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GUIDELINES / CLINICAL TRIALS/META-ANALYSIS (WJ KOSTIS, SECTION EDITOR)

Tai Chi for Essential Hypertension: a Systematic Review of Randomized Controlled Trials

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Abstract

Purpose of Review To investigate the effectiveness and safety of Tai Chi for essential hypertension (EH).

Recent Findings A total of 9 databases were searched from inception to January 1, 2020. Randomized controlled trials (RCTs) investigating the effectiveness and safety of Tai Chi for EH were included. Study selection, data extraction, and quality assessment were performed independently by 2 reviewers. A total of 28 RCTs involving 2937 participants were ultimately included in this systematic review. Meta-analysis showed that, compared with health education/no treatment, other exercise or antihypertensive drugs (AHD), Tai Chi showed statistically significant difference in lowering systolic blood pressure (SBP) and diastolic blood pressure (DBP). The trial sequential analysis suggested that the evidence in our meta-analysis was reliable and conclusive. Subgroup analyses of Tai Chi vs. AHD demonstrated Tai Chi for hypertension patients < 50 years old showed greater reduction in SBP and DBP. Intervention of 12–24 weeks could significantly lower SBP and DBP. Among 28 included RCTs, 2 RCTs reported that no adverse events occurred. The quality of evidence for the blood pressure (BP) of Tai Chi vs. AHD was moderate, and DBP of Tai Chi vs. health education (HE)/ no treatment (NT) was high. Other outcome indicators were considered low or very low quality according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Summary Tai Chi could be recommended as an adjuvant treatment for hypertension, especially for patients less than 50 years old. However, due to poor methodological qualities of included RCTs and high heterogeneity, this conclusion warrants further investigation.

Keywords Tai Chi · Essential hypertension · Systematic review · Meta-analysis · Trial sequential analysis · Randomized controlled trails

Introduction

Hypertension, the leading modifiable risk factor of cardiovascular disease, affects over 1 billion people worldwide [1]. In China, the epidemiology of hypertension is in a dynamic phase. Based on a population-based epidemiological survey conducted in China [2••], 23.2% (≈ 244.5 million) Chinese adults suffered from hypertension, and another 41.3% (≈ 435.3 million) had prehypertension according to the Chinese guideline. It is predicted that the number of hypertension adults in 2025 will increase up to 1.56 billion all over the world [3]. A meta-analysis of 1 million adults in 61 prospective studies [4] showed that among middle-aged and old-aged people, blood pressure is strongly and directly related to vascular mortality. Hypertension was a main or contributing cause of death worldwide [5, 6]. Hypertension healthcare costs account for about $131 billion every year, hypertensive

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individuals spend nearly $2000 higher annual compared with non-hypertensive peers [7].

Studies have shown that, in a significant number of hypertensive patients, high BP was not controlled adequately [8–10]. Multiple types of antihypertensive drugs are commonly prescribed to treat hypertension. However, the unacceptable side effects (e.g., ankle edema, facial flushing, and gingival hyperplasia) and unaffordable economic burden often lead to poor medication compliance. There is an urgent need for better hypertension management.

According to the Joint National Commission (JNC) 8 [11], the Canadian Hypertension Education Program (CHEP) [12], and other professional committees or organizations [13, 14], exercise is recommended for adults with hypertension. Tai Chi, as a traditional Chinese exercise, is an ideal integration of traditional Chinese culture. It combines deep-breath relaxation and gentle movements with awareness, which has become very popular around the world. Previous clinical trials and systematic reviews [15–20] suggested that Tai Chi may be effective for hypertension. However, all the systematic reviews were considered "critically low" when we assessed the methodological quality with the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) [21•]. Due to the limitations of previous reviews, we plan to strictly conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of Tai Chi for hypertension and explore whether cumulative data were adequately powered to evaluate outcomes by performing trial sequential analysis (TSA).

Methods

Study Registration

The protocol of this systematic review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero/) (Registration No. CRD42019126724). This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.

Search Strategy

We conducted the search of 9 databases from inception to January 1, 2020: the Cochrane Library, Medline (Ovid), Embase (Ovid), PsycINFO (Ovid), Web of Science, AMED, Chinese National Knowledge Infrastructure (CNKI), Wanfang data, Chinese Scientific Journal Database (VIP). We also searched the clinical trial registration website (http://www.ClinicalTrial.gov, http://www.chictr.org.cn) and reference lists of identified studies for more potentially eligible trials. The search terms were based on "Tai Chi," "hypertension," and "randomized controlled trial," and the search strategy was shown in Appendix in details.

