after subgroup analysis, and some potential variables remain. Given the substantial heterogeneity in the analytical evidence, we should exercise caution and objectivity in interpreting the outcomes. Second, the results of this study were based on the assumption that different acupoints have the same efficacy. Therefore, the individual efficacy of the selected acupoints was not evaluated. Finally, given that our review included evidence ranging from very low to moderate quality, there is a need for more high-quality RCTs that employ successful blinding techniques and utilize a valid placebo control group. Such studies will help to provide a more robust and reliable assessment of the efficacy of acupuncture.

Conclusion

Our findings suggest that acupuncture can be a safe and valuable therapeutic option for CSA. Additionally, relatively moderate acupuncture dosage showed potentially better effects for CSA in reducing the symptoms.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary materials, and further inquiries can be directed to the corresponding author (Lingqiu Kong, klq521@163.com).

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Disclosure

The authors declare no conflicts of interest in this work.

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