



Systematic Review Oral Administration of East Asian Herbal Medicine for Peripheral Neuropathy: A Systematic Review and Meta-Analysis with Association Rule Analysis to Identify Core Herb Combinations

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Abstract: This review aimed to comprehensively assess the efficacy and safety of oral East Asian herbal medicine (EAHM) for overall peripheral neuropathy (PN). In addition, an Apriori algorithmbased association rule analysis was performed to identify the core herb combination, thereby further generating useful hypotheses for subsequent drug discovery. A total of 10 databases were searched electronically from inception to July 2021. Randomized clinical trials (RCTs) comparing EAHM with conventional analgesic medication or usual care for managing PN were included. The RCT quality was appraised using RoB 2.0, and the random effects model was used to calculate the effect sizes of the included RCTs. The overall quality of evidence was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation. By analyzing the constituent herb data, the potential association rules of core herb combinations were explored. A total of 67 RCTs involving 5753 patients were included in this systematic review. In a meta-analysis, EAHM monotherapy and combined EAHM and western medicine therapy demonstrated substantially improved sensory nerve conduction velocity, motor nerve conduction velocity, and response rate. Moreover, EAHM significantly improved the incidence rate, pain intensity, Toronto clinical scoring system, and Michigan diabetic neuropathy score. The evidence grade was moderate to low due to the substantial heterogeneity among the studies. Nine association rules were identified by performing the association rule analysis on the extraction data of 156 EAHM herbs. Therefore, the constituents of the herb combinations with consistent association rules were Astragali Radix, Cinnamomi Ramulus, and Spatholobi Calulis. This meta-analysis supports the hypothesis that EAHM monotherapy and combined therapy may be beneficial for PN patients, and follow-up research should be conducted to confirm the precise action target of the core herb.

Keywords: association rule analysis; complementary and alternative medicine; East Asian herbal medicine; meta-analysis; peripheral neuropathy; systematic review

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1. Introduction

1.1. Description of the Condition

Peripheral neuropathy (PN) is one of the most common causes for a patient to visit the clinic [1]. The prevalence of diabetic peripheral neuropathy (DPN) or herpetic neuropathy, the commonly observed PNs, is at least 10–20% [2,3]. However, it is not easy to collect the available PN epidemiological data since the causes of pathology are very diverse. In addition, the symptoms can develop not only in a single affected area, but also in multiple nerves [4]. Symptoms that may occur due to this disease include chronic pain, decreased nerve conduction velocity (NCV), sensation loss, and abnormal sensations such as tingling,



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Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations. burning, and numbness [1]. However, PN pathophysiology is not clear. Moreover, its symptoms are not easily improved and often follow a chronic course or worsen continuously [4]. Therefore, the medical management of this disease is challenging due to the various characteristics of PN, which are difficult to manage and reduce the quality of life in patients.

1.2. Description of the Intervention

Several epidemiological studies have reported that the treatment results for PN patients are unsatisfactory [5,6]. This is primarily due to the fact that accurate PN diagnosis and management are difficult, and the prognosis is poor. Moreover, it is a reminder that the development of effective medications and therapeutic tools is urgently needed. The East Asian herbal medicine (EAHM) deserves further investigation as a potential pharmacotherapy for PN since it has long been providing benefits to patients with neurological and painful disorders in Asia [7,8]. Recently, several studies have examined the safety and effectiveness of using plant preparations for neuropathy to confirm the advantages of compliance with high-dose treatment, few side effects, and safety even during long-term administration [9]. Furthermore, the number of scientific studies verifying the efficacy and safety of East Asian medicine in PN has significantly increased over the past decade [10,11]. Previous systematic reviews have comprehensively dealt with the effectiveness and safety of acupuncture interventions in East Asian medicine for treating PN [12]. However, only few systematic reviews have focused on the association between EAHM and PN subcategories, such as DPN and chemotherapy-induced peripheral neuropathy (CIPN) [13,14].

1.3. How the Intervention Might Work

Several EAHMs with pharmacological activities against PN have been reported. A previous study has reported that various herbs, including EAHM, relieve neuropathy symptoms through serotonin 5-HT1A receptors, inhibit axonal degeneration, improve axonal transport, and suppress TNF- α and NO in CIPN [15]. In contrast, the Huang–Qi–Gui–Zhi–Wu–Wu decoction, an EAHM prescription widely used for a long time, can improve CIPN by controlling the inflammatory response and repairing nerve damage [16]. Radix Astragali, one of the most extensively prescribed herbs for chronic pain, including neuropathy, acts as a potential nerve growth factor to induce axon growth in peripheral nerves and promote nerve cell differentiation. Astragaloside IV, one of the main active ingredients of Radix Astragali, contributes to sciatic nerve regeneration and functional recovery in mice [17,18].

1.4. Why It Is Important to Conduct This Review

In the past decade, numerous randomized controlled trials (RCTs) have been conducted to assess the efficacy and safety of EAHM for PN. In addition, studies on drug discovery, which can regulate neuropathic pain based on EAHM, are actively conducted [19]. Several systematic reviews have already focused on this topic [13,14,20,21]. However, unlike acupuncture, a study comprehensively reviewing the efficacy of EAHM for PN has not yet been published. In addition, the EAHM prescriptions used for the individual RCTs included in previous reviews are heterogeneous, and a single dose and composition of herbs are not often utilized. Therefore, it was difficult to derive useful pharmacological information that can be used for follow-up studies or clinical practice in a previous review. Separately, although most of the herbal medicines have been orally administered in East Asia, whether studying different formulations, such as injection or topical formulations, in one review are appropriate, is controversial.

Therefore, the aim of this study was to comprehensively assess the efficacy and safety of oral EAHM in overall PN with multiple underlying causes. Additionally, an Apriori algorithm-based association rule analysis was performed on the various herb data to identify the core herb combination, thereby further generating useful hypotheses for subsequent drug discovery.

2. Methods

This study was conducted in accordance with the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [22], as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (Supplementary Material S1) [23]. The protocol of this systematic review has been registered in PROSPERO (registration number: CRD42021252277, available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021252277, accessed on 9 October 2021).

2.1. Search Strategy

A comprehensive electronic search through four English databases (PubMed, Cochrane Library, Cumulative Index to Nursing & Allied Health Literature [CINAHL], EMBASE), four Korean databases (Korean Studies Information Service System [KISS], Research Information Service System [RISS], Oriental Medicine Advanced Searching Integrated System [OASIS], and Korea Citation Index [KCI]), one Chinese database (Chinese National Knowledge Infrastructure Database [CNKI]), and one Japanese database (CiNii) were performed from inception to July 2021 by two investigators. The following Boolean format was used for the search: (mononeuropathy [MeSH] OR nerve compression syndromes [MeSH] OR neuralgia [MeSH] OR polyneuropathies [MeSH]) AND ("neuropathy"[Title/abstract] OR "peripheral neuropathy"[Title/abstract] OR "neuropathic pain"[Title/abstract] OR "neuralgia"[Title/abstract]) AND ("Medicine, Chinese Traditional"[MeSH] OR "Medicine, Kampo"[MeSH] OR "Medicine, Korean Traditional"[MeSH] OR "Herbal Medicine"[MeSH]). In the Korean, Chinese, and Japanese databases, these search terms were appropriately modified to perform a search. The detailed search strategy has been explained in Supplementary Material S2.

2.2. Inclusion and Exclusion Criteria

2.2.1. Types of Studies

Only RCTs evaluating the efficacy and safety of oral EAHM administration for PN were included. There were no restrictions on language or publication time. A few studies were excluded if they met the following criteria: (a) Not an RCT or quasi-RCT; (b) the control group was not used or was inappropriate; (c) unrelated to PN; (d) animal studies; (e) review; and (f) not published in peer-reviewed scientific journals, including postgraduate theses or dissertations.

2.2.2. Types of Patients

All of the adults (age > 18 years) diagnosed with PN were included without restrictions on gender and nationality. The types of PN were classified into diabetic, chemotherapy-induced, postherpetic, and other causes, according to the underlying pathology.

2.2.3. Types of Interventions

All of the EAHM forms, such as decoction, granules, capsules, and a combination of EAHM and another active treatment for PN management were included. The mode of delivery was restricted to the oral intake. Studies in which East Asian medical interventions, such as acupuncture, massage or non-drug therapy, were only combined in the treatment group were excluded. Studies in which the comparators included other EAHMs were excluded. Moreover, studies that exemplify the details of herbs constituting the revealed EAHM prescriptions were excluded.

2.2.4. Types of Outcome Measurements

Primary Outcomes

NCV: Improvement in NCV measured in each body part.

Response rate: Rate of improvement or no improvement in symptoms, such as NCV, pain, numbness, tingling, and weakness.

Secondary Outcomes

Incidence rate: Occurrence rate of PN due to multiple underlying causes. Pain intensity: Intensity of PN related to pain symptoms, as measured by instruments, such as the visual analog scale (VAS) or numerical rating scale (NRS).

Toronto clinical scoring system (TCSS) [24].

Michigan diabetic neuropathy score (MDNS) [25].

Adverse events (AEs).

2.3. Data Extraction

Two review investigators (H.-G.J. and D.L.) extracted the following information: (1) First author and year of publication; (2) type of underlying cause; (3) patient characteristics, including sample size, gender distribution, age range, and disease duration; (4) intervention group; (5) control group; (6) treatment duration; (7) main outcome measures and intergroup differences; (8) AEs; and (9) detailed EAHM composition.

2.4. Risk of Bias in Individual Studies

Two review investigators (H.-G.J. and D.L.) independently evaluated the RoB of the included studies according to the revised tool for risk of bias in randomized trials, RoB 2.0 [26]. Disagreements between the two reviewers were resolved through discussion. R version 4.1.0 (R core Team (2021). R Foundations for Statistical computing, Vienna, Austria) was used with the 'robvis 'package to generate graphical presentations of biased risk assessments [27,28].

2.5. Statistical Analysis

2.5.1. Meta-Analysis

For continuous outcomes, the mean difference (MD) was calculated with a 95% confidence interval (CI). A standardized MD (SMD) of 95% CI was used to express the intervention effect when the same outcome was measured using different scales. Risk ratios or odds ratios with 95% CI were applied to represent results for dichotomous outcomes. Statistical heterogeneity across the included studies was tested using the χ^2 test and I^2 statistics. Heterogeneity was considered statistically significant when the *p*-value based on the χ^2 test was <0.10 or I^2 was \geq 50%. If heterogeneity was identified, a subgroup analysis was performed to explore the possible causes. Statistical synthesis of individual research results was performed using R version 4.1.0, with the default settings of the 'meta' package and the 'metaprop' function [29]. Only the random effects model was adopted in this review to statistically examine the results conservatively. To distinguish publication bias, a contour-enhanced funnel plot was used for the outcome, which included most of the studies [30]. For the asymmetry on the visually confirmed funnel plot, Egger's test and Begg's test were additionally performed to specifically confirm the existence of publication bias.

2.5.2. Association Rule Analysis

By analyzing the constituent herb data of EAHM collected from the included studies, the potential association rules of core herb combinations were explored. Furthermore, prior to the association rule analysis, the frequency of individual herbs used in this analysis was checked. The R studio program (version 1.4.1106; Integrated Development for R. RStudio, PBC; Boston, MA, USA) was used for the Apriori association rule analysis and plot production. A data fit was performed using the R-package "arules" and the R-package "arulesViz" was applied to generate plots and charts according to the results [31,32]. The association rule analysis according to the Apriori algorithm is a data mining method for discovering meaningful correlations between two or more components included in one event [33]. This identifies the elements that compose the data and the relationship between the elements, and is used in various types of medical research aimed at predicting the variable characteristics [34–36]. This analysis does not identify a separate cause and aims to derive a rule from a combination of characteristics without a target variable.

Support, confidence, and lift are the main metrics used to measure associations using the Apriori algorithm. The metric support evaluates the usefulness of the association rule and is the proportion of prescriptions containing a specific herb combination in the total EAHM prescription. This can be expressed as $P(A \cap B)$. The metric confidence indicates the likelihood that the consequent herb set will be included when an antecedent herb set is specified as an EAHM prescription. Therefore, support is the entire set of standard EAHM prescriptions, whereas confidence limits reference prescriptions to those that include a specific herb combination and is expressed as $P(A \cap B)/P(A) = P(B \mid A)$. The metric lift compensates for the fact that it is not known whether confidence is useful or a random result. The confidence of herbs A and B is divided by the confidence under the independent assumption that A does not affect B, and is expressed as $P(A \cap B)/P(A) \cdot P(B) = P(B \mid A)/P(B)$. When the confidence is approximately 1, herbs A and B are considered irrelevant since they are close to independence in probability. Conversely, if the lift value is large, the correlation is interpreted as strong. In this review, the association rules were identified based on the minimum values for support and confidence of 20 and 80%, respectively. Among them, the core herb combination showing the most distinct association and its constituent herbs was searched.

2.6. Quality of Evidence According to Outcome Measurements

The overall quality of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) pro [37]. The GRADE assessment evaluates the overall quality of evidence in four levels: Very low, low, moderate, and high. The level of evidence is degraded according to factors, such as risk of bias, inconsistency, indirectness, imprecision, and publication bias.

3. Results

3.1. Study Selection

A total of 903 studies were selected through an electronic database search, of which 37 duplicates were removed. After screening for titles and abstracts, 743 studies were excluded for at least one of the following reasons: (i) No clinical trial, (ii) studies unrelated to EAHM, (iii) case reports or reviews, and (iv) irrelevant to PN. A full text assessment was performed on the remaining 123 studies, and 56 studies were excluded for the following reasons: (i) No clinical trials or quasi-RCTs; (ii) no oral administration; (iii) undisclosed herb ingredients; (iv) combination of interventions other than oral administration of EAHM; (v) inappropriate control groups; (vi) not related to PN; (vii) duplicated. A total of 67 studies were identified. The screening process is summarized in Figure 1.

3.2. Study Characteristics

Four RCTs were published in English, and the rest were published in Chinese. Four studies were conducted in Japan, whereas the others were conducted in China. The etiology of PN included studies of 50 DPNs, 11 CIPNs, one HPN, one occipital neuralgia, one trigeminal neuralgia, and one supraorbital neuralgia. The sample size of the included studies ranged from 29 to 247, and a total of 5753 participants were separated into the experimental group (n = 2898) and the control group (n = 2855). The treatment duration ranged from 2 to 26 weeks. The characteristics of the included 67 studies are summarized in Table 1.



Figure 1. PRISMA 2020 flow diagram.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of Participants (Male/Female); Age (Mean ± SD)		Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		J I
Jin (2004) [38]	DPN	RCT	103(54/49) 59.4 ± 5.61 y	99(51/48) 58.81 ± 6.01 y	Tangmaitong tablets (0.5 g × 4 t, t.i.d.)	Mecobalamin tablets (500 μg, t.i.d.)	$3.31\pm1.25y$	$3.82\pm1.17~\mathrm{y}$	1. MMNCV (p > 0.05) 2. MSNCV (p < 0.01) 3. PMNCV (p < 0.05) 4. PSNCV (p < 0.01)	8 w	Trial: 1 AE/diarrhea Control: 3 AEs/abdominal pain with diarrhea
Sun (2008) [39]	DPN	RCT	30(18/12) 40–70 y	30(16/14) 43–69 y	 Ziyinbushen- huoxuetonglou fang decoction (300 mL, b.i.d.) Mecobalamin tablets (500 µg, t.i.d.) 	Mecobalamin tablets (500 μg, t.i.d.)	1–33 m	1–34 m	1. CER (<i>p</i> < 0.05)	4 w	NR
Shen (2009) [40]	DPN	RCT	50(21/29) 60 ± 4.2 y	50(27/23) 58.81 ± 6.01 y	Tangmaining capsule (4.5 g × 5 c, b.i.d.)	Mecobalamin tablets (500 μg, t.i.d.)	8.5 y	7.9 y	1. CER (p < 0.05) 2. MMNCV (p < 0.05) 3. MSNCV (p < 0.05) 4. UMNCV (p < 0.01) 5. USNCV (p < 0.01) 6. PMNCV (p < 0.05) 7. PSNCV (p > 0.05) 8. TMNCV (p > 0.05) 9. TSNCV (p < 0.01)	8 w	Trial: No AE Control: No AE

Table 1. Characteristics of the included studies.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of (Male/Fer (Mear	Participants male); Age $1 \pm$ SD)	Interven	tions	Morbidi (Mean \pm S	ity Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Lin (2010) [41]	DPN	RCT	40(22/18) median 55.6 y	40(23/19) median 54.2 y	1. Tongxinluo capsule (3 c, t.i.d.) 2. Mecobalamin tablets (500 μg, t.i.d.)	Mecobalamin tablets (500 μg, t.i.d.)	NR	NR	1. CER (p < 0.05) 2. PMNCV (p < 0.01) 3. PSNCV (p < 0.01) 4. TMNCV (p < 0.01) 5. TSNCV (p < 0.01)	4 w	NR
Wang (2010) [42]	DPN	RCT	80(45/35) 62.68 ± 7.35 y	79(43/36) 62.78 ± 7.57 y	1. Huangqiguizhi- wuwu decoction (300 mL, b.i.d.) 2. Mecobalamin injection (0.5 mg, q.d., i.m.)	Mecobalamin injection (0.5 mg, q.d., i.m.)	$7.12\pm4.25~\mathrm{y}$	$6.98\pm4.62~\mathrm{y}$	1. CER (p < 0.01) 2. MMNCV (p < 0.01) 3. MNSCV (p < 0.01) 4. PMNCV (p < 0.01) 5. PSNCV (p < 0.01)	12 w	NR
Yan (2010) [43]	DPN	RCT	14(7/7) 57.79 ± 6.73 y	15(6/9) 52.53 ± 8.0 y	Shutangluofang granule (b.i.d.)	Methylcobalamin (500 μg, t.i.d.)	ue 13.14 ± 10.58 m	$\begin{array}{c} 10.67 \pm \\ 11.14 \text{ m} \end{array}$	1. CER (<i>p</i> < 0.05)	12 w	NR
Wu (2011) [44]	DPN	RCT	30(16/14) mean 49.9 y	27(15/12) mean 48 y	Modified yiqi- huoxue decoction (300 mL, b.i.d.)	Vitamin B1 (20 mg, t.i.d.) Vitamin B6 (20 mg, t.i.d.)	mean 12 m	mean 11.4 m	1. CER (p < 0.01) 2. PMNCV (p < 0.01) 3. PSNCV (p < 0.01)	6 w	NR

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of (Male/Fer (Mean	Participants nale); Age 1 ± SD)	Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
()	tion		Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)	meannent	, and a second sec
Gao (2012) [45]	DPN	RCT	30(16/14) NR	30(17/13) NR	 Nourishing the liver to stop the wind and tongluo decoction 2. Methylcobalamine (0.5 mg, t.i.d.) 	Methylcobalamine (0.5 mg, t.i.d.)	NR	NR	1. CER (p < 0.05) 2. MMNCV (p < 0.01) 3. MSNCV (p < 0.01) 4. PMNCV (p < 0.01) 5. PSNCV (p < 0.01)	8 w	Trial: 2 AEs/nausea, upper abdominal discomfort Control: No AE
Gong (2013) [46]	DPN	RCT	60(32/28) 56.42 ± 5.28 y	60(33/27) 57.16 ± 5.34 y	1. Modified aconite decoction (400 mL, b.i.d.) 2. Methylcobalamine (500 μg, t.i.d.)	Methylcobalamine (500 μg, t.i.d.)	7.65 ± 3.84 m	7.83 ± 3.29 m	1. CER ($p < 0.05$) 2. PMNCV ($p < 0.01$) 3. PSNCV ($p > 0.05$)	30 d	Trial: No AE Control: No AE
Han (2013) [47]	DPN	RCT	31(17/14) 54.2 ± 9.6 y	31(16/15) 55.3 ± 10.1 y	1. Modified huangqiguizhi- wuwu decoction (400 mL, b.i.d.) 2. Methylcobalamine (0.5 mg, t.i.d.)	Methylcobalamine (0.5 mg, t.i.d.)	NR	NR	1. CER (<i>p</i> < 0.05)	8 w	Trial: No AE Control: No AE
Zhang (2013a) [48]	DPN	RCT	30(16/14) 54.32 ± 7.14 y	30(15/15) 56.24 ± 7.40 y	 Mudan tong luo fang (b.i.d.) α-Lipoic acid injection (600 mg, q.d., i.v. drip) 	α-Lipoic acid injection (600 mg, q.d., i.v. drip)	8.3 ± 1.67 y	$8.5\pm1.54~\mathrm{y}$	1. CER (p < 0.05) 2. MMNCV (p < 0.05) 3. MSNCV (p < 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05)	3 w	NR

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of Participants (Male/Female); Age (Mean ± SD)		Interver	ntions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0 -	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		<i>v</i> .
Zhang (2013b) [49]	DPN	RCT	30 Total 60(36/14) 56 ± 8 y	30 Total 60(36/14) 56 ± 8 y	Tang bao kang (20 pills, t.i.d.)	1. Methyl- cobalamine (500 μg, t.i.d.) 2. Vitamin B1 (30 mg, t.i.d.) 3. Vitamin B6 (30 mg, t.i.d.)	Total 5–10 y	Total 5–10 y	1. CER (p < 0.01) 2. MMNCV (p < 0.01) 3. MSNCV (p < 0.01) 4. UMNCV (p < 0.01) 5. USNCV (p < 0.01) 6. PMNCV (p < 0.01) 7. PSNCV (p < 0.01)	24 w	Trial: No AE Control: 1 AE/skin rash
Guo (2014) [50]	DPN	RCT	32(19/13) 64.78 ± 8.90 y	32(15/17) 65.59 ± 8.35 y	 Modified huangqiguizhi- wuwu decoction (b.i.d.) Mecobalamin tablets (0.5 mg, t.i.d.) 3. Gabapentin (600 mg, t.i.d.) 	1. Mecobalamin tablets (0.5 mg, t.i.d.) 2. Gabapentin (600 mg, t.i.d.)	NR	NR	1. CER (<i>p</i> < 0.01) 2. VAS (<i>p</i> < 0.05)	8 w	NR
Yang (2014a) [51]	DPN	RCT	60(35/25) 51.30 ± 6.03 y	60(37/23) 51.26 ± 5.38 y	 Shenqixuebi feng (b.i.d.) α-Lipoic acid injection (0.3 g, q.d., i.v. drip) Mecobalamin injection (0.5 mg, q.d., i.v. drip) 	 α-Lipoic acid injection (0.3 g, q.d., i.v. drip) 2. Mecobalamin injection (0.5 mg, q.d., i.v. drip) 	3.65 ± 1.12 y	3.36 ± 1.18 y	1. CER (<i>p</i> < 0.05)	4 w	NR

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design	Number of (Male/Fer (Mean	Participants nale); Age \pm SD)	Intervent	tions	Morbidi (Mean \pm Sl	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion		Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Yang (2014b) [52]	DPN	RCT	36(23/13) 47.8 ± 8.3 y	36(20/16) 46.5 ± 8.1 y	1. Modified huangqiguizhi- wuwu decoction (200 mL, q.d.) 2. Methylcobalamine injection (500 μg, q.d., i.m.)	1. Methyl- cobalamine injection (500 μg, q.d., i.m.)	4.1 ± 1.3 m	3.9 ± 1.4 m	1. CER (<i>p</i> < 0.05)	4 w	NR
Qi (2015) [53]	DPN	RCT	32(17/15) 53.2 ± 7.1 y	32(16/16) 52.4 ± 7.0 y	1. Mudan granule (7 g, t.i.d.) 2. 0.9% Sodium chloride 200 mL and α -Lipoic acid injection (450 mg, q.d., i.v. drip)	1. 0.9% Sodium chloride 200 mL and αLipoic acid injection (450 mg, q.d., i.v. drip)	$2.3\pm2.1~\mathrm{y}$	$2.6\pm1.9~\text{y}$	1. CER (<i>p</i> < 0.05) 2. PMNCV (<i>p</i> < 0.01) 3. PSNCV (<i>p</i> < 0.01)	4 w	Trial: No AE Control: No AE
Wang (2015) [54]	DPN	RCT	40(20/20) mean 68.5 y	40(23/17) mean 71.2 y	1. yinxinshu capsule (3 c, t.i.d.) 2. Maixuekang capsule (3 c, t.i.d.)	1. Oryzanol (20 mg, t.i.d.) 2. Vitamin B1 (10 mg, t.i.d.) 3. Adenosyl- cobalamin (1 mg, t.i.d.)	10–12 у	10–12 у	1. CER (<i>p</i> < 0.05)	4 w	Trial: No AE Control: No AE

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of Participants (Male/Female); Age (Mean \pm SD)		Interven	tions	Morbidi (Mean \pm Sl	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion		Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Xue (2015) [55]	DPN	RCT	42(23/19) 36–78 y	42(22/20) 35–78 y	1. Modified liutengshuilushex- ian decoction (150 mL, q.d.)	1. Methyl- cobalamine tablet (0.5 mg, t.i.d.)	28–73 d	30–73 d	1. CER (p < 0.01) 2. MSNCV (p < 0.01) 3. TSNCV (p < 0.01) 4. PSNCV (p < 0.01)	3 w	Trial: No AE Control: No AE
Ding (2016) [56]	DPN	RCT	30(12/18) 55.16 ± 11.78 y	30(16/14) 54.97 ± 12.05 y	 Buyanghuanwu decoction (b.i.d.) 2. Methylcobalamine (0.5 mg t.i.d.) Alprostadil injection (10 ug, q.d., i.v.) α-Lipoic acid injection (0.3 mg, q.d., i.v. drip) 	 Methyl- cobalamine (0.5 mg, t.i.d.) Alprostadil injection (10 ug, q.d., i.v.) α-Lipoic acid injection (0.3 mg, q.d., i.v. drip) 	$7.51\pm2.12~\mathrm{y}$	$6.59\pm1.91~\mathrm{y}$	1. MDNS (<i>p</i> < 0.05)	8 w	NR
Guo (2016) [57]	DPN	RCT	51(26/25) 69.54 ± 5.06 y	51(28/23) 69.78 ± 5.96 y	1. Qitengtongluo decoction (b.i.d.) 2. Epalrestat (50 mg, 1 t, t.i.d.)	1. Epalrestat (50 mg, 1 t, t.i.d.)	$1.91\pm2.09~\mathrm{y}$	$6.59\pm1.91~\mathrm{y}$	1. CER (p < 0.05) 2. NCSS (p < 0.05) 3. MSNCV (p < 0.05) 4. TSNCV (p < 0.05) 5. PMNCV (p < 0.05) 6. PSNCV (p < 0.05)	12 w	NR

Table 1. Cont.

