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Systematic Review

Randomized controlled trials of acupuncture for the treatment of essential hypertension: a meta-analysis

针刺治疗原发性高血压随机对照试验的Meta分析

LU Yuqing (路隅青)[1], LI Lingjie (李灵杰)[1], WANG Zhaoqin (王照钦)[2], HUANG Yan (黄艳)[1], ZHONG Rui (钟蕊)[1], XU Jing (徐静)[1], LIU Huirong (刘慧荣)[3], WU Huangan (吴焕淦)[3], CHENG Ling (程玲)[4], WU Luyi (吴璐一)[1]

1 Key Laboratory of Acupuncture and Immunological Effects, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

2 Department of Aeronautics and Astronautics, Shanghai Key Laboratory of Acupuncture Mechanism and Acupoint Function, Fudan University, Shanghai 200433, China

3 Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China

4 Shanghai East Hospital, Tongji University, Shanghai 200120, China

Abstract

Objective: To systematically assess the efficacy and safety of acupuncture therapy for essential hypertension.

Methods: A computerized literature search of the Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Database (CQVIP), Wanfang Academic Journal Full-text Database (Wanfang), China Biology Medicine Disc (CBM), PubMed, Excerpta Medica Database (EMBASE), and Cochrane Library was conducted to retrieve randomized controlled clinical trials on acupuncture as the main intervention for the treatment of essential hypertension published from the inception of the database to 30 January 2021. The risk-of-bias assessment was carried out for each included study according to the Cochrane Handbook. Data analysis was performed using Review Manager 5.4.1 and Stata 15.0.

Results: After the screening, 46 randomized controlled trials involving a total of 3 859 subjects were included. Primary outcomes included changes in the diastolic blood pressure after intervention [eight studies showed that the acupuncture plus antihypertensive drug group was better than the antihypertensive drug monotherapy group [mean difference (MD)=1.45, 95% confidence interval (CI) (0.48, 2.43), P=0.004, fixed effects model; I^2=39%] and changes in the systolic blood pressure after intervention {11 studies showed that the acupuncture plus antihypertensive drug group was better than the antihypertensive drug monotherapy group [MD=8.60, 95%CI (7.12, 10.07), P<0.00001, fixed effects model; I^2=26%]}. The secondary outcome was antihypertensive efficacy, 12 studies of acupuncture monotherapy group [risk ratio (RR)=1.20, 95%CI (1.12, 1.28), P<0.00001, fixed effects model; I^2=36%] and 15 studies of acupuncture combined with antihypertensive drug group [RR=1.27, 95%CI (1.20, 1.34), P<0.00001, fixed effects model; I^2=6%] showed better results than the antihypertensive drug monotherapy group in antihypertensive efficacy. In terms of the adverse events, four studies showed that the acupuncture monotherapy group had fewer adverse events than the antihypertensive drug monotherapy group [RR=0.10, 95%CI (0.04, 0.25), P<0.00001, fixed effects model; I^2=0%].

Conclusion: Acupuncture combined with antihypertensive drugs is superior to antihypertensive drugs alone in reducing blood pressure, and acupuncture therapy is effective and safe for the treatment of essential hypertension with fewer side effects. However, there is still a lack of high-quality multicenter randomized double-blinded controlled trials in this field. Rigorous large-sample clinical trials are needed to validate these findings.

Keywords: Acupuncture Therapy; Hypertension; Randomized Controlled Trials; Systematic Review; Meta-analysis

【摘要】目的: 系统评价针刺治疗原发性高血压的疗效和安全性。**方法:** 通过计算机检索中国知网(CNKI)、重庆维普数据库(CQVIP), 万方学术期刊全文数据库(Wanfang)、中国生物医学文献数据库(CBM)、PubMed、荷兰医学文摘数据库(EMBASE)和Cochrane Library数据库自建库至2021年1月30日所收录的以针刺作为主要干预手段治疗原发性高血压的临床随机对照试验。根据Cochrane手册对纳入研究进行偏倚风险评估。使用Review Manager 5.4.1软件和Stata 15.0软件进行数据分析。**结果:** 共纳入46项随机对照试验, 共包括3 859例受试者。主要结局指标包括干预后舒张压变化{8项研究显示针刺联合西药治疗组优于单用降压药组[MD=1.45, 95%CI (0.48, 2.43), P=0.004, 固定效应模型; I^2=39%]}

Co-first Authors: LU Yuqing, M.D., resident physician; LI Lingjie, M.D., resident physician.
Joint Corresponding Authors: CHENG Ling, M.D., chief physician.
E-mail: chlrosy.east@sina.com; WU Luyi, M.D., associate researcher.
E-mail: luyitcm@163.com

和干预后收缩压变化{11项研究表明针刺联合西药治疗组优于单用降压药组[MD=8.60, 95%CI (7.12, 10.07), *P*<0.00001, 固定效应模型; I^2=26%]}。次要结局指标为降压疗效，12项单独针刺治疗组的研究[RR=1.20, 95%CI (1.12, 1.28), *P*<0.00001, 固定效应模型; I^2=36%]与15项针刺联合降压药组的研究[RR=1.27, 95%CI (1.20, 1.34), *P*<0.00001, 固定效应模型; I^2=6%]皆显示其降压效果优于单用降压药。在不良反应方面，4项研究表明单独针刺组不良反应少于单用降压药组[RR=0.10, 95%CI (0.04, 0.25), *P*<0.00001, 固定效应模型; I^2=0%]。**结论:** Meta分析表明，针刺联合降压药物的降压效果优于单用西药，且针刺治疗原发性高血压有效、安全、副作用少。然而，该领域尚缺乏高质量、多中心的随机双盲对照试验，仍需要严谨设计的大样本临床研究对上述结论进行验证。

【关键词】针刺疗法; 高血压; 随机对照实验; 系统评价; Meta分析

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Essential hypertension is a clinical syndrome characterized by elevated arterial blood pressure in the systemic circulation. It is one of the most common cardiovascular diseases and can easily cause damage to organs such as the heart, brain, and kidney[1]. With economic progress, improvement in living standards, and lifestyle changes, the prevalence of hypertension is increasing yearly[2]. According to statistics from the World Health Organization (WHO), the global number of deaths from hypertension complications in 2012 was 9.4 million, and essential hypertension has become a significant public health problem worldwide[3].

The treatment of essential hypertension is usually the life-long use of antihypertensive agents to maintain blood pressure in a relatively stable range. However, long-term medication use produces drug resistance and different toxic and side effects, including excessively decreased blood pressure, which can lead to dizziness and high pulse pressure due to low diastolic blood pressure (DBP) and unchanged systolic blood pressure (SBP). These can increase the possibility of cardiovascular events[4]. Therefore, how to reduce the toxic and side effects of drugs and seek safe, stable, and effective blood pressure reduction methods in treatment has gradually drawn the attention of patients and physicians.

Acupuncture is a treatment method based on the theory of meridians and collaterals of traditional Chinese medicine (TCM). It prevents and treats diseases by needling specific points on the body with needles and has achieved positive clinical effects[5]. As a TCM therapy, acupuncture has been widely accepted because of its effectiveness, tolerability, and lack of significant side effects. In particular, the effect of acupuncture in lowering blood pressure has been recognized[6]. Researchers have demonstrated that acupuncture can lower the levels of plasma endothelin[7], adrenaline, and norepinephrine[8] to lower blood pressure. Moreover, it can increase endorphin and nitric oxide[9] to regulate blood pressure.

In clinical research, some researchers have observed acupuncture's efficacy in treating essential hypertension. Many studies have shown that acupuncture has good efficacy for essential hypertension[10]. However, some controversial voices say that acupuncture alone has no significant difference from Western medicine alone regarding the antihypertensive effects[11]. Therefore, acupuncture's clinical efficacy in treating hypertension remains debatable. To this end, this study involved a systematic review and meta-analysis of the randomized controlled clinical trials of acupuncture treatment for essential hypertension to provide further evidence for the application of acupuncture for essential hypertension.

1 Methods

1.1 Eligibility criteria

1.1.1 Types of studies

We included randomized controlled clinical trials of acupuncture for the treatment of essential hypertension published in formal Chinese or English journals.