Inclusion Criteria

We considered trials to be eligible based on the following inclusion criteria: (1) RCTs comparing Tai Chi (no limit on the duration, frequency or style) with antihypertensive drugs (AHD), other exercises, no treatment (NT), or health education (HE); (2) RCTs enrolling participants older than 18 years old with essential hypertension (no restriction on gender, nation, or ethnic), according to the 2010 Chinese guidelines for the management of hypertension [22], the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [23], or other diagnostic criteria; (3) RCTs providing systolic blood pressure (SBP) and diastolic blood pressure (DBP) data; (4) RCTs published in Chinese and English.

Exclusion Criteria

Exclusion criteria were (1) quasi randomized trials, cluster randomized trials, and cross-over randomized trials; (2) trials of participants with secondary hypertension or serious complications; (3) duplicated publications; (4) the full text was unavailable; (4) data cannot be extracted.

Outcomes

Primary outcomes included SBP and DBP. Secondary outcomes included blood lipid–related indicators.

Studies Selection

After removing duplicates, two authors (H-Y and DL-Z) screened the titles and abstracts independently for the first selection, then screened the full texts when studies were deemed eligible. In case of disagreements, the third author (J-L) involved in.

Data Extraction

Two authors (H-Y and DL-Z) extracted data with a predesigned form independently, including the following information: lead author, publication year, participants' characteristics, intervention and comparisons, outcomes, adverse events, sources of funding. When RCTs had more than two arms, we extracted data separately. Disagreements were resolved by the third author (TY-L).

Risk of Bias Assessments

According to the standards recommended by Cochrane Handbook for Systematic Reviews of Interventions, two authors (YX-L and YJ-H) assessed the risk of bias from the following 7 items independently: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was evaluated as "high," "low," or "unclear." Disagreements were resolved by consensus.

Data Synthesis

We performed statistical analyses by Revman (version 5.3.5) and STATA (version 12.0) software. We used mean difference (MD) and their associated 95% confidence intervals to assess outcomes, and considered a $P < 0.05$ to be statistically significant. Chi-square test and I^2 statistic were conducted to test the heterogeneity. We used the fixed effects model if acceptable heterogeneity was found, or the random effects model were used if significant heterogeneity was detected. Results will be described qualitatively in the text when meta-analysis is not possibly carried out. Publication bias was assessed qualitatively by the funnel plot and quantitatively by the Egger's test and Begg's test. Trim and fill analysis was also performed.

Trial Sequential Analysis

We performed TSA to explore whether the evidence in our meta-analysis was reliable and conclusive [24, 25•]. TSA software (version 0.9.5.10) was used to maintain an overall 5% risk of type I error and 80% power.

Sensitivity and Subgroup Analyses

Sensitivity analysis was performed to test the stability of result. We performed subgroup analysis according to age (≥ 50 and < 50 years old). We conducted retrospective subgroup analyses based on intervention duration (< 12, 12–24, ≥ 24 weeks), exercise frequency (< 3, 3–4, ≥ 4 times weekly), session duration (< 30, 30–45, ≥ 45 min/session), and weekly exercise time (< 150, 150–210, ≥ 210 min/week).

Patient and Public Involvement

No patients were involved in this systematic review. The results will be disseminated to members of the public, patients, health professionals, and experts.

GRADE

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [26•] to evaluate the quality of evidence of outcomes from the following 5 aspects: limitations, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence would be graded as "high," "moderate," "low," or "very low."

Result

Studies Retrieved and Characteristics

Figure 1 showed the progress of selection. A total of 554 potentially eligible studies were initially identified, and 49 full texts of these records were reviewed. Finally, 28 RCTs met the inclusion criteria [27–54]. We excluded 21 trials; the reasons were listed in Supplementary Table S1.

Overall, 28 RCTs involving 2937 participants were ultimately included in this systematic review. All the included studies were conducted in China (one in Tai Pei), between 2003 and 2019. Supplementary Table S2 summarized the characteristics of the included RCTs.

Risk of Bias Assessment

The Supplementary Figure S1-S2 showed the assessment of the risk of bias. Although all studies were randomized, 9 RCTs [31, 34, 38–40, 44–47] described an adequate random sequence generation process. Only 2 RCTs [27, 45] described the methods used for allocation concealment. Since Tai Chi is a behavioral intervention, study participants cannot be easily blinded to intervention group allocation. Besides, none of the included studies separated researchers, outcome assessors, and data collectors, we considered all the RCTs as "high risk" in "Blinding of participants and personnel."