First Author	Type of Condi-	Trial	Number of (Male/Fer (Mean	Participants nale); Age \pm SD)	Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of	Adverse Event
(ieui) [itererence]	tion	Design	Trial	Control	Trial	ControlTrialControl p -Valuation.gluo cine1.Mecobalamin tablets 2.4 ± 1.2 y 2.6 ± 1.3 y1. CE ($p < 0.$.in(500 µg, t.i.d.)	<i>p</i> -Value)	meatment	(Cube/Symptom)		
Han (2016) [58]	DPN	RCT	20(12/8) 54.3 ± 7.2 y	20(11/9) 53.7 ± 6.8 y	1. Zhanjin tongluo chinese medicine (b.i.d.) 2. Mecobalamin tablets (500 μg, t.i.d.)	1. Mecobalamin tablets (500 μg, t.i.d.)	$2.4\pm1.2~\mathrm{y}$	$2.6\pm1.3~\mathrm{y}$	1. CER (<i>p</i> < 0.05)	4 w	NR
Lan (2016) [59]	DPN	RCT	54 Other information NR	54 Other information NR	yiqihuoxue tongluo capsule (1.2 g, t.i.d.)	Epalrestat tablets (50 mg, t.i.d.)	NR	NR	1. CER ($p < 0.05$) 2. PMNCV ($p < 0.05$) 3. SSNCV ($p < 0.05$)	12 w	Trial: No AE Control: No AE
Mo (2016) [60]	DPN	RCT	$\begin{array}{c} 33(19/14) \\ 65.28 \pm \\ 9.098 \mathrm{y} \end{array}$	$\begin{array}{c} 32(17/15) \\ 62.34 \pm \\ 8.168 \text{ y} \end{array}$	yangyinjiedude- coction (300 mL, b.i.d.)	Methylcobalamine (0.5 mg t.i.d.)	^е 2–23 у	2–19 y	1. CER (<i>p</i> < 0.01)	8 w	NR
Wang (2016) [61]	DPN	RCT	124(72/52) 57.3 ± 6.8 y	103(58/45) 58.1 ± 7.2 y	Modified tangbitong feng (150 mL, b.i.d.)	No treatment	$22.1\pm5.4~\text{m}$	$23.5\pm4.8~\text{m}$	1. CER (<i>p</i> < 0.01)	8 w	Trial: No AE Control: No AE
Li (2016a) [62]	DPN	RCT	30(18/12) 49.6 ± 5.6 y	30(17/13) 50.3 ± 5.4 y	1. Wenyanghuox- uetongbi feng (b.i.d.) 2. Methylcobalamine (0.5 mg, t.i.d.)	1. Methyl- cobalamine (0.5 mg, t.i.d.)	$18.21 \pm 12.37 \text{ m}$	17.97 ± 12.54 m	1. CER (p < 0.01) 2. TSNCV (p < 0.01) 3. SSNCV (p < 0.05) 4. PSNCV (p < 0.05)	8 w	Trial: No AE Control: No AE
Zhang (2016a) [63]	DPN	RCT	48(26/22) 54.6 y	48(28/20) 55.2 y	 Huangichifeng decoction combined Dangguisini decoction (q.d.) 2. Methylcobalamine injection (500 μg, q.d., i.m.) 	1. Methyl- cobalamine injection (500 μg, q.d., i.v.)	2.8 y	3.2 у	1. CER (p < 0.01) 2. MSNCV (p < 0.01) 3. USNCV (p < 0.01) 4. PMNCV (p < 0.01) 5. TMNCV (p < 0.01)	4 w	NR

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of Participants (Male/Female); Age (Mean \pm SD)		Intervent	ions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of	Adverse Event
(Year) [Reference]	tion	Design	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)	Treatment	(Case/Symptom)
Li (2016b) [64]	DPN	RCT	60(37/23) 57 y	60(35/25) 56 y	Huangzhitongnaoluo capsule (3 c, t.i.d.)	Mecobalamin dispersible tablets (500 mg, t.i.d.)	1–13 y	1–12 y	1. CER ($p < 0.05$) 2. MSNCV ($p < 0.05$) 3. TMNCV ($p < 0.05$)	12 w	NR
Zhang (2016b) [65]	DPN	RCT	60(36/24) 55.3 ± 6.4 y	60(35/25) 55.6 ± 5.5 y	 Qiming granule (4.5 g, t.i.d.) Nimodipine injection (8 mg, q.d., i.v. drip) 	1. Nimodipine injection (8 mg, q.d., i.v. drip)	$2.0\pm1.1~\text{y}$	$2.2\pm1.0~\mathrm{y}$	1. CER (p < 0.01) 2. MMNCV (p < 0.01) 3. MSNCV (p < 0.01) 4. UMNCV (p < 0.05) 5. USNCV (p < 0.01) 6. TMNCV (p < 0.05) 7. TSNCV (p < 0.01)	12 w	Trial: No AE Control: 1 AE/mild dizziness
Chen (2017) [66]	DPN	RCT	$\begin{array}{c} 30(14/16) \\ 38.72 \pm \\ 20.02 \ \mathrm{y} \end{array}$	30(13/17) 39.11 ± 19.57 y	Dagguisini decoction (300 mL, b.i.d.)	Epalrestat capsule (50 mg, t.i.d.)	$4.32\pm2.05~\mathrm{y}$	$4.20\pm2.01~\text{y}$	1. CER ($p < 0.05$) 2. TCSS ($p < 0.05$)	12 w	Trial: No AE Control: No AE
Shi (2017) [67]	DPN	RCT	32(20/12) 38.7 ± 8.1 y	32(22/10) $40.3 \pm 10.1 \text{ y}$	Fufang danshen dripping pill (10 pills, t.i.d.)	1. Methyl- cobalamine (0.5 mg, t.i.d.) 2. Epalrestat (50 mg, t.i.d.)	$3.87\pm1.5~\mathrm{y}$	$3.69\pm1.3~\mathrm{y}$	1. TSNCV (<i>p</i> < 0.01)	15 w	NR

Table 1. Cont.

First Author Type (Year) [Reference] tio	Type of Condi-	Trial Design	Number of (Male/Fer (Mean	Participants male); Age $1 \pm$ SD)	Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of	Adverse Event (Case/Symptom)
(ieui) [itererence]	tion	Design	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)	meatment	(Cube, by hip toni)
Wang (2017) [68]	DPN	RCT	30(15/15) 58.76 ± 4.32 y	30(16/14) 57.21 ± 3.56 y	Dangguisini decoction (200 mL, b.i.d.)	Mecobalamin tablets (500 μg, t.i.d.)	$3.56\pm1.21~\text{y}$	$3.84\pm1.36~\mathrm{y}$	1. CER (p < 0.05) 2. MMNCV (p > 0.05) 3. MSNCV (p > 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05) 6. TMNCV (p < 0.05) 7. TSNCV (p < 0.05)	8 w	NR
Chen (2018) [69]	DPN	RCT	$\begin{array}{c} 40(19/21)\\ 55.8\pm4.7~\mathrm{y} \end{array}$	40(20/20) 56.2 ± 2.8 y	 Dangguisinin decoction (b.i.d.) Mecobalamin tablets (500 μg, t.i.d.) 	Mecobalamin tablets (500 μg, t.i.d.)	$3.6\pm1.8~\mathrm{y}$	$2.4\pm2.1~\text{y}$	1. CER (<i>p</i> < 0.05)	4 w	Trial: 2 AEs/skin rash, gastrointestinal discomfort Control: 3 AEs/diarrhea (2), skin rash
Dai (2018) [70]	DPN	RCT	40 45–85 y Other information NR	40 45–85 y Other information NR	Modified huangqiguizhi- wuwu decoction (500 mL, b.i.d.)	Epalrestat capsule (50 mg, t.i.d.)	NR	NR	1. CER (p < 0.05) 2. UMNCV (p < 0.05) 3. USNCV (p < 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05)	3 w	NR
Hu (2018) [71]	DPN	RCT	31(13/18) 55.45 ± 11.52 y	31(15/16) 53.76 ± 2.03 y	1. Modified Jiajianhuangqigu- izhiwuwu decoction (200 mL, b.i.d.) 2. Methylcobalamine (0.5 mg, t.i.d.)	1. Methyl- cobalamine tablet (0.5 mg, t.i.d.)	$7.13\pm2.01~\mathrm{y}$	$6.52\pm1.95~\mathrm{y}$	1. CER (p < 0.05) 2. SMNCV (p < 0.05) 3. SSNCV (p < 0.05) 4. MDNS (p < 0.05)	8 w	NR

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design	Number of Participants (Male/Female); Age (Mean ± SD)		Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Huang (2018) [72]	DPN	RCT	120(52/68) 51.3 ± 11.4 y	120(51/69) 50.9 ± 11.6 y	Matong powder (7 g, t.i.d.)	Methylcobalami tablet (0.5 mg, t.i.d.)	ne 8.92 ± 8.6 m	8.97 ± 8.5 m	1. CER (p < 0.05) 2. PMNCV (p < 0.05) 3. TSNCV (p < 0.05) 4. SSNCV (p < 0.05)	8 w	Trial: 3 AEs/ Abdominal bloating with anorexia (3) Control: 2 AEs/Abdominal bloating with anorexia (2)
She (2018) [73]	DPN	RCT	30(18/12) 63.35 ± 7.12 y	30(17/13) 65.13 ± 6.21 y	 Huangqiguizhi- wuwu granule (b.i.d.) Mecobalamin tablet (1 mg, t.i.d.) 	Mecobalamin tablet (1 mg, t.i.d.)	$3.31\pm2.06~\mathrm{y}$	$3.82\pm1.97~\mathrm{y}$	1. CER (<i>p</i> < 0.05) 2. TCSS (<i>p</i> < 0.05)	6 w	NR
Xin (2018) [74]	DPN	RCT	30 Total 60(36/24) 55.3 y	30 Total 60(36/24) 55.3 y	1. Mongolian medicine garidi-13 weiwan (3 g, q.d.)	Mecobalamin tablet (0.5 mg, t.i.d.)	Total 4.2 y	Total 4.2 y	1. CER (<i>p</i> < 0.05)	4 w	NR
Gao (2019) [75]	DPN	RCT	50(26/24) $60.83 \pm$ 5.26 y	50(25/25) 61.17 ± 6.05 y	1. Modified shengmaisan (300 mL, b.i.d.) 2. Mecobalamin tablet (500 μg, t.i.d.)	Mecobalamin tablet (500 μg, t.i.d.)	$3.82\pm1.04~\mathrm{y}$	3.77 ± 1.12 y	1. CER (p < 0.05) 2. MDNS (p < 0.01) 2. MMNCV (p > 0.05) 3. MSNCV (p > 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05) 6. TMNCV (p < 0.05) 7. TSNCV (p < 0.05)	8 w	Trial: No AE Control: No AE

Table 1. Cont.

First Author Type c (Year) [Reference] tion	Type of Condi-	Trial Design	Number of (Male/Fer (Mean	Participants male); Age $1 \pm$ SD)	Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
(1011) [1101010100]	tion	8	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)	ireatificati	()
Wu (2019) [76]	DPN	RCT	30(16/14) 57.60 ± 7.20 y	30(16/14) 57.03 ± 7.63 y	Taohongsiwu decoction (t.i.d.)	Epalrestat tablet (50 mg, t.i.d.)	4.3 y	4.3 y	1. CER ($p < 0.05$) 2. MSNCV ($p < 0.05$) 3. PSNCV ($p < 0.05$)	4 w	Trial: No AE Control: No AE
Yi (2019) [77]	DPN	RCT	60(31/29) 61.36 ± 4.37 y	60(29/31) 61.53 ± 4.64 y	Mongolian medicine zhenbo pill (0.2 g × 15 p, b.i.d.)	α-Lipoic acid tablet (0.3 g × 2 c, q.d.)	$8.23\pm3.21~\mathrm{y}$	$8.23\pm3.12~\mathrm{y}$	1. MDNS (p < 0.05) 2. MMNCV (p < 0.05) 3. MSNCV (p < 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05)	24 w	Trial: 5 AEs/nausea (2), anorexia (3) Control: 6 AEs/ nausea (2), gastric pain (2)
Ji (2019) [78]	DPN	RCT	$\begin{array}{c} 54(32/22)\\ 54.47\pm\\ 9.81\ \mathrm{y}\end{array}$	53(33/20) 54.81 ± 9.44 y	1. yangyinzhuyu decoction (150 mL, b.i.d.) 2. Epalrestat tablet (50 mg, t.i.d.)	Epalrestat tablet (50 mg, t.i.d.)	$10.24 \pm 3.08 \text{ y}$	10.53 ± 2.66 y	1. CER (<i>p</i> < 0.05)	90 d	Trial: No AE Control: No AE
Liu (2019a) [79]	DPN	RCT	40 Other information NR	40 Other information NR	 Shengjinsan combined Taohongyin (200 mL, b.i.d.) Mecobalamin tablet (500 mg, t.i.d.) 	Mecobalamin tablet (500 mg, t.i.d.)	NR	NR	1. MMNCV (p < 0.05) 2. MSNCV (p < 0.05) 3. TMNCV (p < 0.05) 4. TSNCV (p < 0.05)	4 w	NR
Liu (2019b) [80]	DPN	RCT	45(27/18) 58.77 ± 4.26 y	45(26/19) 59.46 ± 4.77 y	 Huangqiguizhi- wuwu decoction (400 mL, b.i.d.) Epalrestat tablets (t.i.d.) Mecobalamin tablet (t.i.d.) 	1. Epalrestat tablets (t.i.d.) 2. Mecobalamin tablet (t.i.d.)	3.28 ± 1.45 m	3.31 ± 1.13 m	1. CER (<i>p</i> < 0.05)	8 w	NR

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design _	Number of Participants (Male/Female); Age (Mean \pm SD)		Interven	tions	Morbidi (Mean \pm S	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	U	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Chen (2021) [81]	DPN	RCT	28(15/13) 57.2 ± 8.1 y	29(16/13) 56.5 ± 7.6 y	 Zicuijuanbi decoction (150 mL, b.i.d.) Normal saline injection (250 mL, i.v.) 	1. gabapentin capsule (0.3 g, t.i.d.) 2. Normal saline injection (250 mL, i.v.)	$\begin{array}{c} 15.57 \pm \\ 3.68 \ \mathrm{y} \end{array}$	$\begin{array}{c} 14.59 \pm \\ 4.35 \ y \end{array}$	1. VAS ($p < 0.05$) 2. PSNCV ($p < 0.05$) 3. CER ($p < 0.05$)	10 w	NR
Hou (2021) [82]	DPN	RCT	39(24/15) 56.74 ± 11.79 y	28(18/10) 55.83 ± 10.60 y	Jiuchongdan (40 pills, t.i.d.)	Mecobalamin tablet (500 μg, t.i.d.)	$15.28 \pm 11.23 \text{ m}$	$16.72 \pm 10.96 \text{ m}$	1. CER (p < 0.05) 2. PSNCV (p < 0.05) 3. MSNCV (p < 0.05) 4. USNCV (p < 0.05)	12 w	NR
Jin (2021) [83]	DPN	RCT	51(NR) 64.36 ± 7.08 y	53(NR) 62.23 ± 7.32 y	Shenxiezhitoing capsule (3 c, t.i.d.)	α-Lipoic acid tablet (0.3 g × 2 t, q.d.)	173.48 ± 84.97 m	145.67 ± 70.68 m	1. TCSS ($p < 0.01$) 2. VAS ($p < 0.05$)	12 w	NR
Li (2021) [84]	DPN	RCT	41(22/19) 59.81 ± 5.63 y	41(23/18) 60.20 ± 5.62 y	1. Huangqiguizhi- wuwu decoction (200 mL, t.i.d.) combined Mudan granule (7 g, t.i.d.) 2. Mecobalamin tablet (500 mg, t.i.d.)	1. Mecobalamin tablet (500 mg, t.i.d.)	$3.15\pm0.45~y$	$3.12\pm0.43~\mathrm{y}$	1. CER (p < 0.05) 2. MMNCV (p < 0.05) 3. MSNCV (p < 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05)	8 w	Trial: 5 AEs/diarrhea (1), nausea (1), constipation (2), dizziness (1) Control: 1 AE/ nausea (1)

Table 1. Cont.

First Author (Year) [Reference]	Type of Condi-	Trial Design	Number of (Male/Fer (Mean	Participants nale); Age 1 ± SD)	Interventions		Morbidity Period (Mean \pm SD or Range)		Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Wang (2021a) [85]	DPN	RCT	30(16/14) 64.63 ± 4.72 y	30(17/13) 64.71 ± 4.68 y	1. yiqiyangyin- tongluo decoction (200 mL, b.i.d.) 2. Epalrestat tablets (50 mg, t.i.d.)	1. Epalrestat tablets (50 mg, t.i.d.)	$6.14\pm1.24~\mathrm{y}$	$6.12\pm1.22~\mathrm{y}$	1. CER (<i>p</i> < 0.05) 2. TCSS (<i>p</i> < 0.05)	12 w	NR
Wang (2021b) [86]	DPN	RCT	50(34/16) 67.13 ± 6.29 y	50(32/18) 67.13 ± 6.29 y	1. Taohongsiwu decoction (b.i.d.) 2. Mecobalamin capsule (0.5 mg, t.i.d.)	1. Mecobalamin capsule (0.5 mg, t.i.d.)	$1.57\pm0.51~\mathrm{y}$	$1.42\pm0.83~\mathrm{y}$	1. TCSS (p < 0.05) 2. MMNCV (p < 0.05) 3. MSNCV (p < 0.05) 4. PMNCV (p < 0.05) 5. PSNCV (p < 0.05) 6. TMNCV (p < 0.05) 7. TSNCV (p < 0.05)	4 w	NR
Zhang (2021) [87]	DPN	RCT	74 Total 148(78/70) 59.64 ± 8.94 y	74 Total 148(78/70) 59.64 ± 8.94 y	 Buqizhitoing decoction (b.i.d.) α-Lipoic acid injection (0.6 g, q.d.) combined 0.9% Sodium chrolide injection (250 mL, q.d.) 	1. α-Lipoic acid injection (0.6 g, q.d.) combined 0.9% Sodium chloride injection (250 mL, q.d.)	Total 9.33 ± 1.25 y	Total 9.33 ± 1.25 y	1. TSNCV ($p < 0.05$) 2. PSNCV ($p < 0.05$) 3. TCSS ($p < 0.05$) 4. NRS ($p < 0.05$)	8 w	NR
Nishioka (2011) [88]	CIPN	RCT	22(14/8) 67(48–77)	23(8/15) 65(52–80)	Goshajinkigan (2.5 g, t.i.d.)	No treatment	NR	NR	Incidence rate (p-value NR)	20 course chemother- apy	Adverse events unrelated to EAHM were reported.
Huang (2013) [89]	CIPN	RCT	$\begin{array}{c} 30(17/13) \\ 62.30 \pm \\ 8.29 \text{ y} \end{array}$	$\begin{array}{c} 31(21/10) \\ 60.00 \pm \\ 8.88 \mathrm{y} \end{array}$	yiqiwenjingyangx- uehuoxue recipe (200 mL, b.i.d.)	No treatment	NR	NR	Incidence rate $(p < 0.05)$	4 w	NR

Table 1. Cont.