1.1.2 Participants

We included patients diagnosed with essential hypertension according to the hypertension criteria defined by the WHO/International Society of Hypertension (WHO/ISH)[12] and the *Chinese Guidelines for the Prevention and Treatment of Hypertension*[1], i.e., SBP ≥140 mmHg and/or DBP ≥90 mmHg. We excluded patients with secondary hypertension due to an identifiable cause, such as parenchymal renal disease, renovascular hypertension, primary aldosteronism, and endocrine hypertension.

1.1.3 Interventions

Acupuncture was the primary intervention in the observation group. Acupuncture intervention here included electroacupuncture or acupuncture therapies. We included only conventional body acupuncture, stimulating points only with metallic needles. And we excluded other point stimulation forms, such as point thread embedding, auriculotherapy, and moxibustion, as the main intervention.

Antihypertensive drugs or sham acupuncture or no treatment or lifestyle management were accepted in the control group. If acupuncture combined with Western medicine was the intervention in the observation group, the same Western medicine treatment had to be used in the control group.

1.1.4 Outcomes

The primary outcome measures included changes in the DBP and SBP. The secondary outcome measures included antihypertensive efficacy[13] and adverse events. Other outcomes, such as plasma neuropeptide Y (NPY) and symptomatic efficacy[13], were accepted if studies were sufficient.

1.2 Search strategy

The database search terms were "hypertension", "essential hypertension", "high blood pressure", "blood pressure", "acupuncture", "point", "acupoint", "randomized controlled trial", "random", "randomized", "randomization", "controlled clinical trial", and "clinical trial". The retrieval team searched reviews and conference abstracts related to acupuncture treatment of essential hypertension in order to reduce the risk of missing studies. An example search of PubMed is shown in Table 1 (similar search run in other databases).

1.3 Data collection and management

According to the above inclusion criteria, two researchers (LU Yuqing and LI Lingjie) independently screened full texts to determine whether we should include the study. If disagreement existed, a third researcher (XU Jing) was consulted.

Data collection and analysis were independently completed and cross-checked by two authors (HUANG Yan and ZHONG Rui). In all included literature, valid information and data were extracted in a data extraction form, including the basic study information, sample characteristics, interventions, outcomes, follow-up, and adverse events. ZHONG Rui checked it to verify the accuracy of the data. Disagreements between the investigators were resolved by discussion.

Table 1 PubMed search strategy

Search	Query	Item found
#1	Search (High Blood Pressures) OR (High Blood Pressure) OR (Blood Pressures, High) OR (Blood Pressure, High) OR (Hypertension) OR (Essential Hypertension)	595 641
#2	Search (Acupuncture) OR (Therapy, Acupuncture) OR (Acupuncture Therapy) OR (Treatment, Acupuncture) OR (Acupuncture Treatments) OR (Acupuncture Treatment)	34 820
#3	Search [Randomized Controlled Trial (Publication Type)] OR [Randomized Controlled Trials (Topic)]	675 873
#4	#1 AND #2 AND #3	97

1.4 Risk of bias assessment

The risk of bias in the included studies was assessed by two reviewers (LU Yuqing and WANG Zhaoqin) according to the bias risk assessment criteria in the *Cochrane Handbook for Systematic Reviews of Interventions*[14]. We resolved disagreements by discussion or with the third review author (XU Jing).

1.5 Data synthesis and analysis

We used Review Manager 5.4.1 software to measure the effect of treatment. The continuous variables were analyzed by mean difference (MD) with a 95% confidence interval (CI). The dichotomous data were analyzed by risk ratio (RR) with a 95%CI. The I^2 statistic was used to measure heterogeneity. The random effects model was used to analyze the combined effect values of the studies with high heterogeneity (P≤0.10 and/or I^2≥50%), and the fixed effects model was used for the studies with low heterogeneity (P>0.10 and I^2<50%). P<0.05 was considered statistically significant. We defined the change in the blood pressure as the pre-treatment blood pressure minus the post-treatment blood pressure, and the mean and standard deviation (SD) were extracted as the continuous outcome. If the mean value and SD were missing, we calculated them according to the formula offered by the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.10)[15-16]. Please see Figure 1[17].

$$SD_{change}=\sqrt{SD_1^2+SD_2^2-2\times(corr\times SD_1\times SD_2)}$$

Note: SD_{change}=Standard deviation of change-from-baseline; SD_1=Standard deviation of baseline; SD_2=Standard deviation of the final; Corr=Correlation coefficient.

Figure 1 Formula for calculation

Here we input the value of correlation coefficient as 0.4. The Review Manager software was used for forest plot analysis to assess study effects, and funnel plot analysis was performed to assess reporting bias if enough studies were included in the meta-analysis (n≥10).

2 Results

2.1 Description of general literature

According to the search strategy, 1 803 potentially qualified studies were initially retrieved in the search. After reading the full texts carefully, 44 qualified studies were finally selected, including 36 Chinese randomized controlled trials (RCTs) and 8 English RCTs (Figure 2 and Table 2).

2.2 Study characteristics

A total of 3 716 patients were recruited in the 44 RCTs, 1 924 (51.8%) in the treatment group and 1 792 (48.2%) in the control group[18-61]. Hypertension

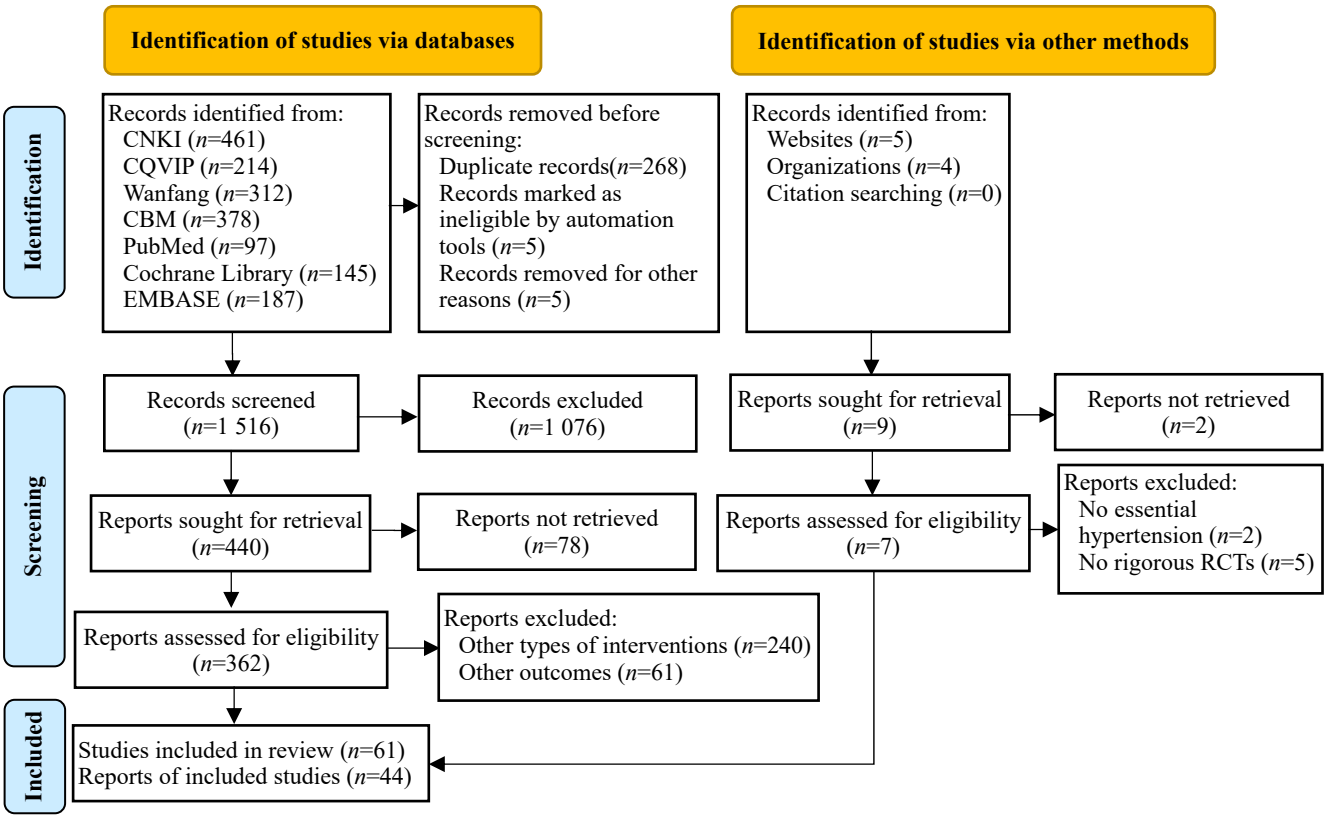
was diagnosed based on the WHO/ISH and the *Chinese Guidelines for the Prevention and Treatment of Hypertension* in the 44 studies[18-29,31-38,40-43]: SBP ≥140 mmHg or DBP ≥90 mmHg.