Primary Outcome: SBP and DBP

Tai Chi vs. Health Education/No Treatment

A total of 9 RCTs [43, 47–54] reported SBP and DBP. As shown in Fig. 2 and Fig. 3, there was statistically significant difference of SBP and DBP between the two groups (MD = − 14.784, 95% CI − 19.587 to − 9.981, I^2 = 94%, $P < 0.05$; MD = − 7.035, 95% CI − 9.083 to − 4.988, I^2 = 74.5%, $P < 0.05$)

Results of subgroup analyses for BP of Tai Chi vs. HE/NT were summarized in Table 1. No differences were found between subgroups in age, intervention duration, exercise frequency, session duration, and weekly exercise time.

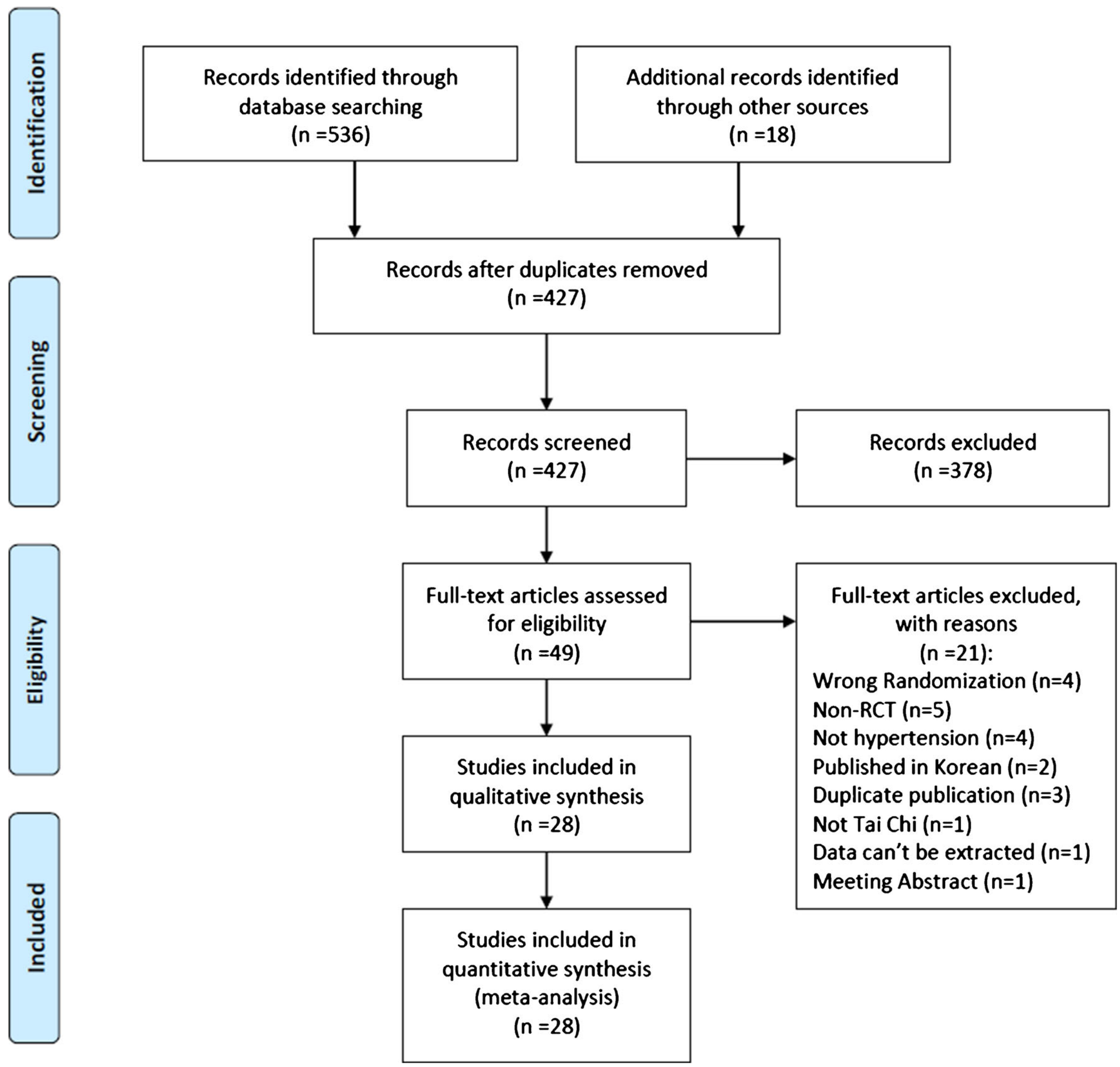

Fig. 1 PRISMA flowchart

Tai Chi vs. Other Exercises

A total of 5 RCTs [42–46] reported SBP and DBP. As shown in Fig. 4 and Fig. 5, there was statistically significant difference of SBP and DBP between the two groups (MD = − 7.934, 95% CI − 14.221 to − 1.674, I^2 = 93.9%, P = 0.013; MD = − 3.856, 95% CI − 6.544 to − 1.168, I^2 = 73.2%, P = 0.005).