First Author (Year) [Reference]		of Trial li- Design	Number of (Male/Fer (Mean	Participants nale); Age \pm SD)	Interven	Interventions		ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		, , , , , , , , , , , , , , , , , , ,
Abe (2013) [90]	CIPN	RCT	33(NR) median 58(35–70)	27(NR) median 55(33–69)	Goshajinkigan (2.5 g, b.i.d. or t.i.d.)	Mecobalamin tablet (500 μg, t.i.d.)	NR	NR	Incidence rate (p < 0.01) 2. VAS (p < 0.01)	18 w	Adverse events unrelated to EAHM were reported.
Kono (2013) [91]	CIPN	RCT	44(23/21) median 67(40–88)	45(25/20) median 61(36–82)	Goshajinkigan (2.5 g, b.i.d. or t.i.d.)	Placebo	NR	NR	Incidence rate (p-value NR)	26 w	Adverse events unrelated to EAHM were reported.
Li (2013) [92]	CIPN	RCT	30(9/21) 52.1 ± 11.50 y	45(25/20) 54.4 ± 11.09	Rongjin fang decoction (200 mL, b.i.d.)	Glutathione injection (1500 mg/m ² , q.d., i.v. drip)	$9.1 \pm 2.42 \mathrm{m}$	$8.3\pm3.02m$	Incidence rate (<i>p</i> < 0.005)	24 w	Adverse events unrelated to EAHM were reported.
Oki (2015) [93]	CIPN	RCT	$\begin{array}{c} 89(48/41) \\ 62.4 \pm 10.6 \text{ y} \end{array}$	$93(51/42) \\ 60.4 \pm 11.5 \text{ y}$	Goshajinkigan (2.5 g, b.i.d. or t.i.d.)	Placebo	NR	NR	Incidence rate $(p < 0.05)$	12 course chemother- apy	Adverse events unrelated to EAHM were reported.
Xu (2017) [94]	CIPN	RCT	34(19/15) 52.4 ± 8.1 y	34(20/14) 51.8 ± 7.6 y	Modified huangqiguizhi- wuwu decoction (b.i.d.)	Mecobalamin tablet (500 μg, t.i.d.)	NR	NR	Incidence rate (p < 0.05)	4 course chemother- apy/56d	NR
Xie (2018) [95]	CIPN	RCT	30(16/14) 57.92 ± 7.33 y	30(17/13) 58.97 ± 6.20 y	1. yiqihuoxue decoction (500 mL, t.i.d.) 2. Duloxetine (30 mg, t.i.d.) 3. Gabapentine (600 mg, t.i.d.)	1. Duloxetine (30 mg, t.i.d.) 2. Gabapentine (600 mg, t.i.d.)	27.65 ± 9.06 d	28.16 ± 7.53 d	1. CER ($p < 0.05$) 2. MMNCV ($p < 0.05$) 3. MSNCV ($p < 0.05$)	12 w	NR

Table 1. Cont.

First Author Type of (Year) [Reference] tion		Trial Design	Number of (Male/Fer (Mean	Participants male); Age $1 \pm$ SD)	Interven	tions	Morbidi (Mean \pm Sl	ty Period D or Range)	Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
()	tion		Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)	meutificiti	, i i i i j i i i i i i i i i i i i i i
Liu (2018) [96]	CIPN	RCT	41(25/16) 62.54 ± 7.86 y	$\begin{array}{c} 41(22/19) \\ 61.69 \pm \\ 8.34 y \end{array}$	yiqiwenyang- tougluo decoction (300 mL, b.i.d.)	Amifostine injection (500 mg/m ² , i.v. drip)	NR	NR	1. Incidence rate $(p < 0.05)$ 2. MMNCV (p < 0.05) 3. MSNCV (p > 0.05) 4. SMNCV (p < 0.05) 5. SSNCV (p > 0.05)	24 w	NR
Zhang (2018) [97]	CIPN	RCT	40(24/16) 56.27 ± 9.22 y	$\begin{array}{c} 40(23/17) \\ 56.80 \pm \\ 9.42 \ \mathrm{y} \end{array}$	Self-prescribed herbal medicine No treatmen (q.d.)		NR	NR	Incidence rate (p < 0.05)	4 course chemother- apy/4 w	NR
Liu (2020) [98]	CIPN	RCT	$\begin{array}{c} 40(28/12) \\ 56.2 \pm 8.4 \ y \end{array}$	$\begin{array}{c} 42(30/12) \\ 52.8 \pm 10.5 \ y \end{array}$	Bushenhuoxue herbal medicine (b.i.d.) Dexamethasone injection (40 mg, i.v. drip)		NR	NR	Incidence rate ($p < 0.05$)	6 course chemother- apy/18 w	NR
Li (2016c) [99]	PHN	RCT	25(12/13) 58.31 ± 7.95 y	25(13/12) 58.31 ± 8.11 y	Self-prescribed Jingdutongluo decoction (t.i.d.)		7.52 ± 2.16 m	7.58 ± 2.38 m	1. CER ($p < 0.05$) 2. VAS ($p < 0.05$)	4 w	NR
Zhang (2012) [100]	PHN	RCT	30(16/14) median 58.32 y	30(17/13) median 59.38 y	Modified chushiweiling decoction (b.i.d.)	1. Vitamin B1 (10 mg, t.i.d.) 2. Mecobalamin tablet (0.5 mg, t.i.d.)	6.8 d	7.5 d	1. CER (<i>p</i> < 0.05) 2. VAS (<i>p</i> < 0.05)	4 w	Trial: No AE Control: No AE

Table 1. Cont.

First Author (Year) [Reference]		of Trial ⁱ⁻ Design	Number of Participants (Male/Female); Age (Mean ± SD)		Interventions		Morbidity Period (Mean \pm SD or Range)		Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	0	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		, , , , , , , , , , , , , , , , , , ,
Zhao (2018) [101]	PHN	RCT	47(29/18) 48.2 ± 9.4 y	46(24/22) 48.5 ± 9.6 y	Shuganzhuyuzhento decoction (300 mL, b.i.d.)	 Calamine lotion Diclofenac sodium emulsion Nitamin B 4. Mecobalamin Oxycodoen hydrochloride sustained release tablet (10 mg, b.i.d.) 	$52.4\pm10.9~\mathrm{d}$	48.5 ± 9.6 d	VAS improvement rate (p < 0.05)	4 w	Trial: 10 AEs constipation (3) nausea and vomiting (2) dizziness (2) xerostomia (2) Control: 14 AEs constipation (9) nausea and vomiting (1) dizziness (1) xerostomia(3)
Gong (2021) [102]	Occipital neural- gia	RCT	30 (16/14) 42.6 ± 6.1 y	30 (17/13) 43.2 ± 6.4 y	1. Modified chuanxiongchadio san 2. Gabapentin capsule (0.3 g, t.i.d.)	1. Gabapentin capsule (0.3 g, t.i.d.)	$4.2\pm1.1d$	$4.6\pm1.3d$	1. CER (<i>p</i> < 0.05) 2. VAS (<i>p</i> < 0.05)	2 w	NR
Huang (2020) [103]	Trigeminal neural- gia	RCT	30 (15/15) 58.50 ± 10.72 y	30 (9/21) 60.07 ± 13.57 y	 Xiongzhiyufeng decoction (b.i.d.) Carbamazepine (0.1 g, b.i.d.) 	1. Carba- mazepine (0.1 g, b.i.d.)	$2.95\pm3.19~\mathrm{y}$	$2.12\pm2.46~\mathrm{y}$	1. CER ($p < 0.05$) 2. VAS ($p < 0.05$)	20 d	NR

Table 1. Cont.

ladie 1. Cont.											
First Author (Year) [Reference]	Type of Condi-	Trial Design	Number of Participants (Male/Female); Age (Mean \pm SD)		Interventions		Morbidity Period (Mean \pm SD or Range)		Outcome Index (Intergroup Differences	Course of Treatment	Adverse Event (Case/Symptom)
	tion	U	Trial	Control	Trial	Control	Trial	Control	<i>p</i> -Value)		
Song (2020) [104]	Supraorbita neural- gia	al RCT	45(NR) 52.2 ± 3.5 y	42(NR) 50.1 \pm 4.2 y	yangxueshugan decoction (b.i.d.)	1. Mecobalamin tablet (500 μg, t.i.d.) 2. Citicoline sodium (q.d.)	NR	NR	1. CER (<i>p</i> < 0.05)	2 w	NR

Table 1. Cont.

AE: Adverse event; b.i.d: Bis in die; c: Capsules; CER: Clinical effective rate; CIPN: Chemotherapy-induced peripheral neuropathy; d: Days; DPN: Diabetic peripheral neuropathy; g: Gram; i.m.: Intramuscular; i.v.: Intravenous; m: Months; MDNS: Michigan diabetic neuropathy scale; mg: Milligram; mL: Milliliter; MMNCV: Median motor nerve conduction velocity; MSNCV: Median sensory nerve conduction velocity; NR: Not reported; p.o: Per os; PHN: Postherpetic neuralgia; PMNCV: Peroneal motor nerve conduction velocity; PSNCV: Peroneal sensory nerve conduction velocity; q.d.: Quaque die; RCT: Randomized controlled trial; SD: Standard deviation; SMNCV: Sural motor nerve conduction velocity; SSNCV: Sural sensory nerve conduction velocity; t: Tablet; t.i.d: Ter in die; TCSS: Toronto clinical scoring scale; TMNCV: Tibial motor nerve conduction velocity; UMNCV: Ulnar motor nerve conduction velocity; y: years; µg: Microgram.

3.3. Risk of Bias

The methodological quality of the 67 included studies is summarized in Table 2 and Figure 2. The risk of bias was assessed using the RoB 2.0 tool [26]. Four studies were assessed to have a "low risk of bias" and the remaining 63 studies were assessed to have a 'high risk of bias'.

 Table 2. Methodological quality of the included studies according to the risk of bias 2.0.

Author (Year) [Reference]	D1	D2	D3	D4	D5	Overall
Jin (2004) [38]	Sc	Н	Н	L	Sc	Н
Sun (2008) [39]	Sc	Н	Н	Sc	Sc	Н
Shen (2009) [40]	L	Н	Н	L	Sc	Н
Lin (2010) [41]	Sc	Н	Н	L	Sc	Н
Wang (2010) [42]	L	Н	Н	L	Sc	Н
Yan (2010) [43]	Sc	Н	Н	Sc	Sc	Н
Wu (2011) [44]	Sc	Н	Н	L	Sc	Н
Gao (2012) [45]	Sc	Н	Н	L	Sc	Н
Gong (2013) [46]	Sc	Н	Н	L	Sc	Н
Han (2013) [47]	L	Н	Н	Sc	Sc	Н
Zhang (2013a) [48]	L	Н	Н	L	Sc	Н
Zhang (2013b) [49]	Sc	Н	Н	L	Sc	Н
Guo (2014) [50]	Sc	Н	Н	Sc	Sc	Н
Yang (2014a) [51]	Sc	Н	Н	Sc	Sc	Н
Yang (2014b) [52]	L	Н	Н	Sc	Sc	Н
Qi (2015) [53]	Sc	Н	Н	L	Sc	Н
Wang (2015) [54]	Sc	Н	Н	Sc	Sc	Н
Xue (2015) [55]	L	Н	Н	L	Sc	Н
Ding (2016) [56]	Sc	Н	Н	L	Sc	Н
Guo (2016) [57]	L	Н	Н	L	Sc	Н
Han (2016) [58]	Sc	Н	Н	L	Sc	Н
Lan (2016) [59]	Н	Н	Н	L	Sc	Н
Mo (2016) [60]	L	Н	Н	Sc	Sc	Н
Wang (2016) [61]	L	Н	Н	Sc	Sc	Н
Li (2016a) [62]	L	Н	Н	L	Sc	Н
Zhang (2016a) [63]	L	Н	Н	L	Sc	Н
Li (2016b) [64]	Sc	Н	Н	L	Sc	Н
Zhang (2016b) [65]	L	Н	Н	L	Sc	Н
Chen (2017) [66]	L	Н	Н	L	Sc	Н
Shi (2017) [67]	Sc	Н	Н	L	Sc	Н
Wang (2017) [68]	L	Н	Н	L	Sc	Н
Chen (2018) [69]	L	Н	Н	Sc	Sc	Н
Dai (2018) [70]	Н	Н	Н	L	Sc	Н
Hu (2018) [71]	Sc	Н	Н	L	Sc	Н
Huang (2018) [72]	L	Н	Н	L	Sc	Н
She (2018) [73]	L	Н	Н	L	Sc	Н

Author (Year) [Reference] Xin (2018) [74]	D1 H	D2 H	D3 H	D4 Sc	D5 Sc	Overall H
Gao (2019) [75]	Sc	Н	Н	L	Sc	Н
Wu (2019) [76]	L	Н	Н	L	Sc	Н
Yi (2019) [77]	L	Н	Н	L	Sc	Н
Ji (2019) [78]	L	Н	Н	Sc	Sc	Н
Liu (2019a) [79]	Sc	Н	Н	L	Sc	Н
Liu (2019b) [80]	Sc	Н	Н	Sc	Sc	Н
Chen (2021) [81]	Sc	Н	Sc	L	Sc	Н
Hou (2021) [82]	Sc	Н	Н	L	Sc	Н
Jin (2021) [83]	L	Н	Sc	L	Sc	Н
Li (2021) [84]	L	Н	Н	L	Sc	Н
Wang (2021a) [85]	L	Н	Н	L	Sc	Н
Wang (2021b) [86]	L	Н	Н	L	Sc	Н
Zhang (2021) [87]	Н	Н	Н	L	Sc	Н
Nishioka (2011) [88]	L	L	L	L	L	L
Huang (2013) [89]	L	Н	Sc	L	Sc	Н
Abe (2013) [90]	L	L	L	L	L	L
Kono (2013) [91]	L	L	L	L	L	L
Li (2013) [92]	L	Н	Н	L	Sc	Н
Oki (2015) [93]	L	L	L	L	L	L
Xu (2017) [94]	Sc	Н	Н	L	Sc	Н
Xie (2018) [95]	L	Н	Н	L	Sc	Н
Liu (2018) [96]	L	Н	Н	L	Sc	Н
Zhang (2018) [97]	Sc	Н	Н	L	Sc	Н
Liu (2020) [98]	Sc	Н	Н	L	Sc	Н
Li (2016c) [99]	L	Н	Н	L	Sc	Н
Zhang (2012) [100]	Sc	Н	Н	L	Sc	Н
Zhao (2018) [101]	L	Н	Н	Sc	Sc	Н
Gong (2021) [102]	Sc	Н	Н	L	Sc	Н
Huang (2020) [103]	Sc	Н	Н	L	Sc	Н
Song (2020) [104]	Н	Н	Н	Sc	Sc	Н

 Table 2. Cont.

D1–D5: 5 Domain criteria. D1: Bias arising from the randomization process; D2: Bias due to deviations from the intended interventions; D3: Bias due to the missing outcome data; D4: Bias in the measurement of the outcome; and D5: Bias in the selection of the reported results. H: High risk of bias; L: Low risk of bias; Sc: Some concerns.



Figure 2. Risk of bias 2.0 graph of the included studies.

3.4. Efficacy

3.4.1. Primary Outcome: Sensory NCV (SNCV)

SNCV was measured in 31 studies, including 10 studies on EAHM monotherapy [38,40,44,49,55,59,70,77,81,82] and 21 studies on combined EAHM and western medicine (WM) therapy [41,42,45,46,48,53,57,63–65,67,68,71,72,75,79,84,86,87,95,96]. The studies on EAHM monotherapy compared the effect of EAHM on SNCV with WM. The combined effect of EAHM monotherapy was significantly better than the WM control (n = 2159; MD 2.68, 95% CI 2.02–3.35, p < 0.0001; heterogeneity chi-square = 167.15, df = 23, p < 0.01; $I^2 = 86$; Figure 3).

Study or	Experim	ental	Contro	1		Mean Difference	Mean Difference
Subgroup	Mean	SD Total	Mean SE	0 Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
Group = MSN	CV:EAHM	versus WN					
Jin 2004	49.13 5.	5400 103	43.38 5.5200	99	4.3%	5.75 [4.22; 7.28]	
Shen 2009	40.60 2.	2000 51	38.80 2.3000	50	5.1%	1.80 [0.92; 2.68]	_ _
Zhang 2013b	43.70 4.	.9000 30	43.10 4.8000) 30	3.2%	0.60 [-1.85; 3.05]	
Xue 2015	46.12 2.	2800 42	42.13 2.6100) 42	4.9%	3.99 [2.94; 5.04]	
Wu 2019	36.52 0.	.9400 30	35.52 0.9400	30	5.5%	1.00 [0.52; 1.48]	
Yi 2019	39.51 3.	4900 54	36.89 4.2100) 53	4.4%	2.62 [1.15; 4.09]	
Hou 2021	48.36 8.	.5100 39	44.68 5.6700) 28	2.3%	3.68 [0.28; 7.08]	
Total (95% CI)	2 - 0.005	349	50 K - 0 (D -)	332	29.7%	2.74 [1.38; 4.10]	-
Heterogeneity:	lau = 2.695	9; Chi = 56	.56, df = 6 (P < 1	J.01); I	= 89%		
Group = BSM		orgue MM					
lip 2004	46.49 4	4400 103	41 22 4 9900	00	4 694	5 27 [3 07: 6 57]	
Shop 2009	37 20 2	7000 51	34.90 2.100	50	5 10/	2.40[1.46:3.34]	
Mu 2011	40.61 2	2100 39	39.79 5 1000	27	3.6%	0.82 [=1.26: 2.00]	
Zhang 2013b	40.40 3	1000 30	39.60 3 3000	30	4 294	0.82 [1.20, 2.30]	
Xue 2015	40.40 3.	2700 42	38 13 3 1600	1 42	4.270	2 31 [0 93: 3 69]	
Dai 2018	30.21 /	0000 42	35 89 3 9100	42	4.0%	3 32 [1 57: 5 07]	
Mu 2010	36.62 0	9800 30	32.22 0.960	30	5.5%	4 40 [3 01 4 80]	
Vi 2019	40.59 3	6200 54	37 15 4 200	53	4.4%	3 44 [1 93: 4 95]	
Chen 2021	36.32 2	9200 29	36 18 3 3800	20	1 2%	0.14 [-1.50; 1.78]	
Hou 2021	40.28.10	4900 30	35 24 5 3400	23	2.0%	5.04 [1.20; 8.88]	Τ
Total (95% CI)	40.20 10.	455	00.24 0.0400	428	42.1%	2 76 [1.67: 3.85]	•
Heterogeneity	, Tau ² = 2.375	1 $Chi^2 = 61$	97 df = 9 (P <)	$(0.1) \cdot ^2$	= 85%	2000 [1001, 0000]	
		.,					
Group = SSN(CV:EAHM	versus WM					
Lan 2016	37.32 5.	3100 50	35.12 4.4400) 52	3.9%	2.20 [0.30; 4.10]	— <u>—</u>
Total (95% CI)		50	1	52	3.9%	2.20 [0.30; 4.10]	-
Heterogeneity: r	, not applicabl	е					
Group = TSN0	CV:EAHM \	ersus WM					
Shen 2009	34.10 2.	1000 51	30.80 2.4000) 50	5.1%	3.30 [2.42; 4.18]	
Xue 2015	38.34 2.	.8700 42	36.24 2.5600) 42	4.8%	2.10 [0.94; 3.26]	
Total (95% CI)		93		92	9.9%	2.76 [1.59; 3.93]	•
Heterogeneity:	$Tau^2 = 0.443$	1; Chi ² = 2.6	6, df = 1 (P = 0.1	1); $ ^2 = ($	62%		
Group = USN	CV:EAHM	versus WM					
Shen 2009	41.20 1.	.9000 51	38.50 2.000	50	5.2%	2.70 [1.94; 3.46]	_ =
Zhang 2013b	43.60 3.	.9000 30	42.90 4.2000) 30	3.7%	0.70 [-1.35; 2.75]	
Dai 2018	41./1 5.	2600 40	38.74 4.8700	40	3.5%	2.97 [0.75; 5.19]	
Hou 2021	52.45 8.	.8300 39	48.24 6.6700) 28	2.0%	4.21 [0.50; 7.92]	
Total (95% CI)	2 0 0 0 0	160		148	14.4%	2.46 [1.42; 3.51]	
Heterogeneity:	rau ⁻ = 0.355	e; Chi⁻ = 4.1	8, at = 3 (P = 0	∠4); I [–] =	28%		
Total (95% CI)		1107		1052	100 0%	2 69 1 2 02: 2 251	
Hotorogonaitu	$T_{2}u^{2} = 2.060$	5. Chi ² - 16	7 15 df - 22 (D	- 0.01):	1 ² - 96%	2.00 [2.02; 3.35]	—
naterogeneity.	iau = 2.000	o, oni = 10	1.10, ui = 20 (P	- 0.01),	00%		-5 0 5
							Favours control Favours experimental
							SNCV



In the 21 studies comparing the effect of combined EAHM and WM therapy with the WM monotherapy control, the combined therapy significantly improved SNCV than

Total (95% CI)

Total (95% CI)