Seventeen studies[18-20,23,26,28,36-38,41,44-45,48-50,52,55] reported acupuncture versus antihypertensive drugs. Seventeen studies[21-22,24-25,27,29,31,33,40,42,46,53-54,57-59,61] reported acupuncture plus antihypertensive drugs versus antihypertensive drugs alone. Four studies[32,35,56,60] reported acupuncture versus sham acupuncture. Only one study[39] reported acupuncture versus no treatment. Two studies[30,34] reported acupuncture plus antihypertensive drugs versus sham acupuncture plus antihypertensive drugs. Three studies[43,47,51] reported acupuncture plus lifestyle management versus lifestyle management alone.

A variety of outcome measures were observed in the study. Thirty-six studies[19-26,28,30-31,34-36,38,40-54,56-61] observed blood pressure after intervention; nine studies[32,34-36,39,42,44,60,61] observed changes in blood pressure after intervention; thirty-one studies[18,20-29,31,33,36-38,40-45,47-49,53-55,57-59] observed the antihypertensive efficacy rate; eight studies[19,26,31,42,44,49,57,59] observed the symptomatic efficacy rate; three studies[24-25,54] observed the plasma level; eight studies[18,26,28,33,49,57-58,60] reported adverse events after treatment.

2.3 Risk of bias in the included studies

Baseline data were similar among the 44 RCTs included. In the 44 RCTs, twenty-eight studies[18-19,26,28-32,34,36-37,39,42,45,47-53,56-58,60-61] used a random number table or software regarding the protocol of random allocation. Allocation concealment was reported in only seven studies[30,32,34-35,39,60-61]. Two studies[60-61] reported the blinding of patients, and blinding of the outcome assessment was reported in four studies[32,39,53,60]. The rest of the studies did not mention the issue of blinding. Ten studies reported missing participants[30,34-35,39-40,43,47,49,56,60]. Thirteen studies[27-28,31,43-44,46,49-50,53,57-59,61] had a high risk of selective reporting. And the rest of the studies reported relevant outcomes in detail, evaluated as a low risk of reporting bias. No other biases were found since insufficient information was provided. Please see Figure 3 and Figure 4.



Note: CNKI=Chinese National Knowledge Infrastructure; CQVIP=Chongqing VIP Database; Wanfang=Wanfang Academic Journal Full-text Database; CBM=China Biology Medicine Disc; EMBASE=Excerpta Medica Database.

Figure 2 Flow chart of randomized controlled trials selection [based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)][17]

Table 2 Characteristics of the included studies

Study	Language	SS (OG/CG)	Gender (M/F)	Age/year	COD	Intervention		COT	OC
						OG	CG		
CHEN T W 2018[18]	Chinese	81/81	95/67	OG: 47.24±5.23 CG: 47.02±5.11	OG: 6-34 ms CG: 5-33 ms	A (30 min, twice a day)	Nifedipine (10-20 mg, twice a day)	7 weeks	3, 5
SONG Z P 2016[19]	Chinese	65/65	NR	35-65	NR	A (30 min, twice a day)	Nifedipine (20 mg, twice a day)	20 d	1, 4
ZHANG Y L 2014[20]	Chinese	53/53	62/44	59.4±3.6	NR	A (30 min a day)	Betaloc (12.5 mg, twice a day)	14 d	1, 3
FAN C L 2013[21]	Chinese	100/100	120/80	OG: 54.65±10.37 CG: 55.23±9.76	OG: 3-12 ys CG: 3-13 ys	A (20 min a day) plus CGD	AHD	3 ms	1, 3
LIU T N 2015[22]	Chinese	44/44	49/39	61.4±6.3	1-12 ys	A plus CGD	Captopril (12.5 mg, 3 times a day)	21 d	1, 3
YE M F 2011[23]	Chinese	50/50	54/46	OG: 58 CG: 56	NR	A (30 min a day)	Betaloc (12.5 mg/d)	14 d	1, 3
JIA X M 2012[24]	Chinese	46/46	62/30	46.9±5.8	2 ms-18 ys	A (30 min a day) plus CGD	Levamlodipine (5 mg, once a day)	4 weeks	1, 3, 6
WANG J 2017[25]	Chinese	90/90	95/85	46.8±4.5	5 ms-21 ys	A (30 min a day) plus CGD	Levamlodipine (5 mg, once a day)	28 d	1, 3, 6
CHEN N Y 2010[26]	Chinese	40/40	41/39	OG: 61.3±8.0 CG: 62.0±7.1	OG: 16.0±6.7 ys CG: 17.3±5.0 ys	A (30 min a day)	Diovan (80 mg, once a day)	30 d	1, 3, 4, 5
QIU Z Y 2016[27]	Chinese	30/30	28/32	OG: 57.02±3.31 CG: 55.30±2.40	OG: 9.1±3.5 ys CG: 8.8±1.3 ms	A (30 min a day) plus CGD	Valsartan (80 mg, once a day)	4 weeks	3
XIE B 2014[28]	Chinese	30/30	30/30	OG: 56±11 CG: 53±10	OG: 5.2±1.2 ys CG: 4.9±2.4 ys	A (30 min a day)	Captopril (25 mg, 3 times a day)	21 d	1, 3, 5
CHEN J 2010[29]	Chinese	30/30	31/29	OG: 48.2±7.2 CG: 50.5±8.4	OG: 6 ms-7 ys CG: 5 ms-9 ys	A (30 min a day) plus CGD	Felodipine (5 mg, once a day)	15 d	1, 3
YIN C 2007[30]	English	15/15	9/21	OG: 52 CG: 54	NR	A plus CGD	SA plus AHD	8 weeks	1
HUANG F 2007[31]	Chinese	30/30	27/33	OG: 56.51±6.28 CG: 58.12±6.15	OG: 5.25±4.44 ys CG: 5.16±4.55 ys	A (30 min a day) plus CGD	Captopril (25 mg, 3 times a day)	4 weeks	1, 3, 4
CHOI W J 2015[32]	English	25/25	NR	OG: 48.04±6.13 CG: 46.20±9.26	NR	A (20 min, 4 times in total)	SA (20 min, 4 times in total)	2 weeks	2
CUI J K 2013[33]	Chinese	46/46	55/37	OG: 56.7±8.9 CG: 54.7±8.1	NR	A plus CGD (once a day except for Sunday)	Irbesartan (150 mg/d)	4 weeks	3, 5
FLACHS-KAMPF F A 2007[34]	English	83/77	66/74	OG: 58.8±8.2 CG: 58.0±7.9	NR	A (30 min a day) plus CGD	SA plus AHD	6 weeks	1, 2
KIM H M 2012[35]	English	12/16	16/12	OG: 2.08±8.69 CG: 2.38±10.3	NR	A (20 min, twice a week)	SA	8 weeks	1, 2
CHEN B G 2006[36]	Chinese	30/30	41/19	OG: 54.75±7.12 CG: 51.72±10.38	OG: 67.8±12.0 ms CG: 70.1±9.7 ms	A (30 min a day)	Metoprolol	4 weeks	1, 2, 3
CHEN Q 2011[37]	Chinese	30/30	29/31	OG: 59±8 CG: 59±8	OG: 8.67±4.74 ys CG: 10.10±4.96 ys	A (30 min a day)	Metoprolol (100 mg/d)	30 d	3
CHEN Y F 2000[38]	Chinese	35/35	38/32	OG: 63.57±8.08 CG: 65.20±8.86	NR	A (30 min a day)	Nifedipine (10-20 mg, 3 times a day)	2 weeks	1, 3
LIU Y 2015[39]	English	15/15	7/23	OG: 49.4±8.4 CG: 53.4±8.2	NR	A (30 min, twice a week)	No treatment	8 weeks	2

Note: SS=Sample size; OG=Observation group; CG=Control group; M=Male; F=Female; COD=Course of disease; COT=Course of treatment; A=Acupuncture; EA=Electroacupuncture; SA=Sham acupuncture; CGD=Control group drug; AHD=Antihypertensive drugs; OC=Outcomes; NR=Not reported; ms=Months; ys=Years; LSM=Lifestyle management; 1=Blood pressure after intervention; 2=Changes in the blood pressure after intervention; 3=Antihypertensive efficacy rate; 4=Symptomatic efficacy rate; 5=Adverse effects; 6=Plasma neuropeptide Y.