Tai Chi vs. AHD

A total of 15 RCTs [27–41] reported SBP and DBP. As shown in Fig. 6 and Fig. 7, there was statistically significant difference of SBP and DBP between the two groups (MD = − 9.070, 95% CI − 14.033 to − 4.108, I^2 = 97.2%, P < 0.05; MD = − 5.625, 95% CI − 8.836 to − 2.414, I^2 = 96.2%, P = 0.001). The meta-analysis results for SBP and DBP were robust in sensitivity analyses (Supplementary Figure S3-S4).

As shown in Table 2, Tai Chi for hypertension patients < 50 years old showed three times the reduction of SBP and DBP than patients ≥ 50 years old. Intervention of 12–24 weeks could significantly lower SBP and DBP than intervention of < 12 weeks and intervention of > 24 weeks. Weekly exercise time of < 150 min/week suggested no significant difference.

Other Outcomes

There was a significant difference in TC, LDL-C of Tai Chi vs. HE/NT and TG of Tai Chi vs. AHD. But, due to small number of included studies, the results of sensitivity analysis were altered, indicating that the result was unreliable (Table 3).

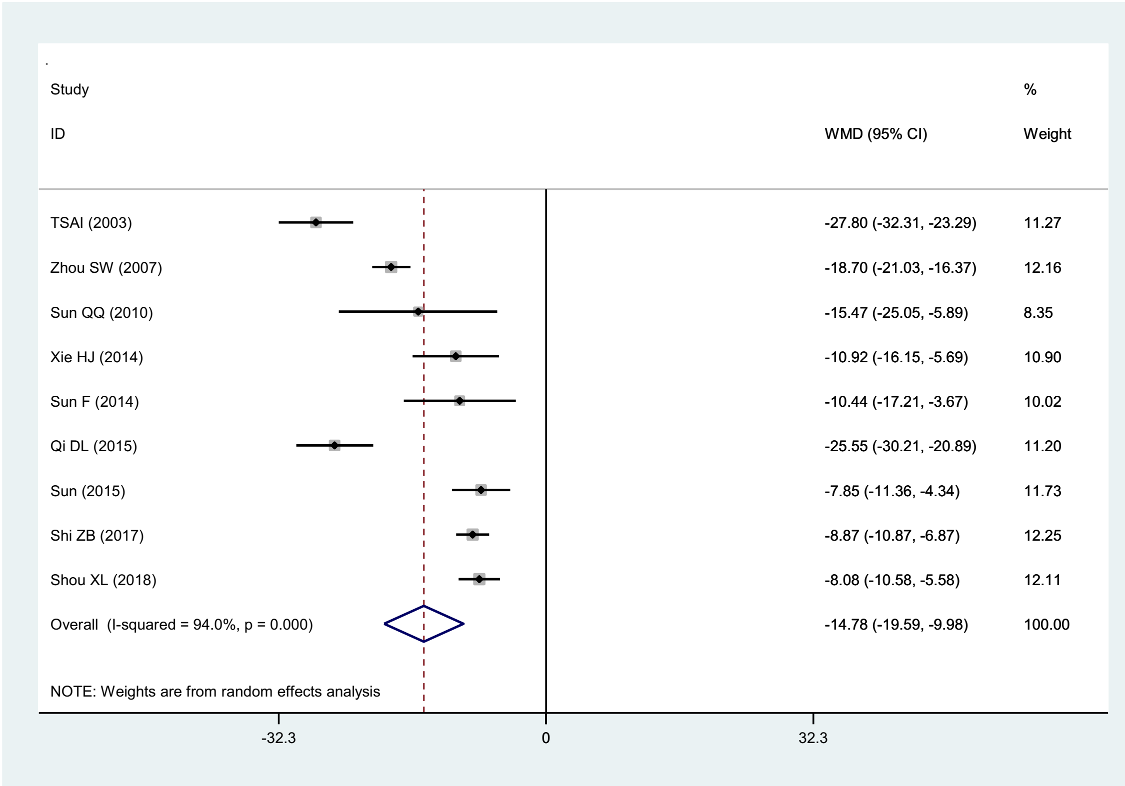