Study or Group = MSNCV:EAHM plus WM versus WM alone Mean Difference (V, Random, 95%, CI Mean Difference (V, Random, 95%, CI Group = MSNCV:EAHM plus WM versus WM alone Vang 2010 43.83 4.7800 76.43.93 4.790 76.23% 3.97 [2.45; 5.49] Gae 2012 47.10 3.0000 30 44.60 2.3% 2.60 [1.16; 4.04] Zhang 2016 46.96 48.30 4.500 80.30 1.2% 0.81 [0.20; 1.42] Zhang 2016 45.04 3.33.1200 60 2.0% 4.16 [2.16; 6.14] [
Subgroup Mean SD Total Mean SD Total Meight IV, Random, 95% CI Wang 2010 48,36 47800 75 44.39 4.7800 76 2.3% 3.97 [246;549] Gae 2012 47.10 3.000 30 44.50 2.700 30 2.3% 2.60 [1.16; 4.44] The 2013 48.96 6330 30 44.50 2.700 50 2.0% 5.10 [3.13; 7.07] Li 2016 49.27 7.210 6 44.33 3.4500 60 2.2% 4.80 [3.10; 7.07] Li 2016 45.00 3.200 60 40.20 3.100 60 2.5% 4.80 [3.67; 5.53] Wang 2017 44.50 2.7200 60 43.37 3.1200 02 2.5% 4.80 [3.67; 5.53] Wang 2017 44.50 2.7200 60 43.20 5.200 50 2.5% 4.80 [3.67; 5.53] Wang 2017 44.50 2.7200 60 54.84 2.500 50 2.5% 4.80 [3.67; 5.53] Wang 2017 44.50 2.7200 60 54.84 2.500 50 2.5% 4.80 [3.67; 5.7] Gae 2019 45.90 2.3300 50 42.42 2.500 50 2.5% 3.41 [2.42; 4.40] Li 2018 44.57 2.2900 30 40.17 1.6400 30 2.5% 4.40 [3.16; 5.62] Li 2012 166 55 4.1200 40 54.84 3.5700 41 2.3% 2.48 [0.52; 4.40] Wang 2017 48.56 4.1200 40 54.84 2.500 40 1.7% 3.87 [0.77; 7.04] Wang 2010 48.36 4.2800 77 42.68 3.7100 76 2.4% 5.68 [4.40; 6.69] Gae 2012 3.20 2.5000 ch ⁻¹ 45.44 2.1700 60 2.7% 0.17 [-0.55; 0.88] Chang 2018 44.57 7.4700 80 37.74 2.1700 60 2.7% 0.17 [-0.55; 0.88] Chang 2018 45.67 7.4700 80 37.74 2.1700 60 2.7% 0.17 [-0.55; 0.88] Chang 2018 45.67 7.4700 80 3.92 2.8000 30 1.4% 1.45 [-3.24; 4.40] Li 2016 40.70 3.3300 30 32.02 2.000 30 2.2% 2.00 [1.33; 2.69] Li 2016 40.70 3.300 30 30 32.02 2.000 30 2.2% 2.00 [1.48; 4.69] Gao 2012 3.20 5.100 30 3.45 2.01 [1.43] Gao 2019 3.20 8.1700 41 2.3% 2.370 [1.27; 1.73 37] Guo 2016 3.19 2.1700 50 3.00 2.270 41 2.4% 3.20 [1.11; 3.01] Li 2016 40.70 3.300 30 32.02 2.000 30 2.4% 2.00 [1.11; 3.01] Li 2016 40.70 3.300 30 33.02 3.200 30 2.2% 2.00 [0.84; 4.16] Wang 2017 4.25 5.400 31 45.44 6.1700 40 2.3% 3.00 [1.58; 4.60] Jamag 2018 4.20 5.5000 Ch ⁻¹ = 108.49, df = 10 (< 0.01) 17 = 68% Group = SSNCV:EAHM plus WM versus WM alone Li 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 3.42 5.1500 30 3.450 2.7000 30 2.3% 2.270 [1.25; 4.15] Heterogenetry Tar ² = 0.080, 2.4700 30 3.850 2.700 1.2% 2.201 [1.57; 2.53] Heterogenetry Tar ² = 0.2	Study or	Experimental	Control		Mean Difference	Mean Difference
Group = MSNC VIEAHM pits WM versus VM alone Wang 2010 48.56 47800 75 4.33 8.700 76 2.3% 3.97 [2.45; 5.49] Gao 2012 47.10 3.000 3 0 44.50 2.7000 30 2.3% 2.60 [1.16; 4.04] Zhang 2016 48.66 6330 0 46.82 6.800 30 1.2% 0.84 [-3.12; 3.80] Guo 2016 43.60 6.310 48.30 4.800 51 2.8% 0.81 [0.20; 1.42] Zhang 2016 41.40 5.300 48 8.30 4.500 50 2.6% 4.80 [3.67; 5.83] Wang 2017 44.50 2.7200 30 43.89 2.5400 30 2.4% 0.61 [-0.72; 1.34] Gao 2019 4.50 2.300 60 42.49 2.000 50 2.6% 4.15 [2.16; 6.14] Li 2016 4.92 7.2100 60 45.37 3.1200 60 2.2% 4.15 [2.16; 6.14] Li 2018 4.50 2.300 60 42.49 2.000 11 2.3% 2.48[0.32; 4.40] Wang 2010 44.50 2.5000 40 38.20 5.8000 40 1.7% 3.60 [1.10; 6.10] Li 2018 6.655 4.120 41 56.44 2.4100 41 2.3% 0.11 [-1.35; 1.57] Group = PSNC/UEAHM pits WM versus WM alone Croup = PSNC/UEAHM pits WM versus WM alone Croup = PSNC/UEAHM pits WM versus WM alone Gao 2019 4.230 2.5000 40 65.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 4.335 4.2800 75 42.68 3.7100 76 2.4% 5.68 [-4.60; 6.66] Gao 2012 4.302 4.500 3.03 6.2.9 1.13% 3.87 [0.70; 7.04] Wang 2010 4.335 4.2800 75 42.68 3.7100 76 2.4% 5.68 [-4.60; 6.66] Gao 2012 4.302 6.000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 4.335 4.2800 75 42.680 30 1.1% 0.01 [-1.35; 1.57] Gao 2012 4.302 6.000 30 4.560 2.000 1.2% 0.01 [-1.35; 2.69] Wang 2010 4.335 4.2800 75 4.2.680 30 1.1% 0.01 [-2.6% 0.56] (-6.6; 1.50] Gao 2012 4.302 6.000 30 3.682 8.2000 30 1.1% 0.04 [-3.42; 4.22] Gao 2016 4.357 4.700 30 3.682 8.2000 30 1.1% 0.04 [-3.42; 4.22] Gao 2016 4.357 4.700 30 3.682 8.2000 30 1.1% 0.04 [-3.42; 4.22] Gao 2016 3.3192 .7100 30 3.682 8.2000 30 1.1% 0.04 [-3.42; 4.22] Gao 2019 3.208 1.700 60 3.0.62 2.9100 50 2.7% 0.17 [-0.55; 6.58] Ju 2016 4.571 9.700 60 3.0.62 2.9100 50 2.7% 0.27 [-1.55; 4.58] Huang 2016 4.250 5.2000 120 3.5% 8.5000 30 2.7% 0.22 [-1.53; 4.16] Huang 2016 4.250 5.2000 120 3.5% 8.500 2.2% 4.56 [-3.51; 4.16] Huang 2016 4.250 5.2000 120 3.5% 8.500 2.2% 4.56 [-3.51; 4.16] Huang 2016 4.551 1.2200 61 3.364 2.1000 40 2.5% 4.50 [-3.51; 4.16]	Subgroup	Mean SD	Total Mean SD T	otal Weigh	t IV, Random, 95% CI	IV, Random, 95% CI
Wang 2010 43.84 1,2000 /s 44.39 4,2000 /s 12.3% 3.37 [2.46; 5.49] Zhang 2013 44.96 6.8300 30 44.50 27.000 30 2.23% 2.80 [1.6; 4.64] Zhang 2016 41.40 5.3000 48 2.66.300 31 1.2% 0.34 [-3.12; 3.60] Zhang 2016 41.40 5.3000 48 2.66.300 51 2.2% 0.31 [-3.02; 0.142] Zhang 2016 45.03 3.2000 60 45.37 31.200 60 2.5% 4.80 [3.67; 5.93] Wang 2017 44.50 2.7200 30 33.89 2.5400 30 2.4% 4.16 [2.16; 1.41] Zhang 2016 45.03 3.2000 60 46.23 31.000 60 2.5% 4.80 [3.67; 5.93] Wang 2017 44.50 2.7200 30 34.38 2.5500 30 2.4% 3.60 [1.67; 21:34] Gauge 2016 45.03 2.2000 40 33.49 2.5000 30 2.5% 4.80 [3.67; 5.93] Wang 2017 44.50 2.7200 30 40.07 24.40 30 2.5% 4.80 [3.67; 5.93] Wang 2017 44.50 2.7200 30 40.07 24.40 30 2.5% 4.80 [3.67; 5.93] Wang 2017 45.93 5.8200 40 34.94 2.8000 50 2.7% 1.72 [0.84; 2.66] Wang 2017 45.93 5.8200 40 34.94 2.8000 50 2.7% 1.72 [0.84; 2.66] Wang 2017 44.53 5.8200 40 34.94 2.8000 50 2.7% 4.72 [0.84; 5.62] Lui 2018 56.55 4.1200 41 56.44 2.4100 41 2.3% 0.11 [-1.35; 1.57] Heterogenety Tru ² = 2.5090; Ch ² = 92.72, df = 13 (P < 0.01), f ² = 80% Group P SNCV:EAHM plus WM versus WM alone Lui 2010 7.02 6 1000 30 2.5% 0.66 [-600; 1.80] Gaug 2010 43.36 4.200 75 42.68 3.7100 76 2.4% 5.68 [4.40; 6.96] Gaug 2013 3.79 [1.8400 60 37.74 2.1700 60 2.7% 0.07 [2.7; 5.05] Jang 2013 a.19 2.1700 32 3.01 2.14100 31 2.2% 2.01 [1.33; 2.69] Ui 2016 40.76 3.3300 30 38.20 3.2200 30 2.2% 2.01 [0.84; 4.16] Wang 2017 43.36 4.000 30 7.68 5.1000 30 1.7% 6.02 [3.44; 4.55] Gaug 2019 3.208 1.7800 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Heterogenety, Tuu ² = 2.5090; Ch ² = 0.7, d ² = 0.000 2.7% 3.07 [2.17, 3.97] Guug 2016 53.142 71 [-0.600 30 7.68 5.100 30 1.7% 6.02 [3.44; 8.56] Gaug 2016 3.208 1.7800 30 3.820 3.2200 30 2.2% 2.70 [1.25; 4.15] Heterogenety, Tuu ² = 2.6092; Ch ² = 0.04, d = 13 (P < 0.01), l ² = 89% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 64.26 5.2000; di 3.244 1.000 11 2.2% 3.50 [1.67; 2.63] Heterogenety, Tuu ² = 2.6020; Ch ² = 0.04, d = 13 (P < 0.01), l ² = 89% Group = SSNCV:EAHM plu	Group = MSN	CV:EAHM plus	WM versus WM alone	e		
Sab 2012 47.10 30000 30 44.82 63.00 30 24.85 2.600 30 2.3% 2.60 11.16.4.04 Guo 2016 36.04 17.400 51 35.23 1.3800 51 2.8% 0.84 [-312.3.80] Guo 2016 44.95 5.300 48 53.04 50.00 48 2.0% 5.10 [313.7.07] Li 2016b 49.52 7.2100 60 45.37 3.1200 60 2.0% 4.15 [2.16; 6.14] Jang 2016b 49.52 7.2100 60 45.37 3.1200 60 2.0% 4.15 [2.16; 5.14] Jang 2016b 49.52 7.2100 50 42.03 2.000 50 2.6% 4.80 [3.57; 5.93] Wang 2017 44.50 2.7200 30 43.89 2.5400 30 2.4% 0.61 [-0.72; 1.54] Jang 2016b 49.52 7.2100 50 42.49 2.000 50 2.6% 4.81 [3.42; 4.40] Li 2021 46.53 3.5200 41 44.43 5.700 41 2.3% 0.51 [-1.05; 1.00] Li 2021 66.55 4.1200 41 6647 4.100 41 2.3% 0.21 [-1.35; 1.57] Wang 2016 46.55 4.1200 41 6644 2.4100 41 2.3% 0.21 [-1.30; 3.66] Heterogenety: Trai ² 2.2000; Chi ² = 52.72, d = 13 (P < 0.01); <i>P</i> = 600% Group = PSNCV-EAHH plater WM versus WM alone Lin 2010 70.28 5.1000 40 65.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 45.36 4.200 75 42.68 3.7100 76 2.4% 5.88 [4.40; 6.96] Gaso 2013 3.79 11.8400 60 42.61 7.1000 30 2.5% 0.60 [-0.60; 1.80] Gaso 2013 3.79 11.8400 60 42.61 7.1000 30 2.5% 0.60 [-0.60; 1.80] Gaso 2014 47.70 4.8800 30 376 42.28 3.7100 76 2.4% 5.88 [4.40; 6.96] Gaso 2012 4.70 5.8100 30 3.87 51 2.2700 30 1.7% 6.22 [3.44; 8.56] Lin 2010 70.28 5.1000 40 65.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Lin 2010 70.28 5.1000 30 3.87 51 2.28% 0.31 [-1.60; 5.189] Jang 216 4.57 7.470 30 377 4 2.1700 30 2.2% 3.20 [1.24; 4.16] Lin 2010 747 5.8300 30 38 6 8.2000 30 2.2% 2.26 [1.113.01] Lin 2016 3.19 2.210 1.41 2.400 51 2.2% 3.02 [1.44; 1.50] Lin 2016 3.19 2.210 1.41 2.400 51 2.2% 3.20 [1.44; 1.50] Lin 2016 3.19 2.210 1.420 41 2.4% 0.35 [-0.66; 1.36] Jang 216 4.27 5.8000 40 65.20 5.41 2.2100 50 2.2% 3.20 [1.56; 3.53] Heterogenety: Trai ² 2.5000; Chi ² = 0.67, r ¹ 2.7% 3.01 [1.7; 6.7] Huang 2016 4.250 5.2000 120 3.500 4.3000 120 2.5% 3.30 [1.66; 3.55] Trai (10%, 01) Corup = TSNCV-EAHH plater WM versus WM alone Li 2016a 34.56 1.200 41 0.452.41 (4.700 40 1.5% 5.00 [1.25; 4.15] Heterogenety: Trai ² = 2.000; Chi ² =	Wang 2010	48.36 4.7800	75 44.39 4.7800	76 2.39	6 3.97 [2.45; 5.49]	
Zhang 2013a 4.3.96 6.3.90 30 4.2.6 6.3.90 1.2.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9 1.3.% 0.3.9	Gao 2012	47.10 3.0000	30 44.50 2.7000	30 2.39	6 2.60 [1.16; 4.04]	
Guo 2019 Go 30 Gu 1, 440 S 300 Gu 2, 51 S 32 1, 500 Gu 2, 51 S 3, 7, 707 Li 2016b 49, 52 7, 2100 Gu 43 S 53 4, 500 Gu 48 2, 20% 4, 40 S 15, 7, 513] Wang 2017 44, 50 2, 3200 Gu 42 53 2, 5000 Gu 2, 24% 0, 61 [-0.72; 1, 94] Gao 2019 44, 50 2, 3200 Gu 42 93 2, 5000 Gu 1, 7% 3, 60 [1, 10, 6, 10] Li 2014 65, 93 3, 620 41 44, 45 3, 770 H 1 2, 3% 2, 48 [0, 62; 4, 40] Li 2014 65, 63 3, 620 40 39, 20 5, 8000 40 1, 7% 3, 60 [1, 10, 6, 10] Li 2014 65, 53 3, 620 41 44, 45 3, 770 H 1 2, 3% 2, 48 [0, 62; 4, 40] Wang 2021b 60, 12 2, 6000 30 40, 17 (4, 400 30 2, 5% 4, 40 [3, 18, 6, 62] Li 2018 65, 54 1, 120 41 65, 44 2, 4100 41 2, 3% 0, 11 [-1, 35; 1, 57] Hoterogenety: Tat ² = 2,5000; Ch ² = 02, 72, d = 13 (P < 01); P ² = 80% Group = PSNCV:EAHM plus WM versus WM alone Li 2010 7, 702 & 5, 1000 40 66, 41 8, 2000 40 1, 3% 3, 87 [0, 70; 7, 04] Wang 2010 43, 36 4, 2800 75 42, 68 3, 7100 76 2, 4% 5, 68 [4, 40, 6, 56] Gao 2012 3, 79 11, 8400 60 37, 74 2, 1700 60 2, 7% 0, 017 [-0, 55; 0, 89] Chang 2013 a, 12, 1700 32 30, 12 1, 4100 32 2, 7% 30, 71 [-1, 73, 37] Guo 2015 33, 19 2, 1700 32 30, 12 1, 4100 32 2, 7% 30, 71 [-1, 73, 37] Guo 2015 33, 19 2, 1700 32 30, 12 1, 4100 32 2, 7% 30, 71 [-1, 73, 97] Wang 2017 43, 73 4, 8500 30 7, 74 6, 1200 30 1, 2% 4, 260 [3, 11, 30, 13] Gao 2012 3, 26 71 8, 700 Gu 33, 76 8, 1200 30 1, 2% 8, 201 [1, 33, 269] Li 2016 40, 70 3, 3300 30 38, 20 3, 2200 30 2, 2% 2, 20 [0, 84, 418] Wang 2017 43, 74 8, 1500 30 3, 74 8, 5100 30 1, 7% 6, 02 [3, 48, 856] Gao 2019 3, 20 8, 1780 Gu 30, 37, 86 5, 1300 30 1, 7% 6, 02 [1, 15, 3, 33] Haterogenety: Tat ² = 2, 5002; Ch ² = 108, 40 d = 13 (P < 0, 17); P ² = 60% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 43, 56 1, 2, 3800 41 54, 81 2, 2700 41 2, 2% 3, 320 [1, 153, 15, 81] Li 2016 43, 56 1, 2, 3800 41 54, 81 2, 2700 41 2, 2% 3, 320 [1, 153, 15, 81] Li 2016 43, 56 1, 2, 3800 41 54, 81 2, 2700 41 2, 2% 3, 320 [1, 153, 15, 81] Li 2016 33, 96 0, 2, 960 30 30 68 92, 7800 30 2, 23% 3, 10 [1, 156, 46] Group = SSNCV:EAHM plus WM versus WM	Zhang 2013a	48.96 6.8300	30 48.62 6.8300	30 1.2%	0 0.34 [=3.12; 3.80]	
Lind golles 1.40 3.300 48 3.50 4.500 60 2.5% 3.60 3.75 7.57 Zhang Z016 45.00 3.200 60 4.20 3.00 4.16 2.16.6 1.41 Zhang Z016 45.00 3.200 60 4.20 3.00 3.68 2.6% 3.41 1.24.24 1.44 Lu Z018 4.50 2.280 5.600 4.00 3.20 4.00 3.20 4.00 3.20 4.16 1.24.24 1.40 1.23% 2.48 1.02.16.6 1.1 4.16 1.10.6 1.00 1.10.70 1.10.6 1.01 1.10.70 1.10.6 1.10 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.11.70 1.10.70 1.11.70 1.11.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 1.10.70 <td>Guo 2016</td> <td>36.04 1.7400</td> <td>51 35.23 1.3800</td> <td>51 2.8%</td> <td>0 0.81 [0.20; 1.42]</td> <td>· · · · · · · · · · · · · · · · · · ·</td>	Guo 2016	36.04 1.7400	51 35.23 1.3800	51 2.8%	0 0.81 [0.20; 1.42]	· · · · · · · · · · · · · · · · · · ·
Li 20100 4:352 1/2100 60 4:357 3.1200 60 2.0% 4:10 [2:10:6.1] Wang 2017 44:50 2.2000 50 42.49 2.0100 60 2.4% 0.61 [-0.72; 1:94] Gao 2019 4:280 2.6000 40 39.20 5.000 40 1.7% 3.60 [1:10:6.10] Li 2019 4:280 5.600 40 39.20 5.000 40 1.7% 3.60 [1:10:6.10] Li 2019 4:280 5.600 41 44:45 5.700 41 2.3% 2.48 [0.92; 4.04] Wang 2021b 60.12 2.6000 50 58.40 3.0900 80 2.7% 1.72 [0.84; 2.60] Kie 2018 4:457 2.9900 30 40.17 1:400 30 2.5% 4.40 (3.18; 5.62] Li 2018 56.55 4:1200 41 56.44 2.4100 41 2.3% 0.11 [-1.38; 1.57] Total [05%, 01] Geo 2012 43.36 2.8000 75 42.68 3.7100 76 2.4% 5.88 [4.40; 6.96] Geo 2012 43.20 2.6000 50 34.26 80.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 45.36 4.2800 75 42.68 3.7100 76 2.4% 5.88 [4.40; 6.96] Geo 2012 43.20 2.6000 30 342.65 2.000 30 2.2% 0.60 [-0.60; 1.80] Geo 2013 37.91 1.8400 60 37.74 2.1700 60 2.7% 0.17 [-0.56; 0.89] Zhang 2013a 45.57 4.700 32 30.12 1.4100 32 2.7% 3.07 [2.17; 3.97] Guo 2016 33.79 1.700 32 30.12 1.4100 32 2.7% 3.07 [2.17; 3.97] Guo 2015 33.19 2.1700 32 30.12 1.4100 50 2.2% 2.60 [0.84; 4.16] Wang 2017 43.70 4.8500 30 37.86 5.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.79 0.4500 41 4.011 3.4200 41 2.3% 2.77 [1.28; 4.16] Wang 2017 43.70 4.8500 41 6.413 2.2700 41 2.6% 4.66 [3.16] Total [05%, 01] Group = SNCV:EAHM plus WM versus WM alone Li 2016 42.10 3.3000 41 3.43.46 6.6100 31 2.4% 2.59 [1.65; 3.53] Heterogenety: Tru ² = 2.5002; Ch ² = 0.677, P ² = 0.% Group = SNCV:EAHM plus WM versus WM alone Li 2016 3.960 2.2600 30 36.90 2.7800 30 2.2% 2.20 [1.15; 4.65] Total [05%, 01] Geo 416 6.470 40 33.800 7 43.357 2.2% 2.40 [1.75; 6.65] Total [05%, 01] Geo 700 50 3.322 0.3000 120 2.5% 3.30 [2.29; 4.71] Heterogenety: Tru ² = 2.5002; Ch ² = 52.42, 41 = 10(P < 0.01); P ² = 80% Group = SNCV:EAHM plus WM versus WM alone Li 2016a 42.10 3.3700 80 3.525 9.7000 40 1.5% 6.00 [3.25; 8.75] Geo 219 3.390 1.700 50 30.322 0.3300 71 2.5% 3.50 [2.94, 3.2] Heterogenety; Tru ² = 2.5002; Ch ² = 52.	Zhang 2016a	41.40 5.3000	40 30.30 4.3000	46 2.0%	0 0.10[0.10;7.07]	
Lang 20160 42.00 2.4000 80 40.20 50 00 2.3% 400 35 (-0.72; 194) Gao 2019 45.90 2.9300 50 42.49 2.0500 50 2.6% 3.41 [2.42; 4.40] Li 2011 45.93 3.6200 41 44.45 3.5700 41 2.3% 2.48 [0.92; 4.04] Wang 2021 60 12 8.600 80 58.40 30 900 80 2.7% 1.72 [0.84; 2.60] Kie 2018 44.57 2.9900 30 40.17 1.6400 30 2.5% 4.40 [3.18; 5.62] Li 2018 44.57 2.9900 31 40.17 1.6400 30 2.5% 4.40 [3.18; 5.62] Li 2018 65.55 4.120 41 56.44 2.4100 41 2.3% 0.11 [-1.38; 1.57] Total [05%, C] 666 67 31.6% 2.73 [1.80; 3.66] Heterogeneity. Tut ² = 2.500; CT ² = 9.27.2 (rf = 13 (P < 0.01); I ² = 80% Group = PSICV:EAHM plus WIV versus WIM alone Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2013 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.46 [-3.42; 4.32] Guo 2015 33.19 2.1700 50 3.01.2 2.9100 50 2.6% 0.206 [-1.65; 0.89] Zhang 2013 45.57 7.4700 30 45.12 7.8200 30 2.2% 2.50 [0.84; 4.16] Wang 2014 43.04 2.800 30 37.85 5.1800 30 2.2% 2.50 [0.84; 4.16] Wang 2015 36.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.69] Li 2016 36.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.69] Guo 2015 33.19 2.1700 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2018 45.57 1.400 30 37.85 5.1800 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.57 4.4500 30 33.62 0.3200 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.57 4.4500 30 33.65.20 5.3100 80 2.3% 3.09 [1.56; 4.60] Zhang 2021 41.03 3.5800 123 9.00 2.30% 0.2.3% 3.09 [1.56; 4.60] Total [05%, C] 664 (-500 31 1.4% 3.72 [0.71; 6.73] Huang 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2016 44.40 3.3000 60 32.80 3.6000 120 2.3% 3.09 [1.56; 4.66] Chang ESNCV:EAHM plus WIV versus WI alone Lin 2010 644 16.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 33.455 1.5200 fil 32.45 1.1000 fil 2.8% 2.10 [1.55; 2.63] Fil deterogeneity. Tut ² = 2.5002, CH ² = 0.67); I ² = 0.5% Croup = SSNCV:EAHM plus WIV versus WI alone Lin 2016 64.41 0.33.000 fil 32.45 1.1000 fil 2.8% 2.10 [1.55; 4.65] Zhang 2016 3.300 01 60 32	Zhong 2016b	49.52 7.2100	60 40 20 2 1000	60 2.0%	0 4.10[2.10, 0.14]	
Wally 2017 4130 2.1200 30 2.4% 301 1.7% 3.801 1.106 6101 Liu 2019a 42.80 5.600 40 3.27% 1.72 0.84 1.106 6101 Liu 2019a 42.80 5.600 40 3.5700 41 2.3% 2.48 0.802 2.4% 1.3% 2.48 0.802 2.4% 1.106 6101 Wang 2021b 60.12 2.6000 80 8.47.75 2.5% 4.401 1.815.65.62 4.44 4.457 2.9900 666 667 3.16% 2.73 1.10:5 3.681 4.401 3.157.157 1.061 5.65 4.400 3.457 1.700 666 667 3.47 1.600 1.3% 3.87 1.70.70.41 Wang 2010 43.64 2.8000 40 1.3% 3.87 1.70.70.41 Wang 2014 43.50 2.600 30 2.7% 0.07 1.71 5.57.8.307 1.71 1.73 5.73 1.71 2.75 3.07 1.71 3.73 1.80.20 3.80 3.80 1.71 3.90	Wang 2017	45.00 3.2000	30 43 99 3 5400	30 2.07	0 4.00 [3.07, 3.93]	
Sab 2013 123 123 1230 1200 0 40 32.05 5200 40 12.7% 3.50 [1.10 6.10] Li 2021 42.83 5.200 41 44.45 3.5700 41 2.3% 2.48 [0.52,4.04] Wang 2021 65.5 4.120 68 05 84.0 3090 80 2.7% 1.72 [0.84 2.60] Xie 2018 44.57 2.9900 30 40.17 1.6400 30 2.5% 4.40 [3.18; 5.62] Li 2018 65.5 4.120 41 56.44 2.4100 41 2.3% 2.178 [1.38; 1.57] Total (95%, CI) 666 67 31.6% 2.7.73 [1.80; 3.66] Heterogenety. Tut ² = 2.500; Ct ² = 0.72 + 13 (P < 0.01); I ² = 80% Group = PSNCV:EAHM plus WM versus WM alone Li 2010 70.28 6.100 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 43.56 4.2800 30 42.60 2.1000 30 2.5% 0.60 [-0.60; 1.80] Geog 2013 3.19 1.1700 50 37.42 (-1.4700 60 2.7% 0.17[-0.56; 0.88] Zhang 2013 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Guo 2016 36.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.68] Wang 2017 43.70 44550 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.32.200 30 2.3% 3.09 [1.58; 4.60] Zhang 2021 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.50] Wang 2017 43.70 44550 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Heterogenety. Tut ² = 2.6002, Cth ² = 108.49, df = 13 (P < 0.01); J ² = 89% Group = SSNCV:EAHM plus WM versus WM alone Lin 2018 47.26 5.4400 31 43.54 6.6100 31 1.1% 3.72 [0.71; 6.73] Heterogenety. Tut ² = 2.6002, Cth ² = 108.49, df = 13 (P < 0.01); J ² = 89% Group = SSNCV:EAHM plus WM versus WM alone Lin 2016 64.4 5.070 00 50 32.6% 3.00 [2.3% 3.09 [1.55; 4.65] Li 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Heterogenety. Tut ² = 2.6002, Cth ² = 0.677; J ² = 0.% Group = SSNCV:EAHM plus WM versus WM alone Lin 2016 64.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 3.45 1.5200 513 2.24% 1100 51 2.8% 2.10 [1.55; 4.65] Li 2018 41.20 3.3100 50 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Li 2018 41.20 3.3100 50 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Li 2018 41.20 3.3100 50 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Li 2018 41.40 4.300 3000 60 33.810 2.8100 30 2.3% 3.10 [1.55; 4.65] Ji 2016 41.40 33.3000 61 32.240 100 5	Gao 2019	44.50 2.7200	50 43.89 2.9400	50 2.49	0 0.01[-0.72, 1.94]	