Table 2 Characteristics of the included studies (continued)

Study	Language	SS (OG/CG)	Gender (M/F)	Age/year	COD	Intervention		COT	OC
						OG	CG		
LUO H 2015[40]	Chinese	44/46	66/34	45-75	4 ms-28 ys	A (30 min a day) plus CGD	Felodipine (5 mg)	20 d	1, 3
MA Z Y 2011[41]	Chinese	40/40	47/33	OG: 66.39±5.47 CG: 64.58±7.13	OG: 179.28±40.17 ms CG: 184.76±36.56 ms	EA (10 min a day)	Nicardipine (20 mg, 3 times a day)	15 d	1, 3
SHEN Z K 2007[42]	Chinese	25/25	31/19	OG: 57.32±8.24 CG: 58.21±7.31	OG: 7.12±3.24 ys CG: 8.34±4.11 ys	A (30 min a day) plus CGD	Nifedipine (20 mg, twice a day)	25 d	1, 2, 3, 4
SUN J 2009[43]	Chinese	44/43	48/39	OG: 47.23±5.66 CG: 48.42±6.13	NR	A (30 min, twice a week) plus LSM	LSM	NR	1, 3
TIAN L 2008[44]	Chinese	30/30	33/27	OG: 59.17±3.16 CG: 59.00±3.01	OG: 7.67±1.45 ys CG: 8.03±1.83 ys	A (30 min a day)	Levamlodipine (2.5 mg a day)	30 d	1, 2, 3, 4
WAN W J 2009[45]	Chinese	30/30	36/24	OG: 63.72±8.23 CG: 65.24±6.41	OG: 181.35±35.64 ms CG: 186.58±38.69 ms	A (10 min a day)	Nicardipine (20 mg, 3 times a day)	15 d	1, 3
WANG C 2006[46]	Chinese	30/29	34/25	25-60	NR	EA (30 min a day) plus CGD	Lotensin (10 mg a day)	8 weeks	1
WU X M 2015[47]	Chinese	49/50	52/47	OG: 49.10±8.75 CG: 48.08±8. 81	NR	A (30 min a day) plus LSM	LSM	4 weeks	1, 3
WU Y R 2011[48]	Chinese	60/60	70/50	OG: 54.75±7.10 CG: 51.72±10.30	OG: 6.78±1.20 ys CG: 7.01±9.60 ys	A (30 min a day)	Metoprolol (100 mg a day)	20 d	1, 3
XING H 2016[49]	Chinese	31/32	35/28	OG: 61.83±9.10 CG: 57.14±9.33	OG: 3.23±4.89 ys CG: 3.16±3.98 ys	A (30 min a day)	Captopril (25 mg, 3 times a day)	4 weeks	1, 3, 4, 5
YANG D H 2010[50]	Chinese	30/30	37/23	OG: 40.4±5.2 CG: 41.7±4.2	OG: 5.2±2.7 ys CG: 4.2±2.5 ys	EA (30 min a day)	Captopril (25 mg, 3 times a day)	2 weeks	1
ZHAO D J 2003[51]	Chinese	30/30	37/23	OG: 40.3±11.4 CG: 46.1±14.2	NR	A (20 min a day) plus LSM	LSM	40 d	1
ZHANG Y 2012[52]	Chinese	14/14	NR	42-46	NR	A (30 min, 3 times a week)	Captopril (25 mg, 3 times a day)	8 weeks	1
ZHANG Y B 2011[53]	Chinese	45/35	53/27	OG: 53.62±9.83 CG: 52.16±10.04	OG: 6.13±1.28 ys CG: 6.29±1.40 ys	A (20 min a day) plus CGD	Amlodipine (2.5 mg/d)	4 weeks	1, 3
ZHANG Y L 2005[54]	Chinese	45/30	47/28	OG: 63.60±8.20 CG: 65.20±8.00	OG: 5.97±1.19 ys CG: 6.13±1.23 ys	A (30 min a day) plus CGD	Nifedipine (10 mg, 3 times a day)	20 d	1, 3, 6
ZHANG Z H 2004[55]	Chinese	30/30	42/18	OG: 56.5 CG: 55.5	OG: 3-15 ys CG: 3-16 ys	A (30 min a day)	Compounds of reserpine and hydrochlorothiazide	15 d	3
ZHENG Y 2016[56]	English	15/15	8/22	OG: 56.53±7.52 CG: 56.73±4.91	OG: 106.00±146.05 ms CG: 84.53±62.52 ms	A (30 min a day except for weekends)	SA (30 min a day except for weekends)	2 weeks	1
BI Y M 2020[57]	Chinese	30/30	28/32	OG: 66.1 CG: 65.6	OG: 125.47±36.47 ms CG: 115.70±37.31 ms	A (30 min, 3 times a week) plus CGD	L-amlodipine besylate (2.5 mg, once a day)	4 weeks	1, 3, 4, 5
LI Y H 2020[58]	Chinese	52/52	61/43	OG: 67±5 CG: 67±5	OG: 4.37±0.86 ys CG: 4.16±0.79 ys	A (30 min, 5 times a week) plus CGD	Enalapril maleate (10 mg a day)	3 ms	1, 3, 5
WANG C X 2020[59]	Chinese	30/30	26/34	OG: 66.4 CG: 65.8	NR	A (20 min a day) plus CGD	Levamlodipine maleate (2.5 mg a day)	4 weeks	1, 3, 4
ZHENG H 2019[60]	English	209/102	153/158	OG: 58.2±9.9 CG: 60.4±9.3	OG: 2 (0-40 ys) CG: 2 (0-25 ys)	A (30 min, 3 times a week)	SA (30 min, 3 times a week)	6 weeks	1, 2, 5
HUANG K Y 2020[61]	English	31/31	21/41	OG: 70.87±5.65 CG: 72.87±5.55	NR	A (30 min, twice a week) plus CGD	AHD	12 weeks	1, 2

Note: SS=Sample size; OG=Observation group; CG=Control group; M=Male; F=Female; COD=Course of disease; COT=Course of treatment; A=Acupuncture; EA=Electroacupuncture; SA=Sham acupuncture; CGD=Control group drug; AHD=Antihypertensive drugs; OC=Outcomes; NR=Not reported; ms=Months; ys=Years; LSM=Lifestyle management; 1=Blood pressure after intervention; 2=Changes in the blood pressure after intervention; 3=Antihypertensive efficacy rate; 4=Symptomatic efficacy rate; 5=Adverse effects; 6=Plasma neuropeptide Y.

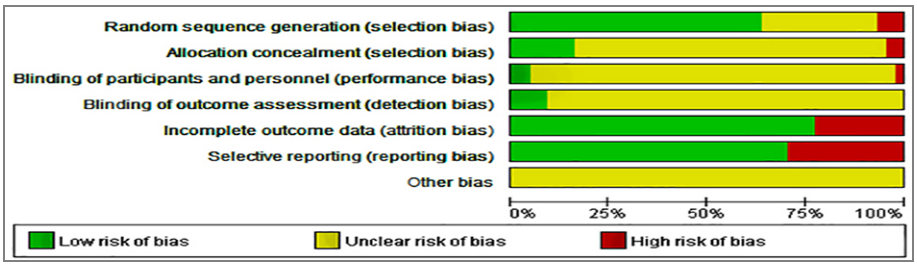


Figure 3 Risk of bias graph of the included trials

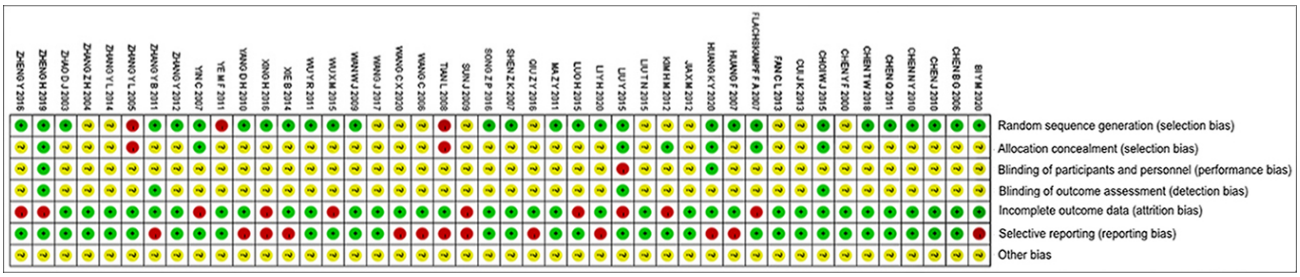


Figure 4 Summary of the risk of bias in seven domains in the 44 randomized controlled trials