Lu 2010 4 46.03 3.2000 41 44.48 3.5700 41 2.3% 2.48 [0.92; 4.04] Wang 2021b 60.12 2.6000 80 58.40 3.0900 80 2.7% 1.72 [0.84; 2.60] Wang 2021b 60.12 2.6000 80 58.40 3.0900 80 2.7% 1.72 [0.84; 2.60] Wang 2021b 66.55 41200 41 56.44 2.4100 41 2.3% 0.11 [-1.35; 1.57] Total [95%, C] 666 667 3.16% 2.73 [1.80; 3.66] Heterogeneity, Tau ² = 2.500, Ch ² = 92.72, d = 13 (P < 0.01), P ² = 80% Group = PSNCV:EAHM plus WM versus WM alone Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 48.36 4.2800 75 42.68 3.7100 76 2.4% 5.68 [4.40; 5.69] Gao 2012 43.20 2.6000 30 42.60 2.1000 30 2.7% 0.17 [-0.56; 0.83] Zhang 2013 37.61 1.8400 60 37.74 2.1700 60 2.7% 0.17 [-0.56; 0.83] Zhang 2013 37.61 1.8400 60 37.74 2.1700 60 2.2% 0.17 [-0.56; 0.84] Zhang 2016 36.79 1.8700 51 34.78 [.4400 51 2.8% 2.01 [1.33; 2.69] Li 2016 40.70 3.300 30 38.20 2.2010 50 2.2% 2.800 [0.84; 4.16] Wang 20215 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 3.00.2 2.9100 50 2.2% 2.205 [0.64; 4.16] Wang 20211 43.35800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Li 2018 47.26 5.160 2.800 74 43.07 4 2.5% 4.56 [-0.66; 1.36] Total (95%, C) 664 665 31.7% 2.59 [-1.65; 3.53] Heterogeneity, Tau ² = 2.0602, Ch ² = 108.40, df = 13 (P < 0.01); P ² 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 84.42.60 5.2000 120 33.00 32 2.3% 3.09 [-1.65; 3.53] Heterogeneity, Tau ² = 0.00, df = 2.700 00 32 2.3% 3.00 [-1.65; 3.53] Heterogeneity, Tau ² = 0.00, df = 2.720 00 32 2.2% 2.40 [0.77; 6.73] Huang 2018 4.55 15.2000 120 33.00 32 2.2% 3.200 [-1.65; 3.53] Heterogeneity, Tau ² = 0.00, df = 2.720 00 32 2.2% 3.200 [-2.58, 5.60] Group = TSNCV:EAHM plus WM versus WM alone Li 2016 84.41 6.0770 0 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 33.30 700 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.3] Heterogeneity, Tau ² = 0.000 42 3.300 120 2.5% 3.20 [-2.68, 5.19] Huang 2018 4.50 5.2000 120 3.32 2.0300 120 2.5% 3.30 [-2.58, 7.56] Group = TSNCV:EAHM plus WM versus WM alone Lin 20108 33.00 1.700 60	Gao 2019	42.80 5.6000	40 39 20 5 8000	40 1.7%	6 3.41 [2.42, 4.40] 6 3.60 [1.10; 6.10]	
Wang 2021b 60.12 2.0000 80 34.0 3.0900 80 2.7% 1.72 [0.84; 2.60] Xie 2018 44.57 2.9900 30 40.17 1.6400 30 2.5% 4.40 [3.18; 5.62] Liu 2018 56.55 4.1200 41 56.42 4.100 41 2.3% 0.11[-135; 1.57] Total [95%, C] 666 61 2.2000 40 66.7 31.6% 2.73 [1.80; 3.66] Heterogenety, Tau ² = 2.500; C.10 ² = 92.72, d = 13 ($P < 0.01$); $P^2 = 80%$ Group = PSNCV:EAHM plus WM versus WM alone Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 43.86 4.2800 30 42.60 2.1000 30 2.5% 0.60 [-0.60; 1.80] Gong 2013 37.91 1.8400 60 37.74 2.1700 60 2.7% 0.17 [-0.55; 0.89] Zhang 2013a 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.46 [-342; 4.32] Glou 2016 51.33.19 2.1700 32 30.12 1.4100 32 2.7% 0.07 [-1.52; 0.83] Zhang 2013a 45.57 7.4700 30 34.51 2.78200 30 1.1% 0.46 [-342; 4.32] Glou 2016 51.91 1.8700 51 34.78 1.18400 61 2.8% 2.01 [1.33; 2.69] Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2021 43.70 4.850 50 30.02 2.9100 60 2.6% 2.06 [1.11; 3.01] Li 2016a 40.70 3.3300 30 36.90 2.7800 30 7.68 5.1800 30 -1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.02 2.9100 60 2.6% 2.06 [1.11; 3.01] Li 2016a 40.70 3.3300 41 40.11 4.30 42 2.3% 2.72 [1.28; 4.16] Wang 2021 b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Total (95%, C] Huang 2017 4.32 5.8200 120 38.00 2.3% 2.70 [1.25; 4.15] Hu 2018 4.250 5.2000 120 38.00 3.00 2.3% 2.70 [1.25; 4.15] Hu 2018 4.250 5.2000 120 38.00 3.00 2.3% 2.70 [1.25; 4.15] Huang 2018 4.250 5.2000 120 38.00 3.000 2.3% 3.10 [1.57; 2.63] Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 4.120 3.3100 00 38.10 2.8100 30 2.3% 2.10 [1.57; 2.63] Group = SSNCV:EAHM plus WM versus WM alone Lin 2016 4.416 0.3700 40 62.24 [-4.700 40 1.5% 5.00 [3.25; 8.75] Gou 2016 3.450 1.5200 120 2.5% 5.40 [1.415; 5.64] Shi 2017 4.303 3.700 03 35.20 5.7000 40 2.2% 3.20 [2.03; 4.32] Gou 2016 3.450 1.5200 74 3.950 2.7000 30 2.2% 2.4% 1.10 [-57; 2.63] Huang 2018 4.540 4.9000 120 4.2.20 3.9000 120 2.5% 5.40 [1.415; 6.54] Fuhag 2016 4.540 0.3000 120 2.5% 5.40 [1.415; 6.54]	Li 2021	46 93 3 6200	40 00.20 0.0000	41 2.3%	6 2.48[0.92:4.04]	
Number 10 and 1	Wang 2021h	60 12 2 6000	80 58 40 3 0900	80 279	6 2.40 [0.32, 4.04] 6 1.72 [0.84: 2.60]	
Liu 2018 56.55 4.1200 41 56.44 2.4100 41 2.3% 0.11 [-1.35; 1.57] Total (95% CI) 666 67 31.6% 2.73 (1.80; 3.66] Heterogenety: Tat ² = 2.500; CM ² = 92.72, 41 = 12 (P < 0.01); P ² = 80% Group = PSNCV:EAHM plus WM versus WM alone Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 43.86 4.2800 57 42.68 3.7100 76 2.4% 5.68 [440; 6.56] Gao 2012 43.20 2.6000 30 42.60 2.1000 30 2.5% 0.60 [-0.60; 1.80] Group 2013 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Clau 2015 33.19 2.1700 32 30.12 1.4100 32 2.7% 0.17; -0.55; 0.88] Zhang 2013a 45.57 7.4700 50 45.12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Clau 2016 36.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.69] Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.60 [0.84; 4.16] Wang 2017 43.70 4.580 1.780 650 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2016a 40.700 33.000 30 74.65 5.71450 74 2.3% 2.72 [1.28; 4.16] Wang 2021 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Total (95% CI) 664 665 31.7% 2.25% 4.56 [3.31; 5.61] Li 2016a 51.6 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 400 31 43.54 4.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 38.00 2.3% 3.50 [2.29; 4.71] Total (95% CI) 664 41 6.700 40 1.5% 6.100 31 1.1% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 38.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Heterogenety: Tau ² = 0.Ch ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Li 2016a 41.200 33.700 33.600 2.7800 30 2.3% 3.10 [1.55; 4.65] Ju 2016a 41.200 33.700 33.600 2.7800 30 2.3% 3.10 [1.55; 4.64] Ju 2018 45.51 5.2000 10 2.42.10 4.700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 33.45 1.5200 50 32.4720 300 2.25% 3.40 [1.415; 6.64] Huang 2017 4.303 3.700 33.600 2.7800 30 2.25% 5.40 [1.415; 6.64] Ju 2018 45.40 9000 120 4.220 3.9000 40 1.5% 5.60 [3.01; 8.19] Wang 2017 4.303 3.700 33.600 5.7000 40 1.5% 5.60 [3.01; 8.19] Wang 2017 4.303 3.700 33.600 5.7000 40 1.5% 5.60 [3.01; 8.19] Wang 2017 4.303 5.700 77 43.95 2.8300 74 2.6% 4.72 [3.37; 5.67] Total (Xie 2018	44 57 2 9900	30 40 17 1 6400	30 2.5%	6 4 40 [3 18; 5 62]	
Total (95%, CI) 666 CI, 1100 667 31.6%, 2.73 [1.80; 3.66] Heterogenetity: Tau ² = 2.5000, Ch ² = 92.72, dt = 13 (P < 0.01), $\Gamma^2 = 80\%$ Group = PSNCV:EAHM plus WW versus WM alone Lin 2010 70.28 6:1000 40 66.41 8.2000 40 1.3%, 3.87 [0.70; 7.04] Wang 2010 48.36 4.2800 76 42.68 3.7100 76 2.4%, 5.68 [4.40; 6.56] Goag 2012 43.20 2.6000 30 4.26 0.21000 30 2.5%, 0.60 [-0.60; 1.80] Gong 2013 37.91 1.8400 60 37.74 2.1700 60 2.7%, 0.17 [-0.55; 0.89] Zhang 2013 45.57 7.4700 30 45.12 7.8200 30 1.1%, 0.45 [-3.42; 4.32] Gu 2016 36.79 1.8700 51 34.78 1.6400 51 2.8%, 2.00 [0.84; 4.16] Wang 20216 40.70 3.3300 30 38.202 3.2200 30 2.2%, 2.50 [0.84; 4.16] Wang 20217 43.70 4.8500 30 37.68 5.1800 30 1.7%, 6.02 [3.48; 8.56] Gao 2019 32.08 1.7800 50 30.02 2.9100 50 2.6%, 2.00 [6.111; 3.01] Li 2018 45.19 2.08 1.7800 50 310.2 0.21%, 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5%, 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.5%, 3.50 [1.58; 1.35] Heterogenetity: Tau ² = 2.5002, Chi ² = 108.49, df = 13 (P < 0.01), $\Gamma^2 = 80\%$ Group = SSNCV:EAHM plus WW versus WM alone Li 2016 35.16 2.3800 41 35.46 6.100 31 1.4%, 3.72 [0.71; 6.73] Huang 20218 42.50 5.2000 120 3.04 90.7800 30 2.2%, 3.20 [1.85; 3.451] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4%, 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 2.5%, 3.50 [2.29; 4.71] Total (95%, CI) 664 4.6700 40 2.5%, 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 30 3.37.90 2.9000 30 2.2%, 2.2% 2.40 [0.77; 4.03] Wang 2017 40.30 3.7000 30 3.37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2018 45.40 4.9000 120 4.220 3.9000 120 2.5%, 3.20 [1.56; 4.65] Ji 2016a 41.20 3.3100 60 32.56 3.700 02 3.2%, 3.20 [2.08; 4.32] Goo 2019 3.930 1.2700 50 30.35 (5.000 120 2.5%, 5.40 [4.16; 6.64] Shi 2017 40.30 3.700 30 35.25 0.2000 120 2.5%, 3.20 [2.08; 4.32] Goo 2019 3.900 1.270 50 30.32 2.0300 50 2.2%, 3.300 [1.55; 4.65] Ji 2016a 41.20 3.3100 120 2.5%, 3.20 [2.08; 4.32] Goo 2019 3.900 1.270 50 30.32 2.0300 50 2.2%, 3.300 [2.08; 4.32] Goo 2019 3.900 1.270 50 30.32 2.0	Liu 2018	56 55 4 1200	41 56 44 2 4100	41 2.3%	6 0 11 [-1 35; 1 57]	
Heterogenetity: Tau ² = 2.5090; Chi ² = 92.72, df = 13 (P < 0.01); f ² = 86% Group = PSNCV:EAHM plus WM versus WM alone Lin 2010 70.22 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 43.86 4.2800 75 44.26 8.37100 75 42.4% 5.68 [4.40; 6.96] Gao 2012 43.20 2.6000 30 42.60 2.1000 30 2.5% 0.60 [-0.60; 1.80] Zhang 2013a 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Qi 2015 33.19 2.1700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.68] Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.70 4.850 30 37.66 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2016a 40.70 3.3300 41 54.10 41 2.3% 2.72 [1.28; 4.16] Wang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [-3.31; 5.81] Li 2015 55.12 4.4100 80 55.20 5.3100 80 2.3% 3.06 [1.56; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [-3.61; 3.64] Total (05% Cl) 664 665 31.7% 2.59 [1.65; 3.53] Heterogenetity: Tau ² = 2.5602; Chi ² = 108.49, df = 13 (P < 0.01); l ² = 8%. Group = SSNCV:EAHM plus WM versus WM alone Li 2018 47.26 5.4400 31 43.544 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 47.26 5.4400 33 65.90 2.7800 30 2.2% 2.30 [1.56; 4.45] Total (05% Cl) 181 181 6.2% 3.22 [2.33; 4.11] Heterogenetity: Tau ² = 0.8, df = 2 (P = 0.67); l ² = 0%. Group = SSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 12 33000 120 2.5% 3.36 [2.52; 4.71] Total (05% Cl) 181 181 6.2% 3.22 [2.33; 4.11] Heterogenetity: Tau ² = 0.2 Chi ² = 0.8, df = 2 (P = 0.67); l ² = 0%. Group = SSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 61 32.45 1.1900 51 2.8% 2.50 [1.65; 3.53] Huang 2016 34.55 1.5200 61 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Wang 20216 34.55 1.5200 61 32.45 1.1900 51 2.8% 2.01 [1.57; 2.63] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2016 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.50 [3.0	Total (95% CI)	00.00 4.1200	666	667 31.6%	2.73 [1.80: 3.66]	
Group = PSNCV:EAHM plus WM versus WM alone Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 48.38 4.2800 75 42.68 3.7100 76 2.4% 5.68 [4.40; 6.96] Gao 2012 43.20 2.6000 33 04.260 2.1000 30 2.5% 0.60 [-0.60; 1.80] Gong 2013 37.91 1.8400 60 37.74 2.1700 60 2.7% 0.17 [-0.55; 0.89] Jang 2013a 45.57 7.4700 30 451 27.8200 30 1.1% 0.45 [-3.42; 4.32] Guo 2016 36.79 1.8700 51 34.78 1.6400 51 2.2% 2.50 [0.84; 4.16] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 2016 36.79 1.8700 55 33.478 1.6400 51 2.2% 2.50 [0.84; 4.16] Wang 2021 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2021 56 82.9 4.140 80 55.20 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2012 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [-3.61; 1.581] Li 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% C) 664 6.55 3.100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.15; 8.81] Heterogenetity: Tau ² = 2.5602, Cht ² = 108.40, df = 13 (P < 0.01); P = 80% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% C) 664 1.5200 51 32.45 1.1900 51 2.8% 2.70 [1.25; 4.15] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% C) 181 181 6.2% 3.22 [2.33; 4.11] Heterogenetity: Tau ² = 0, Cht ² = 0.8, df = 2 (P = 0.67); P = 0.0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 30 3.800 60 2.2% 5.40 [1.15; 1.65] Thang 2016 37.90 3.3000 60 32.50 3.6000 60 2.5% 5.40 [3.15; 5.61] Huang 2018 45.40 4.9000 120 432.00 319% 3.45 [1.40; 5.50] Huang 2016 45.40 9.000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Go 2019 3.90 0.2700 50 33.25 2.0300 50 2.2% 5.40 [3.75; 6.25] Zhang 2016b 37.90 3.0000 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% C) 60 77.25 4.720 30 52.54 7.200 30 5.2% 5.00 [3.75; 6.25] Zhang 2016 42:10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016 42:10 3.5000 48 37.10 2.700	Heterogeneity: 1	$au^2 = 2.5090^{\circ}$ Cl	$hi^2 = 92.72$ df = 13 (P < 0	$(0.1) \cdot 1^2 = 869$	6 2.1.0 [1.100, 0.100]	
Group = PSNCV:EAHM plus WM versus WM alone Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% 3.87 [0.70; 7.04] Wang 2010 48.36 4.2800 75 42.68 3.7100 76 2.4% 5.68 [4.40; 6.96] Gao 2012 43.20 2.6000 30 42.60 2.1000 30 2.5% 0.60 [-0.60; 1.80] Gao 2013 3.79 11.8400 60 37.74 2.1700 60 2.7% 0.07 [-0.55; 0.89] Zhang 2013a 45.57 7.4700 32 0.45,12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Ol 2015 33.19 2.1700 32 30.12 1.4100 32 2.7% 3.07 [2.17; 3.97] Guo 2016 36.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.69] Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2021 43.20 81.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2016a 40.70 3.3300 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Li 2016a 40.70 3.3300 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Li 2016a 51.62 2.3800 41 54.81 2.2700 41 2.5% 4.56 [3.31; 5.81] Li 2016 55.16 2.3800 41 54.81 2.2700 41 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 12 2.5% 3.50 [2.69; 4.71] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Hue 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Hu 2018 47.26 5.4400 31 0.2.8100 42 0.2.5% 5.50 [2.33; 4.11] Heterogeneity: Tau ² = 0.5(Ch ² = 0.87); f ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 3.6.9 2.7800 30 2.3% 2.70 [1.25; 4.15] Group 2116 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] That g2018 45.00 5.2000 51 32.45 1.1900 51 2.25% 5.50 [2.0; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.03; 4.11] Heterogeneity: Tau ² = 0.5(Ch ² = 0.67); f ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 65.41 6.0700 40 62.24 16.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2019 33.90 1.2700 80 32.2.59 2.2000 52.8% 3.58 [2.52; 4.24] Li 2019a 33.20 6.1000 40 33.80 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021 36.67 3.0500 74 34.35 2.8300 74 2.26% 4.72 [3.77; 5.67] Total (95% CI) 607 743.435 2.8300 74 2.26%	filotorogonoity. I	uu – 2.0000, 01	in = 02.12, ui = 10 (i · 0		0	
Lin 2010 70.28 6.1000 40 66.41 8.2000 40 1.3% $3.87 [0.70; 7.04]$ Wang 2010 44.36 4.2800 75 42.68 3.7100 76 2.4% $5.68 [4.40; 6.96]$ Gao 2012 33.7.91 1.8400 60 37.74 2.1700 60 2.7% $0.17 [-0.55; 0.89]$ Jang 2013 35.91 1.8400 60 37.74 2.1700 30 4.5[-2 7.8200 30 1.1% $0.45 [-3.42; 4.32]$ Ol 2015 33.19 2.1700 32 30.12 1.4100 32 2.7% $3.07 [2.17; 3.97]$ Guo 2016 $36.79 1.8700$ 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.69] Li 2016 40.70 3.300 30 32.03 2.2020 32.22% $2.50 [0.84!$ 4.16] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% $6.02 [3.48; 8.56]$ Gao 2019 32.08 1.7900 55 30.02 2.9100 50 2.6% $2.266 [1.113.01]$ Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% $2.72 [1.28; 4.16]$ Wang 2021b 58.29 4.4100 85.52 0.53100 80 2.3% $3.09 [1.58; 4.60]$ Zhang 2021 40.13 3.5600 74 3.557 4.1500 74 2.5% $4.56 [3.315; 8.81]$ Liu 2018 $55.16 2.3800$ 74 35.57 4.1500 74 2.5% $4.56 [1.35; 3.53]$ Heterogeneity: Tau ² = 2.6602; Chi ² = 108.49, df = 13 (P < 0.01); l ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 43.26 5.2000 120 39.00 4.3000 120 2.25% $3.50 [2.29; 4.71]$ Total (95% CI) 181 1 81 6.2% $3.22 [2.33; 3.10]$ 1.81 6.2% $3.22 [2.33; 4.11]$ Heterogeneity: Tau ² = 0; Chi ² = 0.8, dl = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2016 64.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 4.65] Zhang 2016 37.90 3.300 60 32.50 3.6000 60 2.5% $3.20 [2.29; 4.71]$ Total (95% CI) 661 2.600 120 4.22.03 3000 120 2.5% $3.50 [2.29; 4.71]$ Huang 2018 45.04 3.0000 120 4.22.83 0.001 120 2.5% $3.50 [2.29; 4.71]$ Total (95% CI) 607 05 30.32 2.3000 120 2.5% $3.50 [2.29; 4.24]$ Liu 2019 45.01 3.000 30 35.25 4.7200 30 1.9% $3.45 [1.40; 5.66]$ Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 64.41 6.0700 40 62.41 6.4700 40 1.5% 6.20 [3.25; 8.75] Gao 2019 33.90 1.2700 50 30.32 2.3000 74 2.5% $3.50 [2.29; 4.24]$ Liu 2019 45.03 3.5700 200 77.27 3.8200 80 2.6% $3.56 [2.29; 4.24]$ Liu 2	Group = PSNC	V:EAHM plus	WM versus WM alone	è		
Wang 2010 48.36 4.2800 75 42.68 3.7100 76 2.4% 5.68 [4.40; 6.96] Gao 2012 43.20 2.6000 30 42.60 2.1000 30 2.5% 0.60 [-0.60; 1.80] Chang 2013 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Gli 2015 33.19 2.1700 23 30.12 1.4100 32 2.7% 3.07 [2.17; 3.97] Guo 2016 36.79 1.8700 51 34.78 1.6400 51 2.2% 2.00 [0.84; 4.16] Wang 2017 43.70 4.580 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2014 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Li 2015 85.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.68; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Heterogeneity: Tau ² = 2.5602; Chi ² = 108.49, df = 13 (P < 0.01); l ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 44.20 5.200 12 03.00 4.3000 120 2.5% 3.60 [2.29; 4.71] Total (95% Cl) 66.4 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 0.50, df = 2 (P = 0.67); l ² = 0% Group = SSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 130 3.80 2.7800 30 2.3% 3.10 [1.55; 4.65] Shi 2017 40.30 3.7000 32 3.790 2.9000 50 2.2% 5.40 [4.10; 5.64] Shi 2017 40.30 3.7000 32 2.590 2.5000 50 2.8% 3.50 [2.29; 4.71] Heterogeneity: Tau ² = 0; Chi ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2016 64.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 3.455 1.5200 51 32.42 5.1000 50 2.2% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 2.590 500 2.2 5.% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 2.500 500 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.5% 5.60 [3.01; 8.19] Wang 2021b 43.90 1.2700 50 3.22 0.2000 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 3.900 1.204 2.203 3000 1.20 2.5% 5.40 [4.17; 6.64] Group = USNCV:EAHM plus WM versus WM alone Lin 2016a 42.10 3.5000 74 33.45 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% Cl) Group = USNCV:EAHM plus WM versus WM	Lin 2010	70.28 6.1000	40 66.41 8.2000	40 1.3%	6 3.87 [0.70: 7.04]	
Gao 2012 43.20 2.6000 30 42.60 2.1000 30 2.5% 0.60 $[-0.60; 1.80]$ Gong 2013 37.91 1.8400 60 57.74 2.1700 60 2.7% 0.17 $[-0.55; 0.89]$ Zhang 2013 34.557 7.4700 30 45.12 7.8200 30 1.1% 0.45 $[-3.42; 4.32]$ Glou 2016 35.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 $[1.33; 2.69]$ Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 $[0.84; 4.16]$ Wang 2017 43.70 4.8500 50 30.02 2.9100 50 2.6% 2.06 $[1.11; 3.01]$ Li 2016a 40.70 3.3300 74 35.57 4.1500 74 2.3% 2.72 $[1.28; 4.16]$ Wang 2021 58.29 4.410 80 55.20 5.3100 80 2.3% 3.09 $[1.58; 4.60]$ Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 $[3.31; 5.81]$ Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 $[-0.66; 1.36]$ Heterogeneity: Tau ² = 2.5602; Ch ² = 108.49, df = 13 (P < 0.01); P ² = 88% Group = SNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 30.500 2.2% 3.00 $[1.55; 3.53]$ Heterogeneity: Tau ² = 2.5602, Ch ² = 108.49, df = 13 (P < 0.01); P ² = 88% Group = SNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 $[3.25; 8.75]$ Guo 2016 34.55 1.520 51 21.26 3.100 30 2.3% 3.10 $[1.55; 4.65]$ Zhang 2017 40.30 3.7000 32 3.7.90 2.3000 32 2.2% 2.40 $[0.77; 4.03]$ Wang 2021 40.33 3.100 30 38.10 2.8100 30 2.3% 3.10 $[1.55; 4.65]$ Zhang 2016 34.50 1.5200 51 2.845 1.1900 51 2.8% 5.401 $[1.55; 2.63]$ Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 $[1.55; 4.65]$ Zhang 2017 43.70 3.2700 80 47.27 3.8200 32 2.2% 2.40 $[0.77; 4.03]$ Wang 2021 40.30 3.7000 32 3.7.90 2.9000 32 2.2% 3.20 $[2.08; 4.32]$ Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 $[2.92; 4.24]$ Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 $[1.55; 4.65]$ Zhang 2016b 3.73 0.3.700 80 47.27 3.8200 80 2.6% 5.00 $[3.75; 6.25]$ Group = USNCV:EAHM plus WM versus WM alone Zhang 2016 42.01 3.9000 120 2.5% 5.00 $[3.75; 6.25]$ Group = USNCV:EAHM plus WM versus WM alone Zhang 2017 38.70 3.2000 60 3.200 50 2.8% 3.58 $[2.92; 4.24]$ Liu 2019a 33.20 6.1000 40 33.65 2.7000 60 2.6% 5.00 $[3.75; 6.25]$ Group = USNCV:EAHM plus WM versus WM al	Wang 2010	48.36 4.2800	75 42.68 3.7100	76 2.4%	5.68 [4.40; 6.96]	
Gong 2013 37.91 1.8400 60 37.74 2.1700 60 2.7% 0.17 [-0.55: 0.89] Zhang 2013a 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.45 [-3.42; 4.32] Gu 2016 33.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33: 2.69] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Wang 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31: 5.81] Liu 2018 55.16 2.3800 41 64.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Ch ² = 108.49, df = 13 (P < 0.01); ² = 88% Group = SNCV:EAHM plus WW versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 3.455 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.700 510 32.63 0.5000 120 2.5% 3.20 [1.65; 4.55] Gao 2019 33.90 1.2700 50 30.362 0.300 120 2.5% 2.10 [1.57; 2.63] Li 2016a 41.0700 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 80 47.27 3.8200 80 2.6% 3.20 [2.03; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.3000 50 2.8% 3.56 [2.92; 4.24] Liu 2018a 45.40 4.9000 120 4.20 3.9000 120 2.5% 2.03 [1.95; 4.55] Group = USNCV:EAHM plus WW versus WM alone Lin 2010 68.41 6.0700 40 3.65 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2017 38.70 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.933.13] Zhang 2016 37.90 3.3700 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.933.13] Zhang 2016 42.01 3.900 120 42.03 9.9000 120 2.5% 5.50 [2.79; 4.39] Heterogeneity: Tau ² = 1.971; Ch ² = 52.42, df = 10 (P < 0.01); 1 ² = 81% Group = USNCV:EAHM plus WW versus WM alone Zhang 2016 42.01 3.5000 f0 3.310 2.9000 60 2.6% 5.10 [4.01; 6.19]	Gao 2012	43.20 2.6000	30 42.60 2.1000	30 2.5%	6 0.60 [-0.60; 1.80]	
Zhang 2013a 45.57 7.4700 30 45.12 7.8200 30 1.1% 0.45 ⁻ [-3.42; 4.32] Gl 2015 33.19 2.1700 32 30.12 1.4100 32 2.7% 3.07 [2.17: 3.97] U1 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2014 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Chi ² = 108.49, df = 13 (P < 0.01); l ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 616 6.2% 3.7% 2.10 [1.57; 2.63] Heterogeneity: Tau ² = 0.Chi ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2016 37.40 33 0.300 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.300 120 32.54 7.7200 30 1.9% 3.45 [1.40; 5.60] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 3.322 5.4 7.7200 30 1.9% 3.45 [1.40; 5.60] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.3700 50 2.8% 3.58 [2.92; 4.24] Heterogeneity: Tau ² = 1.2971; Chi ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2015 42.10 3.5000 64 37.10 2.7000 60 2.6% 5.00 [3.75; 6.25] Zhang 2016 42.10 3.0000 60 3.40 1.6% 5.00 [3.75; 6.25] Total (95% CI) 607 607 76 72 5.5% 5.00 [3.75; 6.25] Total (95% CI) 607 60 76 72 5.5% 5.00 [3.75; 6.25] Total (95% CI) 607 60 70 2.5.% 5.00 [3.75; 6.25] Zhang 2016 42.10 3.5000 64 83 7.10 2.7000 6	Gong 2013	37.91 1.8400	60 37.74 2.1700	60 2.7%	6 0.17 [-0.55; 0.89]	
Qi 2015 33.19 2.1700 32 30.12 1.4100 32 2.7% 3.07[2.17;37] Guo 2016 36.79 1.8700 51 34.78 1.6400 51 2.8% 2.01 [1.33; 2.69] Li 2016 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.00 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 3.557 4.1500 74 2.5% 4.56 [3.3; 15.81] Li 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.36 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Chi ² = 108.49, df = 13 (P < 0.01; J ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 47.26 5.4000 120 30.90.04.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0; Chi ² = 0.8, df = 2 (P = 0.67; J ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Li 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Group = TSNCV:EAHM plus WM versus WM alone Li 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.6700 40 06.241 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.210 30 2.3% 3.10 [1.55; 4.65] Jang 2016b 37.90 3.300 60 32.50 3.6000 02 2.5% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 2.37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 6.54] Jang 2016b 3.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.29; 4.24] Li 2018a 3.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.29; 4.24] Li 2019a 3.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.29; 4.42] Heterogeneity: Tau ² = 1.2971; Chi ² = 52.42, df = 10 (P < 0.01); J ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016b 42.20 3.9000 f00 2.6% 5.00 [3.75; 6.25] Theterogeneity: T	Zhang 2013a	45.57 7.4700	30 45.12 7.8200	30 1.19	6 0.45 [-3.42; 4.32]	_
Guo 2016 $36.79 + 1.8700$ 51 $34.78 + 1.6400$ 51 2.8% 2.01 [$1.33; 2.69$] Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [$0.84; 4.16$] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [$3.48; 8.56$] Gao 2019 $32.08 + 1.7900$ 50 $30.02 2.9100$ 50 2.6% 2.06 [$1.11; 3.011$] Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [$1.28; 4.16$] Wang 2021b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [$1.58; 4.60$] Zhang 2021 40.13 3.5800 74 $35.57 4.1500$ 74 2.5% 4.56 [$3.31; 5.81$] Li 2018 $55.16 2.3800$ 41 $54.81 2.2700$ 41 2.6% 0.35 [$-0.66; 1.36$] Total (95% CI) 664 $458 2.2700$ 41 2.6% 0.35 [$-0.66; 1.36$] Total (95% CI) 664 $458 2.2700$ 41 2.6% 3.50 [$1.65; 3.53$] Heterogeneity: Tau ² = 2.5602 ; Ch ² = 108.49 , df = 13 (P < 0.01); P ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a $39.60 2.9600$ 30 $3.6.92.7800$ 30 2.3% 2.70 [$1.25; 4.15$] Huag 2018 $42.250 5.2000$ 120 $39.00 4.3000$ 120 2.5% $3.50 [2.29; 4.71]Total (95% CI) 181 13.54 6.6100 31 1.4\% 3.72 [0.71; 6.73]Huag 2018 42.50 5.2000 120 39.00 4.3000 120 2.5\% 3.50 [2.29; 4.71]Total (95% CI) 181 12.245 1.1900 51 2.8\% 2.10 [1.57; 2.63]Li 2016a 34.55 1.5200 51 32.45 1.1900 51 2.8\% 3.10 [1.55; 4.65]Zhang 2016b 37.90 3.3000 60 32.50 3.6000 60 2.5\% 5.40 [4.16; 6.64]Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2\% 3.20 [2.08; 4.32]Gao 2019 33.900 120 242.20 3.9000 120 2.5\% 3.20 [2.08; 4.32]Gao 2019 33.900 120 42.20 3.9000 120 2.5\% 3.20 [2.08; 4.32]Gao 2019 33.900 1.2700 50 3.32 2.54\% 3.200 [2.8\% 3.55 [2.79; 4.39]Heterogeneity: Tau2 = 1.2971; Ch2 = 52.42, df = 10 (P < 0.01); P2 = 81%Group = USNCV:EAHM plus WM versus WM aloneZhang 20156 42.10 3.5000 74 8.37.10 2.7000 48 2.5\% 5.00 [3.75; 6.25]Chan 20156 42.20 3.9000 60 2.6\% 5.101 (401; 6.191]$	Qi 2015	33.19 2.1700	32 30.12 1.4100	32 2.7%	6 3.07 [2.17; 3.97]	4
Li 2016a 40.70 3.3300 30 38.20 3.2200 30 2.2% 2.50 [0.84; 4.16] Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 8.56] Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021b 48.280 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tat ² = 2.5602; Ch ² = 108.49, df = 13 (P < 0.01); P ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tat ² = 0; Ch ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Li 2016 64.1 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 64.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2017 40.30 3.7000 32 27.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 32.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021 43.03 3.700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Heterogeneity: Tat ² = 1.2971; Ch ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 74 83.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tat ² = 1.2971; Ch ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNC	Guo 2016	36.79 1.8700	51 34.78 1.6400	51 2.8%	6 2.01 [1.33; 2.69]	
Wang 2017 43.70 4.8500 30 37.68 5.1800 30 1.7% 6.02 [3.48; 856] Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total [95%, CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Chl ² = 108.49, df = 13 ($P < 0.01$); $P^{2} = 88\%$ Group = SSNCV:EAHM plus WW versus WM alone Li 2016a 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total [95%, CI) 84.45 1.5200 51 22.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.50 3.3100 30 32.790 2.2000 30 2.2% 3.301 [1.55; 4.66] Zhang 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.50 3.3000 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 2.790 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 8.70 3.2700 30 35.25 4.7200 30 1.2 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.03; 1.31] Huang 2018 45.0 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.79; 2.42] Liu 2013 39.20 6.1000 40 33.60 5.7000 40 1.6% 6.60 [3.01; 8.19] Wang 2017 45.70 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Zhang 2021 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Zhang 2021 49.30 3.2700 80 47.27 3.8200 80 2.6% 4.72 [3.77; 5.67] Total [95%, CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Ch ² = 52.42, df = 10 ($P < 0.01$); $P^{2} = 81\%$ Group = USNCV:EAHM plus WW versus WM alone Zhang 2016a 42.10 3.5000 74 34.95 2.8300 74 2.6% 5.00 [3.75; 6.25] Theterogeneity: Tau ² = 1.2971; Ch ² = 52.42, df = 10 ($P < 0.01$); $P^{2} = 81\%$	Li 2016a	40.70 3.3300	30 38.20 3.2200	30 2.2%	6 2.50 [0.84; 4.16]	
Gao 2019 32.08 1.7900 50 30.02 2.9100 50 2.6% 2.06 [1.11; 3.01] Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Chl ² = 108.49, df = 13 (P < 0.01); l ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.200 120 30.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0; Chl ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2016b 37.90 3.3000 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Goa 2019 33.90 1.2700 50 30.32 2.0300 50 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Mang 2021 49.30 3.2700 80 47.27 3.8200 80 2.6% 5.00 [3.01; 8.19] Wang 2021 19.67 3.0500 74 43.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chl ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 74 8.37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chl ² = 52.42, df = 10 (P < 0.01); l ² = 81%	Wang 2017	43.70 4.8500	30 37.68 5.1800	30 1.7%	6.02 [3.48; 8.56]	— <mark>— —</mark>
Li 2021 42.83 3.2100 41 40.11 3.4200 41 2.3% 2.72 [1.28; 4.16] Wang 2021b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total [95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Chi ² = 108.49, df = 13 (P < 0.01); l ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0; Chi ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2016 37.90 3.3000 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 3.03.2 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chi ² = 5.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Total (95% CI) 607 607 25.4% 5.00 [3.75; 6.25] Total (95% CI)	Gao 2019	32.08 1.7900	50 30.02 2.9100	50 2.6%	6 2.06 [1.11; 3.01]	
Wang 2021b 58.29 4.4100 80 55.20 5.3100 80 2.3% 3.09 [1.58; 4.60] Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602, Chi ² = 108.49, df = 13 (P < 0.01); I^2 = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0; Chi ² = 0.8, df = 2 (P = 0.67); I^2 = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2016 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.65 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2017 38.70 3.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chi ² = 5.242, df = 10 (P < 0.01); I ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chi ² = 5.242, df = 10 (P < 0.01); I ² = 81%	Li 2021	42.83 3.2100	41 40.11 3.4200	41 2.3%	6 2.72 [1.28; 4.16]	_ _
Zhang 2021 40.13 3.5800 74 35.57 4.1500 74 2.5% 4.56 [3.31; 5.81] Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Ch ² = 108.49, df = 13 (P < 0.01); I ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu ang 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0; Chl ² = 0.8, df = 2 (P = 0.67); I ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.75; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.75; 2.63] Li 2016a 41.20 3.3100 30 35.25 4.7200 30 1.9% 3.45 [1.40; 6.64] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 6.50] Huang 2018 45.40 4.9000 120 42.20 3.0000 120 2.5% 3.50 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [3.01; 8.19] Wang 2021b 49.30 3.2700 74 34.95 2.8300 74 2.6% 4.72 [3.77; 6.67] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chl ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Total (95% CI) 607 607 25.4% 5.10 [4.01; 6.19]	Wang 2021b	58.29 4.4100	80 55.20 5.3100	80 2.3%	6 3.09 [1.58; 4.60]	- <mark>#</mark> -
Liu 2018 55.16 2.3800 41 54.81 2.2700 41 2.6% 0.35 [-0.66 ; 1.36] Total (95% CI) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Ch ² = 108.49, df = 13 (P < 0.01); I ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% CI) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0; Chr ² = 0.8, df = 2 (P = 0.67); I ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 50 30.32 2.0300 50 2.8% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.68 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chr ² = 52.42, df = 10 (P < 0.01); I ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 60 3.9100 2000 60 2.6% 5.10 [4.01:6.19]	Zhang 2021	40.13 3.5800	74 35.57 4.1500	74 2.5%	6 4.56 [3.31; 5.81]	
Total (95% Cl) 664 665 31.7% 2.59 [1.65; 3.53] Heterogeneity: Tau ² = 2.5602; Chi ² = 108.49, df = 13 (P < 0.01); l ² = 88% Group = SSNCV:EAHM plus WM versus WM alone Li 2016a 39.60 2.9600 30 36.90 2.7800 30 2.3% 2.70 [1.25; 4.15] Hu 2018 47.26 5.4400 31 43.54 6.6100 31 1.4% 3.72 [0.71; 6.73] Huang 2018 42.50 5.2000 120 39.00 4.3000 120 2.5% 3.50 [2.29; 4.71] Total (95% Cl) 181 181 6.2% 3.22 [2.33; 4.11] Heterogeneity: Tau ² = 0, Chi ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.55; 4.65] Zhang 2016b 37.90 3.3000 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 30 38.52 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 50 30.32 2.0300 50 2.8% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.68 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% Cl) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chi ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Total (95% Cl) 60.7 60.3 9102 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 3.710 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016	Liu 2018	55.16 2.3800	41 54.81 2.2700	41 2.6%	6 0.35 [-0.66; 1.36]	
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Total (95% Cl) 181 181 6.2% $3.22 [2.33; 4.11]$ Heterogeneity: Tau ² = 0; Ch ² = 0.8, df = 2 (P = 0.67); l ² = 0% Group = TSNCV:EAHM plus WM versus WM alone Lin 2010 68.41 6.0700 40 62.41 6.4700 40 1.5% 6.00 [3.25; 8.75] Guo 2016 34.55 1.5200 51 32.45 1.1900 51 2.8% 2.10 [1.57; 2.63] Li 2016a 41.20 3.3100 30 38.10 2.8100 30 2.3% 3.10 [1.55; 4.65] Zhang 2016b 37.90 3.3000 60 32.50 3.6000 60 2.5% 5.40 [4.16; 6.64] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2700 30 35.25 4.7200 30 1.9% 3.45 [1.40; 5.50] Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Zhang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% Cl) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Ch ² = 52.42, df = 10 (P < 0.01); l ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016b 44.210 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016b 44.20 3.2000 60 39 10 2.9000 40 2.6% 5.10 [4.01; 6.19]	Huang 2018	42.50 5.2000	120 39.00 4.3000	120 2.5%	6 3.50 [2.29; 4.71]	
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Zhang 2018b 37.50 35.000 60 32.50 3.6000 60 2.5% 3.40 [4.16, 6.64] Shi 2017 40.30 3.7000 32 37.90 2.9000 32 2.2% 2.40 [0.77; 4.03] Wang 2017 38.70 3.2000 120 2.2% 2.40 [0.77; 4.03] Huang 2018 45.40 4.9000 120 42.20 3.900 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24]	Zhong 2010b	41.20 3.3100	50 30.10 2.8100	50 2.3%	5.10[1.55; 4.65]	
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Wang 2017 36.70 350.25 47.200 30 1.5% 3.40 1.40 3.60 1.40 3.60 1.40 4.50 Huang 2018 45.40 4.9000 120 42.20 3.9000 120 2.5% 3.20 [2.08; 4.32] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 0.93; 3.13] Zhang 2021 39.67 3.050 74 3.49 2.6% 4.72 [3.77; 5.67] Total (95% CI) 607 607 25.4% 3.59 [2.79; 4.39] Heterogeneity: Tau ² = 1.2971; Chi ² = 52.42, df = 10 (P < 0.01); I ² = 81% </td <td>Wang 2017</td> <td>40.30 3.7000</td> <td>32 37.50 2.5000</td> <td>30 1.00</td> <td>2.40 [0.77, 4.03]</td> <td></td>	Wang 2017	40.30 3.7000	32 37.50 2.5000	30 1.00	2.40 [0.77, 4.03]	
Gao 2019 33.90 1.20 2.20 3.500 1.20 2.15% 3.20 [2.06, 4.52] Gao 2019 33.90 1.2700 50 30.32 2.0300 50 2.8% 3.58 [2.92; 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Zhang 2021 39.67 3.0500 74 3.495 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% Cl) 607 607 25.4% 3.59 [2.79; 4.39]	Wang 2017	45 40 4 9000	120 42 20 2 0000	120 2.50	0 3.40 [1.40; 0.00]	
Gao 2015 33.50 1.2100 50.32 2.0300 50 2.576 5.50 [2.32, 4.24] Liu 2019a 39.20 6.1000 40 33.60 5.7000 40 1.6% 5.60 [3.01; 8.19] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Zhang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% Cl) 607 607 25.4% 3.59 [2.79; 4.39]	Gao 2019	33 90 1 2700	50 30 32 2 0200	50 2.0%	0 3.20 [2.00, 4.32]	
Lid 2013a 33.20 51.000 40 35.00 51.000 40 1.5% 5.00 [3.01, 6.15] Wang 2021b 49.30 3.2700 80 47.27 3.8200 80 2.6% 2.03 [0.93; 3.13] Zhang 2021 39.67 3.0500 74 34.95 2.8300 74 2.6% 4.72 [3.77; 5.67] Total (95% Cl) 607 607 25.4% 3.59 [2.79; 4.39]	Gao 2019	39.20 6 1000	40 33 60 5 7000	40 4.09	0 0.00 [2.02, 4.24]	
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Zhang 2021 35.07 35.00 74 25.800 74 25.87 5.07 <td>Zhang 2021D</td> <td>49.30 3.2700</td> <td>74 34 95 2 8200</td> <td>74 2.6%</td> <td>0 ∠.∪ວ[∪.⊎ວ, ວ.13] 4 70 [3 77:5 67]</td> <td></td>	Zhang 2021D	49.30 3.2700	74 34 95 2 8200	74 2.6%	0 ∠.∪ວ[∪.⊎ວ, ວ.13] 4 70 [3 77:5 67]	
Heterogeneity: Tau ² = 1.2971; Chi ² = 52.42, df = 10 (P < 0.01); I ² = 81% Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016b 44 20 3 2000 60 39 10 2 9000 60 2 6% 5 10 [4.01: 6.19]	Total (05% CI)	39.67 3.0000	14 34.33 2.0300 607	607 25.49	0 4.72[3.77, 0.07]	
Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25] Zhang 2016b 44 20 3 2000 60 39 10 2 9000 60 2.6% 5 10 [4.01: 6.19]	Hotorogonoity: 7	$au^2 = 1.2074$	$hi^2 = 52.42 df = 10.02 < 0.02$	$101 \cdot 1^2 = 010$	o 0.09 [Z.19; 4.09]	
Group = USNCV:EAHM plus WM versus WM alone Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25]	neterogeneity. I	au – 1.2971, U	III – J2.42, UI – IU (P ≤ U	.01),1 - 019	v	
Zhang 2016a 42.10 3.5000 48 37.10 2.7000 48 2.5% 5.00 [3.75; 6.25]	Group = USNO	V:EAHM nlus	WM versus WM alone	9		
Thang 2016b 44 0 3 2000 60 39 10 2 9000 60 2 6% 5 10 14 01 6 19	Zhang 2016a	42 10 3 5000	48 37 10 2 7000	48 2.5%	5 00 [3 75: 6 25]	
	Zhang 2016b	44.20 3.2000	60 39.10 2.9000	60 2.6%	5.10 [4.01: 6.19]	