2.4 Effects of interventions

2.4.1 Comparison of DBP

Forty studies reported changes in the DBP after treatment, involving a total of 3 345 patients. Ten studies[23,26,36,38,41,44,48-49,50,52] compared acupuncture alone versus antihypertensive drugs (MD=0.52, 95%CI: -0.36 to 1.41, Z=1.16, P=0.25, I^2=39%). Eight studies[24-25,31,46,54,57,59,61] compared acupuncture combined with antihypertensive drugs versus antihypertensive drugs alone (MD=1.45, 95%CI: 0.48 to 2.43, Z=2.91, P=0.004, I^2=39%). Four studies[32,35,56,62] compared acupuncture versus sham acupuncture (MD=1.64, 95%CI: 0.11 to 3.17, Z=2.10, P=0.04, I^2=46%). Only one study[39] compared acupuncture versus no treatment (MD=3.70, 95%CI: -1.13 to 8.53, Z=1.50, P=0.13). Two studies[30,34] compared acupuncture plus antihypertensive drugs versus sham acupuncture plus antihypertensive drugs (MD=4.47, 95%CI: 2.28 to 6.66, Z=4.00, P<0.0001, I^2=36%). Two studies[43,51] compared acupuncture plus lifestyle management versus lifestyle management alone (MD=0.84, 95%CI: -0.17 to 1.85, Z=1.64, P=0.10, I^2=0%). Please see Figure 5 and Figure 6.

2.4.2 Comparison of SBP

Forty studies reported changes in the SBP after treatment, involving a total of 3 345 patients. Ten studies[23,28,36,38,41,45,48-50,52] compared acupuncture alone versus antihypertensive drugs (MD=1.62, 95%CI: 0.04 to 3.20, Z=2.02, P=0.04, I^2=41%). Eleven studies[22,24-25,31,40,46,53-54,57-58,61] compared acupuncture combined with antihypertensive drugs versus antihypertensive drugs alone (MD=8.60, 95%CI: 7.12 to 10.07, Z=11.44, P<0.00001, I^2=26%). Three studies[32,56,62] compared acupuncture versus sham acupuncture (MD=3.87, 95%CI: 1.80 to 5.95, Z=3.66, P=0.0003, I^2=0%). Only one study[39] compared acupuncture versus no treatment (MD=5.20, 95%CI: -2.99 to 13.39, Z=1.24, P=0.21). Two studies[30,34] compared acupuncture plus antihypertensive drugs versus sham acupuncture plus antihypertensive drugs (MD=7.00, 95%CI: 2.88 to 11.12, Z=3.33, P=0.0009). Two studies[43,47] compared acupuncture plus lifestyle management versus lifestyle management alone (MD=6.67, 95%CI: 4.71 to 8.62, Z=6.69, P<0.00001, I^2=0%). Please see Figure 7 and Figure 8.

2.4.3 Comparison of the rate of antihypertensive efficacy

A total of 12 studies[18,20,23,26,28,36-37,41,44-45,48,55] compared acupuncture alone versus antihypertensive drugs (RR=1.20, 95%CI: 1.12 to 1.28, Z=5.56, P<0.00001, I^2=36%). Fifteen studies[21,22,24-25,27,29,31,33,40,42,53-54,57,60-61] compared acupuncture combined with antihypertensive drugs versus antihypertensive drugs (RR=1.27, 95%CI: 1.20 to 1.34, Z=9.02, P<0.00001, I^2=6%). Two studies[43,47] compared acupuncture plus lifestyle management versus lifestyle management (RR=1.22, 95%CI: 1.06 to 1.40, Z=2.85, P=0.004, I^2=0%). Please see Figure 9 and Figure 10.

2.4.4 Comparison of the symptomatic efficacy

Four studies[19,26,44,49] studied the symptomatic efficacy of acupuncture alone versus antihypertensive drugs. The heterogeneity test showed χ^2=3.92 (P=0.27, I^2=23%). The meta-analysis showed RR=1.20 (95%CI: 1.09 to 1.32, Z=3.60, P=0.0003). Three studies[31,42,61] reported the symptomatic efficacy of acupuncture combined with antihypertensive drugs versus antihypertensive drugs alone. The heterogeneity test showed χ^2=1.34 (P=0.51, I^2=0%). The meta-analysis showed RR=1.42 (95%CI: 1.18 to 1.71, Z=3.76, P=0.0002). Please see Figure 11.

2.4.5 Other outcome measures

Two studies[24-25] observed the plasma NPY level between acupuncture combined with antihypertensive drugs and antihypertensive drugs alone, and the heterogeneity test showed χ^2=0.04 (P=0.84, I^2=0%). The meta-analysis showed MD=95.03 (95%CI: 79.72 to 110.33, Z=12.17, P<0.00001). Please see Figure 12.

2.4.6 Adverse effects

Four studies[18,26,28,49] compared the adverse effects between acupuncture alone and antihypertensive drugs (RR=0.10, 95%CI: 0.04 to 0.25, Z=4.98, P<0.00001, I^2=0%), showing that acupuncture alone causes fewer adverse events than antihypertensive drugs, and the difference was statistically significant. Two studies[33,60] compared acupuncture combined with antihypertensive drugs versus antihypertensive drugs (RR=1.13, 95%CI: 0.61 to 2.11, Z=0.39, P=0.69, I^2=0%). Only one study[62] compared acupuncture versus sham acupuncture. The meta-analysis showed that RR=0.61 (95%CI: 0.17 to 2.22, Z=0.75, P=0.45). See Figure 13.

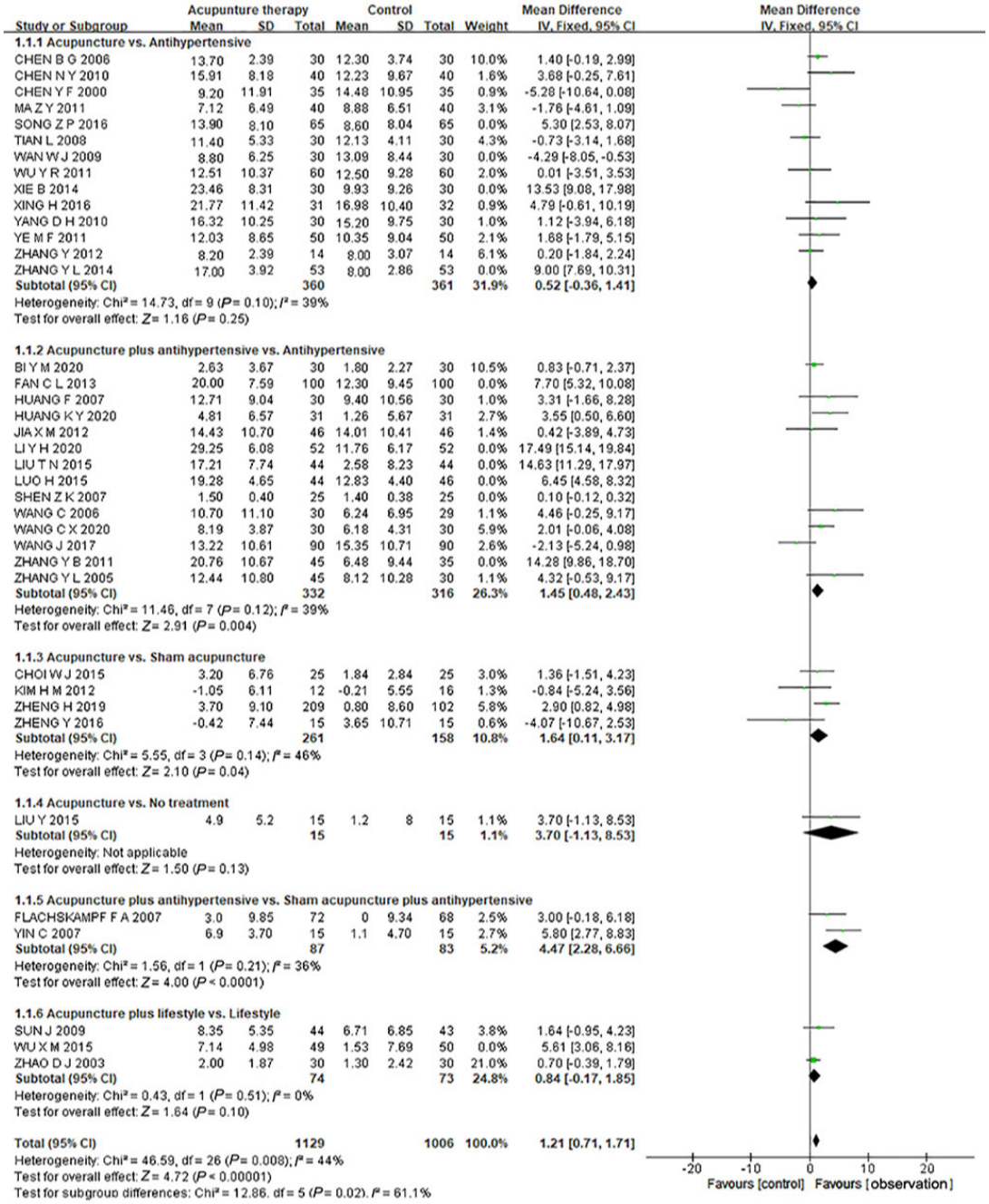
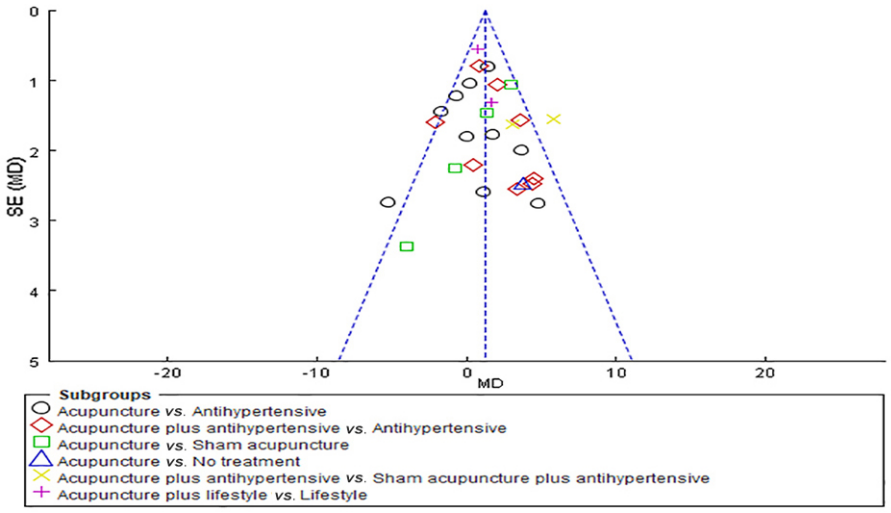


Figure 5 Forest plot of changes in the diastolic blood pressure



Note: SE=Standard error; MD=Mean difference.

Figure 6 Funnel plot of changes in the diastolic blood pressure

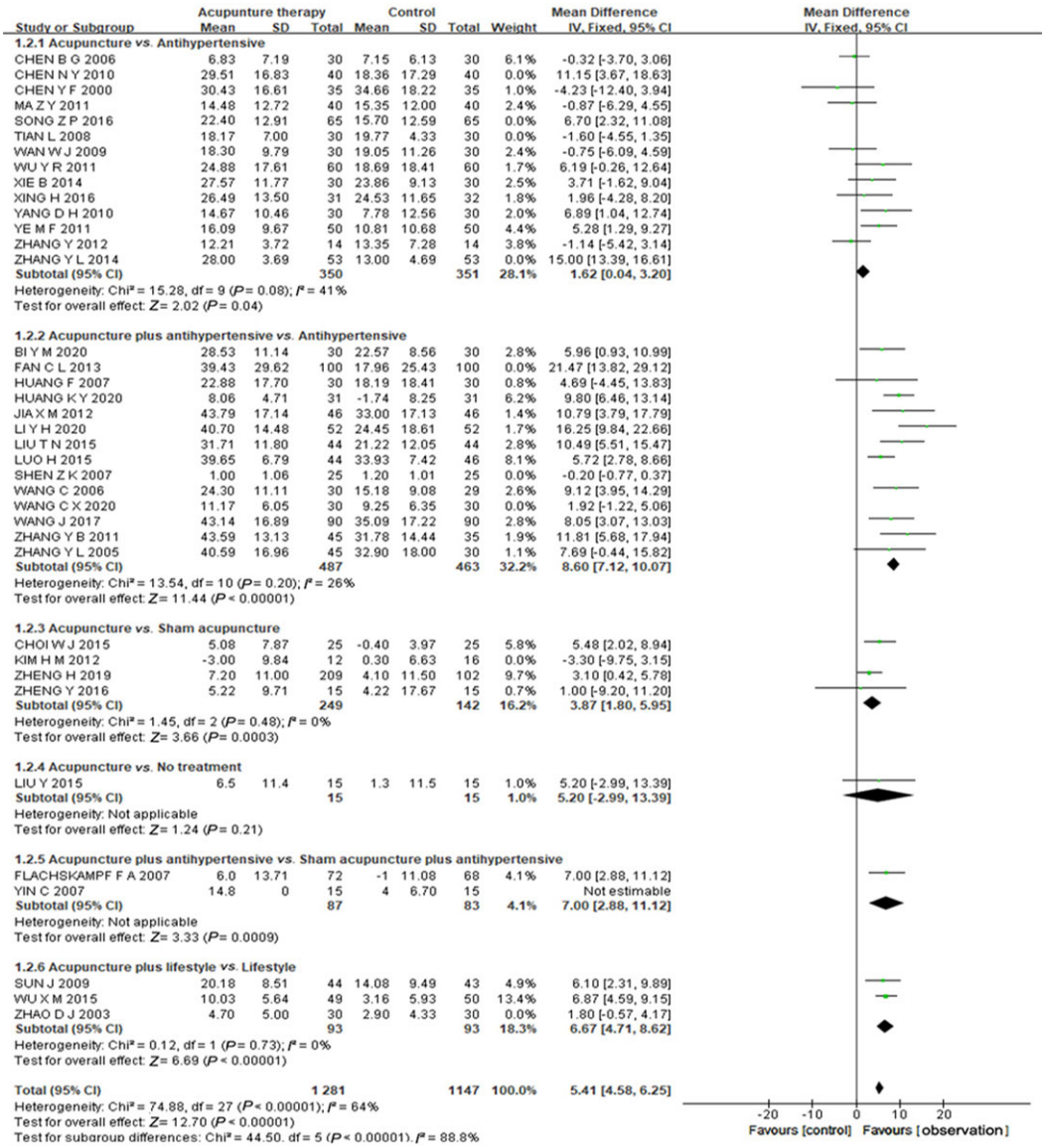
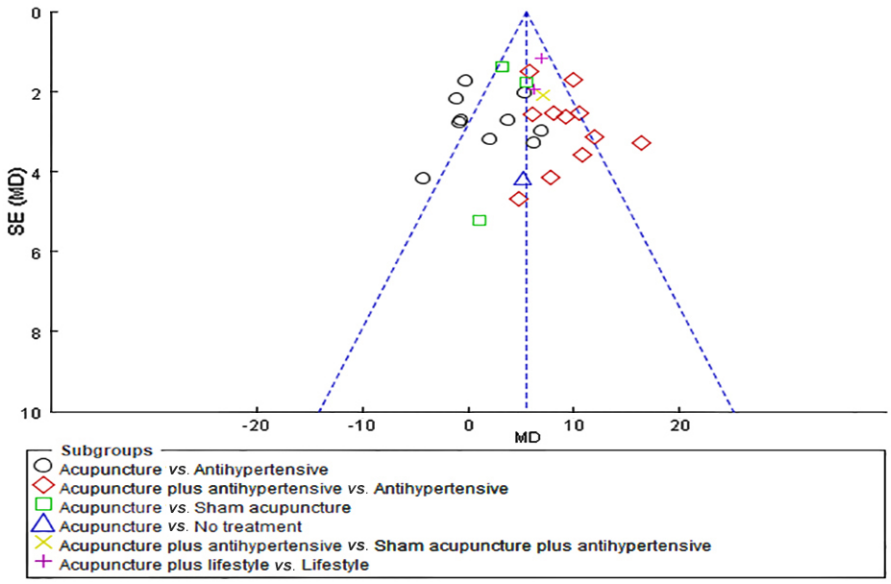


Figure 7 Forest plot of changes in the systolic blood pressure



Note: SE=Standard error; MD=Mean difference.