the WM monotherapy control (*n* = 4454; MD 3.06, 95% CI 2.56–3.56, *p* < 0.0001; heterogeneity chi-square = 317.64, df = 43, *p* < 0.01; I² = 86%; Figure 4).



5.0%

2228 100.0%

5.06 [4.23; 5.88]

3.06 [2.56; 3.56]

-5

0

Favours control Favours experimental SNCV

5

108

2226

Heterogeneity: Tau² = 2.2096; Chi² = 317.64, df = 43 (P < 0.01); I² = 86%

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0\%$

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3.4.2. Primary Outcome: Motor NCV (MNCV)

MNCV was measured in 25 studies, including nine studies on EAHM monotherapy [38,40,44,49,59,68,70,72,81] and 16 studies on combined EAHM and WM therapy [41,42,45,46,48,53,57,63,65,71,77,79,84,86,95,96]. The combined effect of EAHM monotherapy on MNCV was significantly higher than the WM control (n = 1788, MD 2.38, 95% CI 1.43–3.32, p < 0.0001; heterogeneity chi-square = 179.27, df = 17, p < 0.01; I² = 84%; Figure 5).



Figure 5. Forest plot of the trials reporting the effect of East Asian herbal medicine monotherapy on motor nerve conduction velocity for peripheral neuropathy.

In addition, the combined EAHM and WM therapy significantly improved MNCV than WM monotherapy (n = 2860, MD 3.23, 95% CI 2.58–3.88, p < 0.0001; heterogeneity chi-square = 179.27, df = 28, p < 0.01; I² = 84%; Figure 6).

Study or	Experimental		Control		Mean Difference	e Mean Difference	
Subgroup Group = MMN	Mean SD	Total Mean	SD Total	Weight	IV, Random, 95%	CI IV, Random, 95% C	21
Wang 2010	52.34 4.5700	80 45.53	5.5700 79	3.5%	6.81 [5.23; 8.3	9]	
Gao 2012	47.40 2.8000	30 45.70	2.3000 30	3.8%	1.70 0.40; 3.0	oj –	
Zhang 2013a	50.46 4.3700	30 49.68	6.9400 30	2.3%	0.78 [-2.15; 3.7		_
Zhang 20160 Yi 2019	48.00 3.1000	54 41 29	2.5000 60 4.2100 53	4.0%	5.50 [4.49, 6.5 3 4 3 [1 92 [.] 4 9	1]	- -
Liu 2019a	42.80 5.6000	40 39.20	5.8000 40	2.7%	3.60 [1.10; 6.1		
Li 2021	52.55 4.8200	41 50.22	4.7100 41	3.1%	2.33 [0.27; 4.3	ej 🚽 📕	
Wang 2021b	55.40 4.2400	80 52.56	4.1200 80	3.8%	2.84 [1.54; 4.1		_
Liu 2018	43.86 1.7000	41 56 44	2.4700 30	3.9%	0.11[-1.35] 1.5	ין ⊐ 71 –	—
Total (95% CI)	00.00 11200	486	484	34.1%	3.31 [1.96; 4.6	5] 🕇 🔶	
Heterogeneity: 7	āu ² = 3.9673; Ch	ni ² = 73.33, df	= 9 (P < 0.01); I	² = 88%			
Group = PMN(WM vorcus	WM alone				
Lin 2010	58.61 5.1500	40 52.33	5.2500 40	2.9%	6.28 [4.00: 8.5	51 –	_
Wang 2010	47.32 4.7800	80 44.65	5.4500 79	3.5%	2.67 [1.08; 4.2	5j –	_
Gao 2012	42.20 3.2000	30 39.70	2.8000 30	3.6%	2.50 [0.98; 4.0	2]	
Gong 2013	38.76 2.6700	60 37.29	3.1300 60	4.0%		1]	
Qi 2015	45.61 1.7600	32 41.18	1.9700 32	4.1%	4.43 [3.51: 5.3	5]	
Guo 2016	36.79 1.8700	51 34.78	1.6400 51	4.2%	2.01 [1.33; 2.6	-] <mark></mark> -	
Zhang 2016a	40.70 5.8000	48 35.50	5.3000 48	2.9%	5.20 [2.98; 7.4	2]	
Hu 2018	50.58 2.8600	31 46.46	3.1800 31	3.6%	4.12 [2.61; 5.6]	3]	_
Li 2021	43.05 4.3000	41 41.03	4.2800 41	3.2%	2.02 [0.16: 3.8	31	
Wang 2021b	48.27 4.1700	80 44.89	4.6900 80	3.7%	3.38 [2.00; 4.7	5]	
Liu 2018	55.16 2.3800	41 54.81	2.2700 41	4.0%	0.35 [-0.66; 1.3	6] -	
Total (95% CI)	-1.9579 Ck	618 ² = 62.16 df	616 - 12 (D < 0.01):	45.0%	2.98 [2.12; 3.8	5] 🔶	
Heterogeneity.	au – 1.6576, Ci	ii – 03.10, ui -	-12(F < 0.01),	1 - 0170			
Group = TMN	CV:EAHM plus	WM versus	WM alone				_
Lin 2010	56.70 3.6500	40 50.54	3.5400 40	3.5%	6.16 [4.58; 7.7	4] -	
Zhang 2016b	41 40 3 6000	60 38 80	3 2000 60	2.9%	2.60 [0.38, 4.8, 2.60 [1.38, 3.8]	2]	
Liu 2019a	39.20 6.1000	40 33.60	5.7000 40	2.6%	5.60 [3.01; 8.1	-]	- <mark></mark>
Wang 2021b	50.59 2.7700	80 48.86	2.8700 80	4.1%	1.73 [0.86; 2.6)] 	
Total (95% CI)	-2.2075	268	268	16.9%	3.62 [1.84; 5.3	9]	-
Heterogeneity.	au = 3.3275, Cr	11 = 27.8, d1 =	4 (P < 0.01), 1	= 80%			
Group = UMN	CV:EAHM plus	WM versus	WM alone				
Zhang 2016b	46.60 3.0000	60 43.30	2.7000 60	4.0%	3.30 [2.28; 4.3	2] –	
Heterogeneity: r	ot applicable	60	60	4.0%	3.30 [2.28; 4.3	2]	
. leterogeneity. I	iot appriousio						
Total (95% CI)	2	1432	1428	100.0%	3.23 [2.58; 3.8	B] 🔶	-
Heterogeneity: 1	āu∸ = 2.4770; Cł	hi∸ = 179.27, di	f = 28 (P < 0.01); I [∠] = 84%	6	-5 0	1 5
						Favours control Favours	experimental
						MNCV	

Figure 6. Forest plot of the trials reporting the effect of combined East Asian herbal medicine and western medicine therapy on motor nerve conduction velocity for peripheral neuropathy.

3.4.3. Primary Outcome: Response Rate

The response rate was assessed in 48 studies, including 22 studies on EAHM monotherapy [40,43,44,49,54,55,59,60,64,66,68,70,72–76,81,82,99,100] and 26 studies on combined EAHM and WM therapy [39,41,42,45–48,50–53,57,58,61–63,65,69,71,78,80,85,95,102–104]. Twentyfive studies [39,41,42,45–48,50,58,62,63,65,69,71,78,80,85,95,103,104] compared the effect of EAHM monotherapy on the response rate with WM, and the remaining study [61] compared it with the untreated control. The combined effect of EAHM monotherapy on the response rate was significantly better than the WM control (n = 1651, risk ratio (RR) 1.30, 95% CI 1.21–1.40, p < 0.0001; heterogeneity chi-square = 39.53, df = 20, p < 0.01; $I^2 = 49\%$; Figure 7). Additionally, the combined EAHM and WM therapy significantly improved the response rate than the WM monotherapy (n = 1997, RR 1.20, 95% CI 1.15–1.25, p < 0.0001; heterogeneity chi-square = 26.03, df = 24, p = 0.35; $I^2 = 8\%$; Figure 8). The effect on the response rate was also significant in one study comparing EAHM monotherapy with the untreated control (n = 227, RR 1.19, 95% CI 1.03–1.37, p < 0.01). A visual summary of the confidence level for individual studies and pooled estimates using the response rate is presented through a drapery plot (Figure 9).

Study or Subgroup	Experin Events	nental Total	Co Events	ontrol Total	Weight	Risk Ratio IV, Random, 95% C	Risk Ratio I V, Random, 95% Cl
Group = EAH	VI versus	WM				,	
Shen 2009	48	50	47	50	9.7%	1.02 [0.93; 1.12]	<u>+</u>
Yan 2010	14	14	14	15	8.4%	1.07 [0.94; 1.22]	
Wu 2011	24	30	14	27	2.5%	1.54 [1.03; 2.31]	
Zhang 2013b	23	30	16	30	2.7%	1.44 [0.97; 2.12]	
Wang 2015	33	40	16	40	2.5%	2.06 [1.37; 3.09]	
Xue 2015	39	42	30	42	5.9%	1.30 [1.05; 1.60]	 ₽
Lan 2016	47	50	34	52	5.9%	1.44 [1.17; 1.77]	- <u>-</u>
Mo 2016	30	32	21	33	4.4%	1.47 [1.12; 1.94]	
Li 2016b	58	60	45	60	7.6%	1.29 [1.11; 1.50]	
Chen 2017	26	30	17	30	3.3%	1.53 [1.09; 2.16]	
Wang 2017	26	30	19	30	3.8%	1.37 [1.01; 1.86]	
Dai 2018	34	40	25	40	4.4%	1.36 [1.04; 1.79]	
Huang 2018	94	120	74	120	7.1%	1.27 [1.07; 1.51]	
She 2018	23	30	14	30	2.3%	1.64 [1.07; 2.53]	
Xin 2018	28	30	22	30	5.2%	1.27 [1.01; 1.61]	
Gao 2019	45	50	35	50	6.1%	1.29 [1.05; 1.58]	-
Wu 2019	22	30	16	30	2.6%	1.38 [0.92; 2.05]	
Chen 2021	20	29	17	28	2.7%	1.14 [0.77; 1.67]	
Hou 2021	35	39	19	28	4.4%	1.32 [1.00; 1.74]	
Li 2016c	23	25	18	25	4.5%	1.28 [0.98; 1.67]	
Zhang 2012	27	30	19	30	4.0%	1.42 [1.06; 1.91]	
Total (95% CI)		831		820	100.0%	1.30 [1.21; 1.40]	•
Heterogeneity: 7	Tau ² = 0.0	123; Cł	ni ² = 39.5	3, df =	20 (P < 0	.01); l ² = 49%	
Total (95% CI)	0	831	0	820	100.0%	1.30 [1.21; 1.40]	<u> </u>
Heterogeneity: 7	lau [∠] = 0.0	123; Cł	ni [∠] = 39.5	3, df =	20 (P < 0	.01); I [∠] = 49%	
							0.5 1 2
							Favours control Favours exprimental

Response rate

Figure 7. Forest plot of the trials reporting the effect of East Asian herbal medicine monotherapy on the response rate for peripheral neuropathy.

Study or	Experim	ental	Co	ontrol	Mainht	Risk Ratio	Risk Ratio
Group = EAHA	Events	I otal	Events	lotal	vveight	IV, Random, 95% C	I IV, Random, 95% CI
Sup 2008	26 n	30	10	30	1.8%	1 37 [1 01: 1 86]	
Lin 2010	20	40	21	40	1.0%	1.48 [1.05; 2.07]	
Wang 2010	70	75	69	76	14.6%	1 03 [0 94 1 13]	
Gao 2012	27	30	19	30	1 9%	1 42 [1 06: 1 91]	
Gong 2012	54	60	45	60	5.6%	1 20 [1 01 1 42]	
Han 2013	28	31	24	31	3.4%	1 17 [0 93: 1 46]	
Zhang 2013a	26	30	22	30	2.6%	1 18 [0 91 1 53]	
Guo 2014	29	32	24	32	3.2%	1 21 [0 96: 1 52]	
Yang 2014a	57	60	51	60	9.9%	1 12 [0 99 1 26]	<u> </u>
Yang 2014b	33	36	26	36	3.3%	1 27 [1 01: 1 59]	
Qi 2015	27	32	20	32	1.8%	1 35 [0 99: 1 84]	
Guo 2016	44	51	35	51	3.6%	1.26 [1.01: 1.56]	
Han 2016	18	20	14	20	1.7%	1.29 [0.93: 1.77]	
Li 2016a	21	30	14	30	0.9%	1.50 [0.96; 2.35]	
Zhang 2016a	44	48	39	48	6.1%	1.13 [0.96; 1.32]	4
Zhang 2016b	49	60	31	60	2.3%	1.58 [1.20; 2.08]	
Chen 2018	32	40	25	40	2.1%	1.28 [0.96; 1.70]	
Hu 2018	28	31	20	31	2.1%	1.40 [1.05; 1.86]	
Ji 2019	46	54	36	53	3.6%	1.25 [1.01; 1.56]	
Liu 2019b	44	45	38	45	8.5%	1.16 [1.01; 1.32]	
Wang 2021a	28	30	21	30	2.6%	1.33 [1.04; 1.72]	
Xie 2018	26	30	18	30	1.6%	1.44 [1.04; 2.00]	
Gong 2021	29	30	24	30	4.5%	1.21 [1.00; 1.46]	
Huang 2020	30	30	25	30	6.3%	1.20 [1.02; 1.40]	
Song 2020	43	45	31	42	4.5%	1.29 [1.07; 1.57]	
Total (95% CI)		1000		997	100.0%	1.20 [1.15; 1.25]	•
Heterogeneity: T	au ² = 0.00	009; Cl	$hi^2 = 26.0$	3, df =	24 (P = 0	.35); l ² = 8%	
Total (95% CI)		1000		997	100.0%	1.20 [1.15; 1.25]	♦
Heterogeneity: T	au ² = 0.00	009; Cl	$hi^2 = 26.0$	3, df =	24 (P = 0	.35); I ² = 8%	
							0.5 1 2
							Favours control Favours exprimental
							Response rate

Figure 8. Forest plot of the trials reporting the effect of combined East Asian herbal medicine and western medicine therapy on the response rate for peripheral neuropathy.



Figure 9. Drapery plot of the trials reporting the effect of East Asian herbal medicine monotherapy on the response rate for peripheral neuropathy.

3.4.4. Secondary Outcome: Incidence Rate

The incidence rate was reported in 11 studies [88–94,96–98]. Compared with no treatment, the odds of the incidence rate were significantly lower in the EAHM monotherapy group (one trial, n = 45, OR 0.04, 95% CI 0.00–0.68, p < 0.0001, Figure 10). In addition, the odds of the incidence rate in the EAHM monotherapy group were significantly lower than that in the WM group (four trials, n = 249, OR 0.17, 95% CI 0.07–0.38, p < 0.0001; heterogeneity chi-square = 4.81, df = 3, p = 0.19; I² = 38%; Figure 10). The incidence rate in the combined EAHM and WM therapy group was also significantly lower than the WM monotherapy group (three trials, n = 232, OR 0.12, 95% CI 0.03–0.59, p < 0.0001; heterogeneity chi-square = 12.66, df = 2, p < 0.01; I² = 84%; Figure 10). However, there was no significant difference in the odds of incidence rate between the EAHM monotherapy group and the placebo group (two trials, n = 271, OR 1.21, 95% CI 0.33–4.39, p = 0.7763; heterogeneity chi-square = 6.24, df = 1, p = 0.01; I² = 84%; Figure 10).



Figure 10. Forest plot of the trials reporting the effect of East Asian herbal medicine monotherapy on the incidence rate for peripheral neuropathy.

3.4.5. Secondary Outcome: Pain Intensity

Pain intensity was reported in nine studies [50,81,83,87,90,99,100,102,103]. The reduction in pain intensity was significantly greater in the EAHM monotherapy group than the WM monotherapy group (five trials, n = 294, SMD -0.94, 95% CI -1.18--0.69, p < 0.0001; heterogeneity chi-square = 8.78, df = 3, p = 0.07; I² = 45%; Figure 11). Compared with the WM monotherapy group, the meta-analysis showed a significantly lower effect of combined EAHM and WM therapy (four trials, n = 232, SMD -1.21, 95% CI -1.63--0.78, p < 0.0001; heterogeneity chi-square = 8.78, df = 3, p = 0.03; I² = 66%; Figure 11).



Figure 11. Forest plot of the trials reporting the effect of East Asian herbal medicine monotherapy on pain intensity for peripheral neuropathy.

3.4.6. Secondary Outcome: TCSS

The effect of EAHM on the TCSS was described in seven studies [57,66,73,83,85–87]. A significant improvement in TCSS by EAHM monotherapy was identified by the WM monotherapy (three trials, n = 187, MD 1.04, p < 0.0001; heterogeneity chi-square = 0.74, df = 2, p = 0.69; I² = 0%; Figure 12). Compared with WM monotherapy, the combined EAHM and WM therapy also showed a significantly lower effect on TCSS (four trials; n = 470, MD -1.83, p < 0.0001; heterogeneity chi-square = 2.05, df = 3, p = 0.69; I² = 0%, Figure 12).



Figure 12. Forest plot of the trials reporting the effect of East Asian herbal medicine monotherapy on the Toronto clinical scoring system (TCSS) for peripheral neuropathy.

3.4.7. Secondary Outcome: MDNS

The effect of EAHM on the MDNS was proven in four studies [56,71,75,77]. The metaanalysis revealed a significant reduction in MDNS by EAHM monotherapy (two trials, n = 207, MD 4.29, p < 0.0001; heterogeneity chi-square = 7.25, df = 1, p < 0.01; I² = 86%; Figure 13). Compared with WM monotherapy, the combined EAHM and WM therapy also showed a significantly lower effect on MDNS (two trials, n = 122, MD -2.21, p < 0.0001; heterogeneity chi-square = 0.1, df = 1, p = 0.75; I² = 0%; Figure 13).



Figure 13. Forest plot of the trials reporting the effect of East Asian herbal medicine monotherapy on the Michigan diabetic neuropathy score (MDNS) for peripheral neuropathy.

3.5. AEs

Of the total 67 studies included in this review, 26 studies reported adverse event monitoring [38,40,45–47,49,53–55,59,61,62,65,69,72,75–77,84,88,90–93,100,101]. Among these, nine studies [38,45,49,65,69,72,77,84,101] reported multiple AEs possibly related to EAHM, and five studies [88,90–93] reported AEs unrelated to EAHM. No AEs were observed in the 12 studies [40,46,47,53–55,59,61,62,75,76,100]. The number of patients with AEs was 28/1322 (2.12%) in the experimental group and 31/1296 (2.4%) in the control group. Seven studies (seven in experimental groups and six in control groups) reported that the most frequent AEs were gastrointestinal symptoms, including abdominal pain, diarrhea, abdominal bloating, nausea, vomiting, anorexia, xerostomia, diarrhea, and constipation [38,45,69,72,77,84,101]. Skin rash was reported as an adverse event related to the integumentary system in two studies [49,69] (one in experimental group and two in control groups). Dizziness was reported as an adverse event related to the nervous system in three studies [65,84,101] (two in experimental groups and three in control groups). In all of the included studies, no severe AEs, which were life-threatening or required treatment for a long period of time, were reported. The details of the AEs reported in each study are presented in Table 1.

3.6. Subgroup Analysis

Table 3 summarizes the results of subgroup analysis based on individual causative diseases of PN and NCV for each site measured in five or more studies. There were no substantial changes in the results of the subgroup analysis.

Intervention and Comparator		Subgroup Analysis		Number of	Mean	Heterogeneity	
	Outcomes			Studies)	(95% CI)	I ² , %	р
EAHM in combination with the other treatment – vs. active control	MSNCV	Main analysis		1333(14)	2.73 (1.80 to 3.66)	86%	p < 0.01
		Patient types	DPN	1191(12)	2.80 (1.83 to 3.78)	85%	p < 0.01
			CIPN	142(2)	2.27 (-1.93 to 6.48)	95%	<i>p</i> < 0.01
		Duration of treatment	\leq 4 weeks	635(6)	3.01 (1.20 to 4.82)	93%	p < 0.01
			>4 weeks, ≤11 weeks	302(4)	2.31 (1.05 to 3.56)	73%	<i>p</i> = 0.01
			>11 weeks	396(4)	2.81 (0.84 to 4.78)	74%	<i>p</i> < 0.01
	PSNCV	Main analysis		1329(14)	2.59 (1.65 to 3.53)	88%	<i>p</i> < 0.01
		Patient types	DPN	1247(13)	2.79 (1.81 to 3.76)	88%	<i>p</i> < 0.01
			CIPN	82(1)	0.35 (-0.66 to 1.36)	-	-
		Duration of treatment	\leq 4 weeks	364(4)	3.02 (2.29 to 3.76)	0%	<i>p</i> = 0.57
			>4 weeks, ≤11 weeks	235(3)	2.64 (0.10 to 5.19)	95%	<i>p</i> < 0.01
			>11 weeks	630(7)	2.49 (1.09 to 3.89)	89%	<i>p</i> < 0.01

Table 3. Subgroup analysis for patient type and nerve conduction velocity outcome.