Figure 8 Funnel plot of changes in the systolic blood pressure

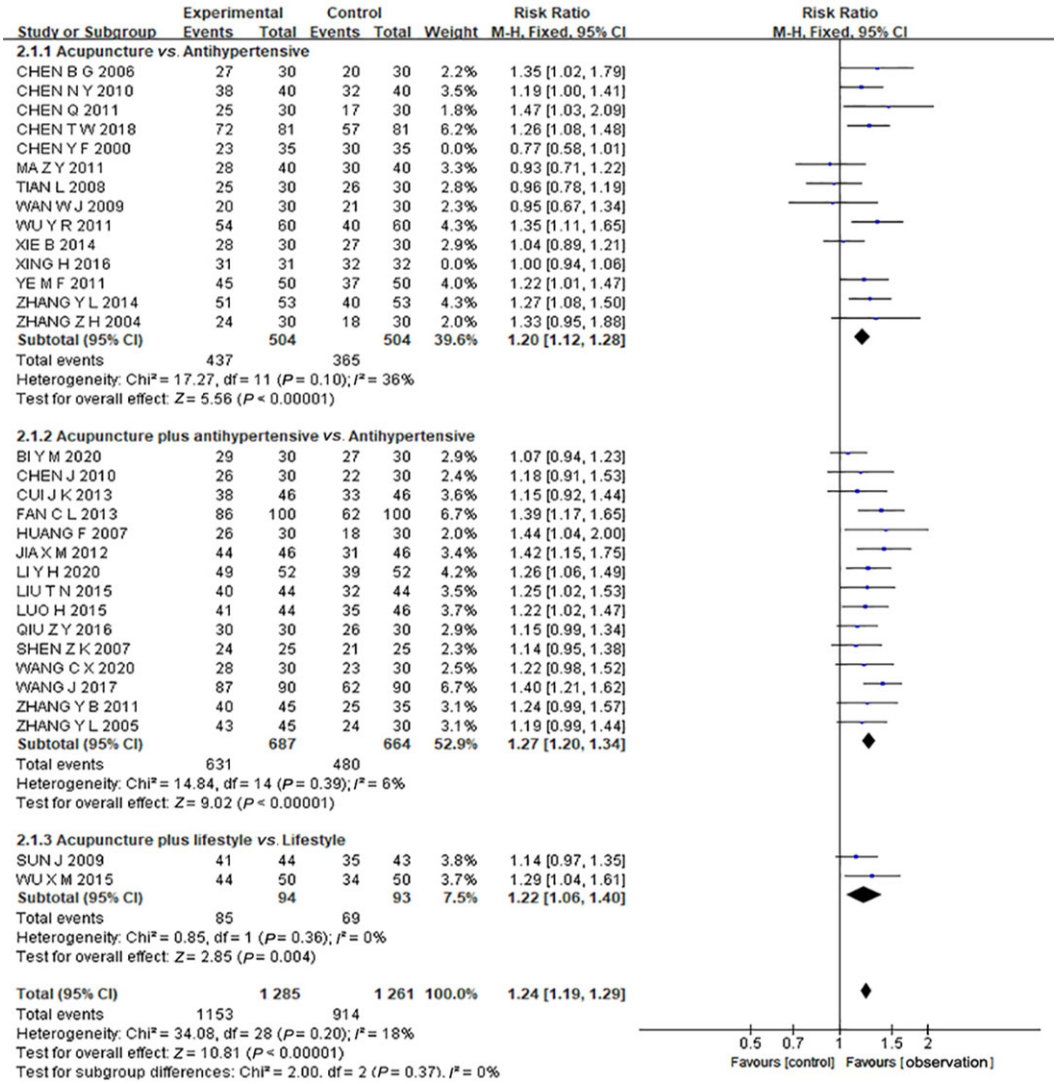
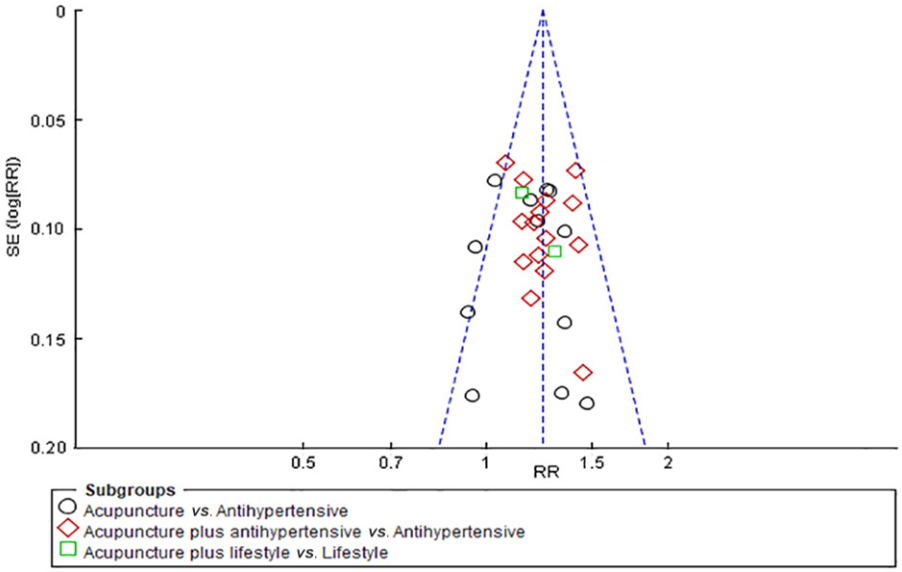


Figure 9 Forest plot of the antihypertensive efficacy rate



Note: SE=Standard error; RR=Risk ratio.

Figure 10 Funnel plot of the antihypertensive efficacy rate

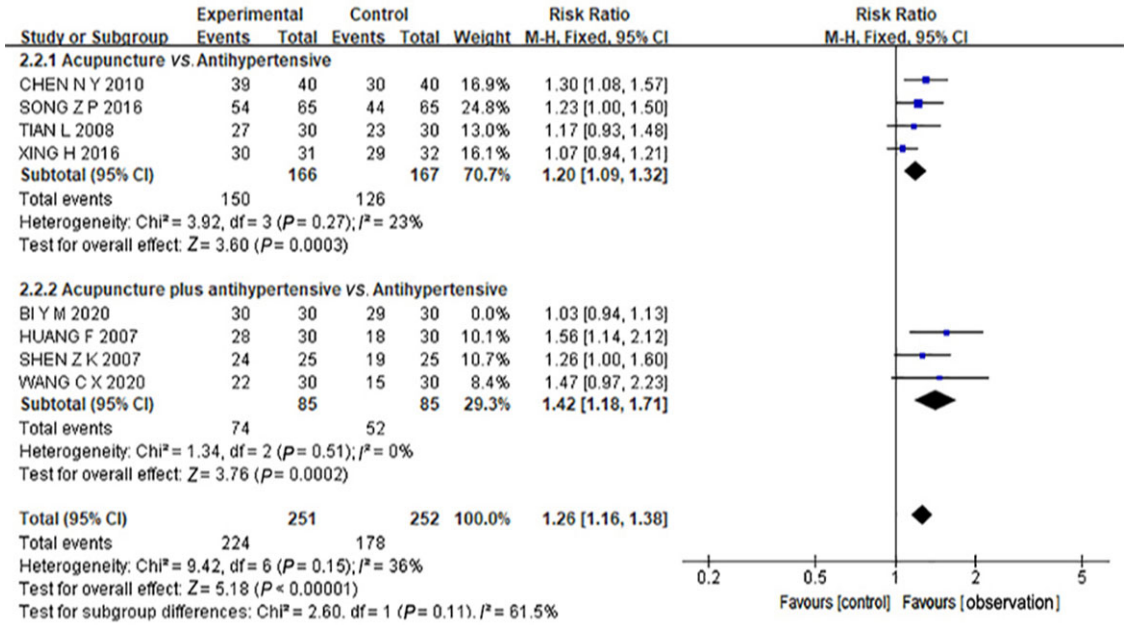


Figure 11 Forest plot of the symptom efficacy rate

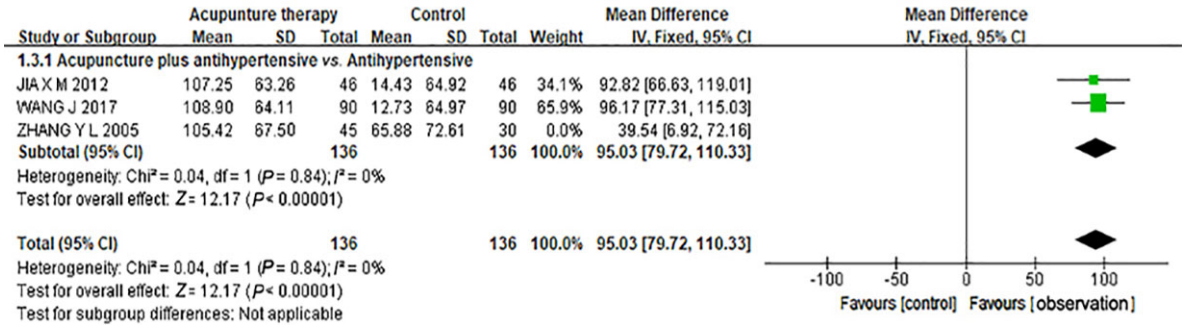


Figure 12 Forest plot of the effect on the plasma neuropeptide Y

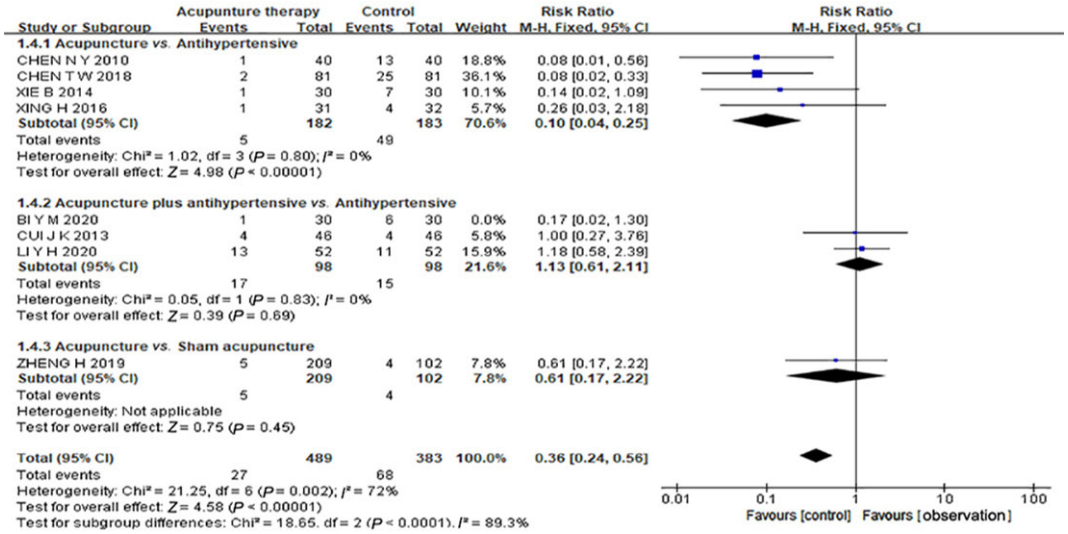


Figure 13 Forest plot of the adverse effect rate

3 Discussion

3.1 Summary of findings

In reducing blood pressure, the antihypertensive effect of acupuncture combined with antihypertensive drugs was better than that of antihypertensive drugs alone or sham acupuncture plus antihypertensive drugs. However, the effect of acupuncture alone did not show a significant advantage over antihypertensive drugs alone in reducing SBP or DBP. Regarding the antihypertensive efficacy rate, the antihypertensive efficacy in both the acupuncture alone group and acupuncture combined with antihypertensive drug group was more significant than that in the antihypertensive drug monotherapy group.

The systematic review showed that the studies had heterogeneity in reducing blood pressure. The effect of acupuncture can be affected by many factors, including the time of needle retention, treatment course, and the interval between treatments. In the included studies, the duration of acupuncture in each treatment session ranged from 10 min to 30 min, and the course of intervention went from 14 d to 3 months. Most articles did not report the interval between treatments. The minimum frequency of interventions was twice a week, and the maximum was five times a week in the included articles. The high clinical heterogeneity regarding acupuncture intervention may blame for the considerable variation in acupuncture time. In terms of the control group, high heterogeneity is attributed partly to the selection of different antihypertensive drugs. These factors may be responsible for the high heterogeneity in the blood pressure reduction effect.

According to the meta-analysis result of the symptomatic efficacy rate, the efficacy rate of acupuncture alone was better than that of antihypertensive drugs alone. But our findings showed that the symptomatic efficacy was similar between acupuncture plus antihypertensive drugs and antihypertensive drugs alone. This contradictory result implies that the symptomatic efficacy rate may not be a reasonable or adequate outcome measure for evaluating the efficacy of treating essential hypertension. Four studies[18,26,28,49] reported adverse events after treatment compared to the acupuncture alone group and the control group. The incidence of adverse events was significantly lower in the acupuncture group than in the control group, indicating one of the advantages of acupuncture in treating essential hypertension, which is a high safety rating.

Regarding the plasma NPY, acupuncture combined with antihypertensive drugs showed a stronger effect than antihypertensive drugs alone in reducing its level, and the result showed low heterogeneity in the studies. NPY is a critical vasoactive polypeptide that can raise blood pressure levels directly or indirectly[62-63]. Therefore, this indicator indirectly reflects the antihypertensive effect of acupuncture treatment.

We found that the point used most in the included studies was Quchi (LI11), followed by Taichong (LR3), Zusanli (ST36), and Fengchi (GB20). It is suggested that Quchi (LI11) may be a key point in the treatment of essential hypertension.

3.2 Strengths and limitations of this study

As one of the meta-analyses of randomized controlled trials to assess the clinical efficacy and safety of acupuncture in treating essential hypertension, this study has preliminarily confirmed that acupuncture is safe and effective for essential hypertension.

However, although the statistical results showed that the acupuncture alone group was better than the antihypertensive drugs alone group in terms of the antihypertensive efficacy rate, the description of the severity classification of hypertension in the included

RCTs was unclear, which could also result in publication biases. Besides, the risk of bias in most included RCTs was evaluated as unclear, such as selection bias, potential publication bias might exist due to the lack of methodological details, and the variable design of methodology is also a potential source of high heterogeneity in the included studies.

4 Conclusion

This study shows that acupuncture plus antihypertensive drugs should be better than using antihypertensive drugs alone in reducing SBP and DBP. In addition, either used alone or combined with antihypertensive drugs, acupuncture can produce a higher antihypertensive efficacy rate than antihypertensive drugs alone. Furthermore, a lower adverse effect rate was reported in acupuncture treatment of essential hypertension compared with antihypertensive drugs alone. Therefore, this study preliminarily proves the efficacy and safety of acupuncture therapy for essential hypertension, and it can be considered a supplementary combination therapy for this medical condition.

Conflict of Interest

Author WU Huangan is editor-in-chief of the *Journal of Acupuncture and Tuina Science*. The paper was handled by other editors and has undergone a rigorous peer review process. Author WU Huangan was not involved in the journal's review or decisions related to this manuscript.

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Authors' contributions

LU Yuqing and LI Lingjie participated in the design of this study and drafted the manuscript. LU Yuqing and WANG Zhaoqin screened the literature to determine whether the literature should be included and revised this manuscript. XU Jing and ZHONG Rui revised and edited this manuscript. HUANG Yan and ZHONG Rui checked data collection and data analysis. LIU Huirong was responsible for the statistical plan and design. WU Huangan contributed to the design of this study and critical revisions of the manuscript. CHENG Ling and WU Luyi conceived this research and were the research managers. All authors have read and approved this final manuscript.

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