Intervention and	0.1	Subgroup Analysis		Number of	Mean	Heterogeneity	
Comparator	Outcomes			Participants (Studies)	Ofference - (95% CI)	I ² , %	р
		Main analysis		1214(11)	3.59 (2.79 to 4.39)	81%	p < 0.01
		Patient types	Only DPN	-	-	-	-
	TSNCV		\leq 4 weeks	440(4)	4.60 (2.38 to 6.82)	85%	p < 0.01
		Duration of treatment	>4 weeks, ≤ 11 weeks	166(2)	2.13 (1.62 to 2.63)	0%	<i>p</i> = 0.73
		_	>11 weeks	608(5)	3.72 (3.11 to 4.32)	33%	<i>p</i> = 0.20
		Main a	nalysis	980(10)	3.31 (1.96 to 4.65)	88%	p < 0.01
			DPN	828(8)	3.49 (2.10 to 4.89)	84%	<i>p</i> < 0.01
	MMNCV	Patient types	CIPN	142(2)	2.64 (-2.26 to 7.54)	97%	<i>p</i> < 0.01
		Duration of treatment	>11 weeks	528(5)	4.21 (2.18 to 6.24)	92%	p < 0.01
			>4 weeks, ≤ 11 weeks	142(2)	1.88 (0.78 to 2.98)	0%	<i>p</i> = 0.61
			\leq 4 weeks	300(3)	2.68 (1.51 to 3.85)	9%	<i>p</i> = 0.33
-	Pat PMNCV — Du tr	Main a	nalysis	1234(13)	2.98 (2.12 to 3.85)	81%	p < 0.01
		Patient types	DPN	1152(12)	3.22 (2.43 to 4.01)	73%	<i>p</i> < 0.01
			CIPN	82(1)	0.35 (-0.66 to 1.36)	-	-
		Duration of treatment	\leq 4 weeks	460(5)	4.42 (3.51 to 5.33)	29%	p = 0.23
			>4 weeks, ≤ 11 weeks	450(4)	1.91 (0.79 to 3.02)	75%	<i>p</i> < 0.01
			>11 weeks	324(4)	2.48 (1.29 to 3.68)	63%	<i>p</i> = 0.04
		Main a	nalysis	681(7)	2.74 (1.38 to 4.10)	89%	p < 0.01
EAHM monotherapy vs. active control	MSNCV y	Patient types	Only DPN	-	-	-	-
		Duration of treatment	\leq 4 weeks	144(2)	2.46 (-0.47 to 5.39)	96%	<i>p</i> < 0.01
			>4 weeks, ≤11 weeks	303(2)	3.72 (-0.15 to 7.59)	95%	<i>p</i> < 0.01

 Table 3. Cont.

Intervention and Comparator	0 .	California Arabasia		Number of	Mean	Heterogeneity	
	Outcomes Subgroup Ar		Analysis Participants (Studies)		Difference - (95% CI)	I ² , %	р
			>11 weeks	234(3)	2.23 (0.75 to 3.71)	25%	<i>p</i> = 0.26
		Main analysis		883(10)	2.76 (1.67 to 3.85)	85%	
		Patient types	Only DPN	-	-	-	-
	PSNCV	Duration of treatment	\leq 4 weeks	224(3)	3.46 (2.04 to 4.88)	77%	<i>p</i> = 0.01
			>4 weeks, ≤ 11 weeks	425(4)	2.23 (0.09 to 4.38)	89%	<i>p</i> < 0.01
				>11 weeks	234(3)	2.73 (0.45 to 5.02)	73%
	PMNCV D'	Main a	nalysis	967(9)	2.47 (1.40 to 3.53)	75%	<i>p</i> < 0.01
		Patient types	Only DPN	-	-	-	-
		Duration of treatment	\leq 4 weeks	80(1)	3.61 (1.43 to 5.79)	-	-
			>4 weeks, ≤11 weeks	725(6)	2.37 (0.91 to 3.83)	83%	p < 0.01
			>11 weeks	162(2)	2.40 (0.85 to 3.96)	35%	<i>p</i> = 0.21

Table 3. Cont.

CIPN: Chemotherapy-induced peripheral neuropathy; DPN: Diabetic peripheral neuropathy; EAHM: East Asian herbal medicine; MSNCV: Median sensory nerve conduction velocity; PSNCV: Peroneal sensory nerve conduction velocity; TSNCV: Tibial sensory nerve conduction velocity; MMNCV: Median motor nerve conduction velocity; PMNCV: Peroneal motor nerve conduction velocity.

3.7. Further Analysis of EAHM Intervention

3.7.1. EAHM Composition Distribution

A total of 156 herbs were prescribed in the 67 studies included in this review. The cumulative use frequency of the top 10 herbs was 40%. The list of herbs constituting the EAHM used for each study is separately organized in a Supplementary File (Supplementary Material S3). The top 10 most frequently prescribed herbs for PN were Astragali Radix, Angelicae Gigantis Radix, Paeoniae Radix, Cnidii Rhizoma, Cinnamomi Ramulus, Spatholobi Caulis, Achyranthis Radix, Glycyrrhyziae Radix et Rhizoma, Salviae Militorthizae Radix. The frequency distributions of the herbs are shown in Table 4.

Table 4. The top	p 10 frequent h	erbs prescribed	for periphera	l neuropathy.

EAHM (Latin Name)	Frequency of Utilization	Relative Frequency (%)	Cumulative Percentiles (%)
Astragali Radix	42	6.27	6.27
Angelicae Gigantis Radix	33	4.93	11.20
Paeoniae Radix	33	4.93	16.13
Cnidii Rhizoma	29	4.33	20.46
Cinnamomi Ramulus	28	4.18	24.64
Spatholobi Caulis	24	3.58	28.22
Achyranthis Radix	20	2.99	31.21
Glycyrrhyziae Radix et Rhizoma	20	2.99	34.20
Salviae Miltiorrhizae Radix	20	2.99	37.19
Carthami Flos	18	2.69	39.88

EAHM: East Asian herbal medicine.

3.7.2. Apriori Algorithm-Based Association Rule Analysis

Nine association rules were identified in the analysis based on the composition of the 67 EAHM prescriptions included in this study (Table 5).

Table 5. Apriori algorithm-based association rules for EAHM prescribed for peripheral neuropathy.

No.	Associations Rules	Support	Confidence	Lift
1	{Glycyrrhizae Radix et Rhizoma} => {Astragali Radix}	0.239	0.800	1.276
2	{Spatholobi Caulis} => {Astragali Radix}	0.313	0.875	1.396
3	{Cinnamomi Ramulus} => {Astragali Radix}	0.373	0.893	1.424
4	{Cinnamomi Ramulus, Spatholobi Caulis} => {Astragali Radix}	0.254	0.944	1.507
5	{Astragali Radix, Spatholobi Caulis} => {Cinnamomi Ramulus}	0.254	0.810	1.937
6	{Angelicae Gigantis Radix, Cinnamomi Ramulus} => {Paeoniae Radix}	0.224	0.882	1.791
7	{Cinnamomi Ramulus, Paeoniae Radix} => {Astragali Radix}	0.284	0.864	1.378
8	{Angelicae Gigantis Radix, Cinnamomi Ramulus} => {Astragali Radix}	0.209	0.824	1.314
9	{Cnidii Rhizoma, Paeoniae Radix} => {Angelicae Gigantis Radix}	0.239	0.842	1.710

Subsequently, the distribution of the lift value was recognized through a scatter plot consisting of the association rule, with the support value on the *x*-axis and the confidence value on the *y*-axis (Figure 14).



Figure 14. Scatter plot of the association rules in the meta-analysis of EAHM prescribed for peripheral neuropathy.

The color depth of each association rule, determined by its lift value, confirmed that the distribution of the overall lift value ranged from 1.276 to 1.937. Meanwhile, a grouping matrix diagram was presented to examine the overall distribution of the identified association rule (Figure 15).



Figure 15. Grouping matrix of the association rules in the meta-analysis of East Asian herbal medicine prescribed for peripheral neuropathy.

The horizontal ordinate shows eight association rules, and the vertical ordinate shows the items created by the eight rules. In this diagram, the depth of the color inside the circle represents the degree of lift, and the circle size represents the degree of support. From Figures 14 and 15, the association rules of #2 {Spathologi Caulis} => {Astragali Radix}, #3 {Spathologi Caulis} => {Astragali Radix}, #4 {Astragali Radix, Spatholobi Caulis} => {Cinnamomi Ramulus}, and #5 {Astragali Radix, Spatholobi Caulis} => {Cinnamomi Ramulus} relevance can be identified. Looking at the specific value, there were two association rules with support exceeding 0.3, {Spatholobi Caulis} => {Astragali Radix} and {Spatholobi Caulis} => {Astragali Radix}. On the contrary, the only association rule indicating a confidence exceeding 0.9 was {Cinnamomi Ramulus, Spatholobi Caulis} => {Astragali Radix}. The association rule with the highest lift is {Astragali Radix, Spatholobi Caulis} => {Cinnamomi Ramulus}. Therefore, the constituents of the herb combinations with consistent association rules were Astragali Radix, Cinnamomi Ramulus, and Spatholobi



Calulis. The relationship between these association rules is presented through a network graph (Figure 16).

Figure 16. Network graph of the association rules in the meta-analysis of East Asian herbal medicine prescribed for peripheral neuropathy.

3.8. Publication Bias

The contour-enhanced funnel plot analysis was performed to explore the publication bias through the response rate, which is an outcome of most of the included studies (Figure 17). The pattern of the funnel plot with 47 studies shows a clear asymmetry, indicating that there might have been publication bias (Figure 11). This was further confirmed by Egger's test (p < 0.0001) and Begg's test (p < 0.0001).



Contour-Enhanced Funnel Plot (Response rate)

Figure 17. Contour-enhanced funnel plot for the meta-analysis of East Asian herbal medicine prescribed for peripheral neuropathy.

3.9. Quality of Evidence According to the Outcome Measurements

In the comparison between the combination EAHM and WM therapy and WM monotherapy, the overall quality of evidence according to all of the outcome measures was low to moderate. Meanwhile, the overall quality of evidence according to all of the outcome measures was low to moderate in EAHM monotherapy compared with WM monotherapy. The results of the GRADE assessment are listed in Table 6.

Intervention and Comparator Intervention	Outcomes	Number of Participants (Studies)	Anticipated Absolute of Relative Effects (95% CI)	Quality of the Evidence (GRADE)
	SNCV	4454 (21 RCTs)	MD 3.06 higher (2.56 higher to 3.56 higher)	⊕⊕⊕⊖ MODERATE
-	MNCV	2860 (16 RCTs)	MD 3.23 higher (2.58 higher to 3.88 higher)	⊕⊕⊕⊖ MODERATE
EAUM combination of WM	Response rate	1997 (25 RCTs)	RR 1.20 (1.15 to 1.25)	⊕⊕⊕⊖ MODERATE
compared to WM for peripheral neuropathy	Incidence rate	232 (3 RCTs)	OR 0.12 (0.03 to 0.59)	⊕⊕⊖⊖ LOW
-	Pain intensity	332 (4 RCTs)	SMD 1.21 SD lower (1.29 lower to 0.83 lower)	⊕⊕⊕⊖ MODERATE
	TCSS	470 (4 RCTs)	MD 1.83 lower (2.11 lower to 1.55 lower)	⊕⊕⊖⊖ LOW
	MDNS	122 (2 RCTs)	MD 2.21 lower (2.94 lower to 1.47 lower)	⊕⊕⊖⊖ LOW
	SNCV	2159 (10 RCTs)	MD 2.68 higher (2.02 higher to 3.35 higher)	⊕⊕⊕⊖ MODERATE
	MNCV	1788 (9 RCTs)	MD 2.38 higher (1.43 higher to 3.32 higher)	⊕⊕⊕⊖ MODERATE
	Response rate	1651 (21 RCTs)	RR 1.30 (1.20 to 1.29)	⊕⊕⊖⊖ LOW
EAHM monotherapy compared WM for peripheral neuropathy	Incidence rate	249 (4 RCTs)	OR 0.17 (0.07 to 0.38)	⊕⊕⊖⊖ LOW
	Pain intensity	294 (4 RCTs)	SMD 0.94 SD lower (1.18 lower to 0.69 lower)	⊕⊕⊕⊖ MODERATE
	TCSS	187 (3 RCTs)	MD 1.04 lower (1.75 lower to 0.34 lower)	⊕⊕⊖⊖ LOW
-	MDNS	207 (2 RCTs)	MD 2.95 lower (4.2 lower to 1.7 lower)	⊕⊕⊖⊖ LOW

Table 6. Summary of findings for the studies in this meta-analysis.

EAHM: East Asian herbal medicine; MD: Mean difference; MDNS: Michigan diabetic neuropathy score; MNCV: Motor nerve conduction velocity; RCT: Randomized clinical trial; SNCV: Sensory nerve conduction velocity; SMD: Standardized mean difference; TCSS: Toronto clinical scoring system; OR: Odds ratio; RR: Risk ratio; CI: Confidence interval. Working group grades of Evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: Very uncertain about the estimate.

4. Discussion

4.1. Summary of the Main Finding

In this systematic review, 67 RCTs including 5753 PN patients were obtained and analyzed. The main finding of this study is that EAHM monotherapy or combined EAHM and WM therapy was superior to the control group without EAHM in improving nerve conduction velocity, response rate, incidence rate, pain intensity, and other overall symptoms. Additionally, EAHM is generally safe and tolerable for PN patients. Therefore, EAHM can be considered a recommended option for PN treatment in clinical practice based on the evidence presented in this study. On the contrary, in the association rule analysis of various EAHM prescription data included in this study, Astragali Radix, Cinnamomi Ramulus, and Spatholobi Calulis were identified as components constituting the core herb combination. It may be worthwhile to conduct further studies on whether EAHM containing the three individual herbs or their combination can exert a remarkable effect in the PN-treated group.

4.2. Limitations

This review has various limitations. Therefore, caution is required before using the results. First, most of the studies were conducted in China. As a result, additional well-designed multicenter clinical trials in East Asia are needed to generalize the positive results identified by the analysis. Second, the methodological quality of the clinical trials included in this study was generally poor. The overall risk of evaluated bias according to RoB 2.0 reported that only four included studies have a 'low risk of bias.' All of the other studies have a 'high risk of bias' due to methodological flaws in domains, such as the randomization process, deviations from the intended intervention, and missing outcome data. Therefore, it is difficult to draw firm conclusions, even though the review contains relatively large sample data and primary trials. Rigorous conclusions regarding EAHM can be drawn only in well-designed clinical trials to minimize the risk of future bias. Third, a high level of heterogeneity was observed in the meta-analysis of NCV, which is one of the primary outcomes of this study. This high heterogeneity is a problem that cannot be overlooked, as it reduces the significance of the synthesized evidence. In this study, the cause of heterogeneity could not be identified, even though a subgroup analysis was performed according to the underlying disease and treatment duration. It is estimated that the cause of the estimated troubleshooting is that the NCV at the basement and the amount of change in participants are different for each included study. This reflects the difficulty in diagnosing and measuring PN severity. Another possible cause of heterogeneity is the extreme diversity in the composition and dose of EAHMs used in individual clinical trials. This leads to inconsistency among interventions, except for the commonality of 'the combination of herbal medicines in East Asia.' In this review, the association rule analysis was performed on herb data to overcome this heterogeneity and derive useful information. The potential heterogeneity may be partially overcome in similar future systematic reviews by actively utilizing data mining methods. Fourth, the goal of this study was to identify valuable candidates for drug discovery or locate material information that may be employed in direct patient treatment in the clinic. Therefore, it was not possible to focus on quality control in the manufacturing process, such as pre-treatment, active ingredient extraction methods, and moisture content assessment, all of which significantly impact the efficacy of specific goods. Moreover, this was suspected to have influenced the heterogeneity of the results. In the future, an animal study meta-analysis on the same issue will be used to compensate for these flaws.

4.3. Implications of Clinical Practices

The evidence related to the use of EAHM therapy for PN supported by this study is consistent with the results of previous studies on similar subjects. A study analyzing the clinical data for DPN after using 216 EAHM prescriptions found that the combination of Astragali Radix-Cinnamomi Ramulus and Ligusticum Chuanxiong-Moutan Radicis Cortex highly correlated with MDNS improvement [105]. Moreover, considering that Astragali Radix and Cinnamoni Ramulus are among the top 10 herbs utilized and their combination was identified as a core herb pattern, the findings of the previous study are similar to this study. A systematic review in 2016 evaluating the effectiveness of EAHM formulation containing Astragali Radix as a central component for CIPN, also demonstrated a significant effect on the effective percentage and NCV [13]. Unlike this review, which dealt only with oral administration, this study elucidates the effects of topical preparation and injection. The differences between the two studies suggest that similar EAHMs can be effective when applied to PN even if they are administered through various routes. In 2020, a meta-analysis evaluating the effect of EAHM foot bath on DPN [106] was published, which also reported a significant improvement in SNCV, MNCV, and response rate in DPN patients after the EAHM treatment. However, the herbs frequently used in this study were Cinnamomi Ramulus, Carthami Flos, Herba Speranskiae Tuberculatae, and Cnidii Rhizoma, indicating that they are almost irrelevant to the frequently used herbs described in this review. According to the comprehensive evidence of this study and related topics to date, it is relatively clear that using various EAHM forms in clinical practice can be a meaningful treatment for PN patients. However, both the administration route and data from individual studies must be considered to identify whether a specific formulation

or herb can be an effective choice. In addition, it cannot be concluded from only a few clinical studies. Therefore, further studies should focus on the possible mechanisms related to this topic.

4.4. Implications of the Research

The characteristic of EAHM to treat complex diseases by stimulating many networks of human interaction systems at the systematic level through a multi-targeted approach is being investigated [107]. Therefore, the multicomponent-derived EAHM exerts a synergistic effect between multiple compounds in the process of acting on multiple targets, resulting in efficacy with decreased toxicity and side effects [107,108]. Therefore, for efficient EAHM utilization, it is important to consider the synergistic combination of herbs rather than the primary mechanism of individual herbs. In this regard, the principle of prescription using botanical medicine called "Kun-shi-Choa-sa" has traditionally been used to combine two or more herbal medicines in East Asia, and recently, the simplest form of multi-herbal mixture, "herb-pair" is also studied [109]. As the associated case, the combination of Astragali Radix and Angelicae Gigantis Radix, which are mostly used, has been reported to improve axonal growth by primarily stimulating the neurotrophic signaling pathway against damage to the central nervous system [110]. The authors of this study argued that the combination of two drugs through a network pharmacology and a methodology could promote neurological recovery by inhibiting the expression of NogoA by triggering a multipath pathway. In another case, studies on the combination of Cinnamomi Ramulus and Glycyrrhyziae Radix et Rhizoma, the herbs frequently featured in this review, showed significant differences in pharmacokinetic parameters compared to the use of each single herb [111]. Based on this mechanism, high peak concentration, slow elimination, and great exposure were observed in Cinnamomi Ramulus and Glycyrrhyziae Radix et Rhizoma. According to several studies reviewed to date, appropriate herbal combinations are highly likely to produce excellent pharmacological and pharmacodynamic results. As a research hypothesis to develop efficient EAHM-based drugs for PN in the future, some core herb patterns identified by the association rule analysis in this review are meaningful.

Information on the pharmacological action of individual herbs is also important for achieving the above purpose. Research on various pharmacotherapeutic targets is required for an effective drug treatment for diseases in which the overall pathology, such as PN, is not fully understood. Combining this basic study with the action-related information of the individual active ingredient of EAHM will make it possible to clearly predict the direction of the synergistic effect expected from multiple herb combinations. Even for DPN, research on several molecular targets, including the polyol pathway, hexamine pathway, PKC signaling, oxidative stress, AGEs pathway, PARP pathway, MAPK pathway, NF- κ B signaling, TNF- α signaling, and cyclooxygenase pathway is conducted [112]. In this review, the mechanisms by which major herbs induce PN pathology through various pathways are included. First, Astragali Radix downregulates the phosphorylation of heavy neurofilaments to prevent axonal damage and suppress pain hypersensitivity by reducing astrocytes and microglia scattered in the spinal cord and brain [113]. In another study, the mechanism by which APS protects against nerve damage is through miR-138 upregulation in rat neural stem cells [114]. Cinnamomi ramulus not only exerts neuroprotective effects by reducing oxidative damage and MDA and NO production, but also significantly suppresses pain hypersensitivity associated with inflammation [115,116]. Total glucosides in Paeoniae Radix protect against neurotoxicity, lower the level of neuronal nitric oxide synthase, and exhibit anti-nociceptive activity related to calcium channels [117,118]. Spatholobi Caulis demonstrated the therapeutic effects on neurological disorder-associated cell death by inhibiting JNK and p38 MAPK activation and reducing oxidative stress and apoptosis in a rat model of induced middle cerebral artery occlusion [119]. As mentioned above, studies related to the mechanism of action of herbs theoretically support the clinical effect of EAHM on PN, as confirmed in this review. However, in addition to these individual mechanisms, experimental studies are needed to identify targets that can reproducibly exert

the synergistic effects of EAHM. Furthermore, future studies on whether the combined effects of EAHM actually produce clinical results distinguishable from the additive effects of individual agents, need to be performed.

4.5. Challenges and Perspectives

The following problems must be considered until the aforementioned discoveries are meaningfully exploited in clinical practice and medication discovery. Natural medicines, including EAHM and synthetic drugs, have significantly distinct modes of action, target pathways, and pharmacologically active components from a macroscopic point of view. The most well-known difference is that multiple compounds present in herbal medicine operate on many targets and single compound synthetic medications work on single targets [109]. As demonstrated in this review, most of the EAHM prescriptions comprise a blend of several components in specific amounts, frequently in a single formula. In this instance, each component alone frequently does not demonstrate several therapeutic actions, such as the entire combination. The pharmacological activity of EAHM is thought to be due to the synergetic action of several chemical components targeting multiple sites and the simultaneous action of multiple chemical components targeting a single site [120,121]. This is thought to be the most significant difference between synthetic medicines and EAHM. As a result of these EAHM characteristics, it has been difficult to discover possible indications and mechanisms in the past. In addition, there has been a belief that it is difficult to derive social and medical contributions as much as synthetic medications. Recent scientific research, on the contrary, has indicated that the combinatorial effect of mixed EAHM preparation can be particularly effective for complicated disorders, such as PN, autoimmune disease, degenerative disease, and cancer, which do not react well with single compound-based modern pharmaceutics [121–124]. As an example, recent research has demonstrated that EAHM can be used in large-scale public health emergencies, such as COVID-19 or preventive medicine using modern analytical tools, such as synthetic biology, data mining, and genomics [123,125-128]. Future studies need to be conducted to identify the properties of EAHM to be utilized in actual drug discovery.

First, this review was undertaken with the goal of finding EAHM materials that may provide prospective advantages to PN patients, and it does not go into detail regarding the formulation process of the materials. However, as mentioned above, estimating a consistent impact even for the same herb material in a condition where there is a lack of adequate consensus and discussion on the processing technique, pre-treatment, and extraction method of individual EAHM materials may be challenging [129,130]. Since most of the EAHM dosage forms discussed in this study are decoctions, it is also important to include various methods for determining the water content of the product [131]. These issues need to be addressed in a review of animal studies focusing on this subject. Simultaneously, it is thought that providing standardized information on the above in future EAHM-related clinical trials would help in enhancing the quality control of herbal materials. Second, while comparing EAHM to natural materials with efficacy against PN is outside the scope of this review, it is deemed necessary. For example, several clinical trials have gathered early data for Cannabis sativa. Moreover, additional materials, such as mulberry, Citrullus colocynthis, Matricia chamomilla, and Myristica fragrans have promising benefits for PN [9,132]. It is envisaged that relevant drug discovery information will be generated through a comparison of the phytochemical and clinical effectiveness with those of conventional herbal medicine in follow-up investigations.

5. Conclusions

This meta-analysis supports the hypothesis that EAHM monotherapy may be beneficial for PN patients. Moreover, the combined EAHM and WM therapy may be recommended for these patients. EAHM monotherapy improves severe pain intensity and abnormal sensations, such as tingling, burning, and numbness, which impair the quality of life in PN patients. Additionally, unlike the PN treatment with WM alone, which has a poor prognosis, a combination of EAHM and WM treatment alleviated the symptoms of PN including tingling, burning, and numbness and prevented chronic PN. However, high quality RCTs evaluating the effects of EAHM are needed due to limitations, such as heterogeneity, to understand this result clearly. In addition, it is worth conducting a follow-up study to verify the specific action target of the core herb combination derived from the present review and the hypothesis of superiority in clinical practice.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/ 10.3390/ph14111202/s1. Table S1: PRISMA_2020_checklist; Table S2: Search strategy; Table S3: The Ingredients of EAHM used in clinical trials included in this study.

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