Fig. 2 Forest plot of SBP of Tai Chi vs. HE/NT

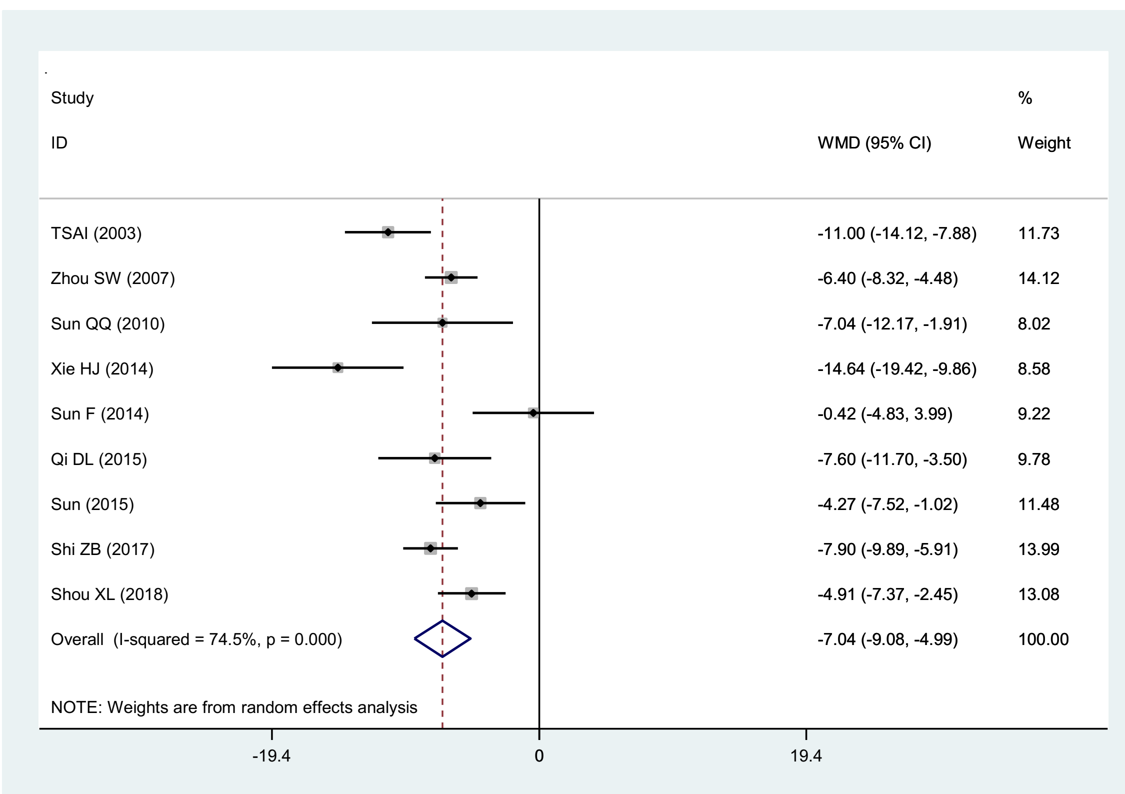

Fig. 3 Forest plot of DBP of Tai Chi vs. HE/NT

Table 1 Subgroup analyses of BP of Tai Chi vs. HE/NT

	SBP			DBP		
	n	Effect size (95% CI)	*P*	*n*	Effect size (95% CI)	*P*
Age, year						
< 50	1 [43]	− 8.870 (− 10.870, − 6.870)	< 0.05	1 [43]	− 7.900 (− 9.894, − 5.906)	< 0.05
≥ 50	8 [47–54]	− 15.610 (− 21.158, − 10.062)	< 0.05	8 [47–54]	− 6.918 (− 9.363, − 4.473)	< 0.05
Intervention duration, week						
< 12	1 [52]	− 10.440 (− 17.209, − 3.671)	0.003	1 [52]	− 0.420 (− 4.834, 3.994)	0.852
12 to 24	7 [43, 48–51, 53, 54]	− 16.393 (− 22.129, − 10.657)	< 0.05	7 [43, 48–51, 53, 54]	− 8.123 (− 10.135, − 6.111)	< 0.05
> 24	1 [47]	− 7.850 (− 11.357, − 4.343)	< 0.05	1 [47]	− 4.270 (− 7.516, − 1.024)	0.01
Exercise frequency, times weekly						
< 3	0	-	-	0	-	-
3 to 4	1 [48]	− 27.800 (−32.311, − 23.289)	< 0.05	1 [48]	− 11.000 (− 14.119, 7.881)	< 0.05
> 4	7 [43, 49–54]	− 13.919 (− 18.842, − 8.995)	< 0.05	7 [43, 49–54]	− 6.835 (− 9.091, − 4.578)	< 0.05
Session duration, min/session						
< 30	0	-	-	0	-	-
30 to 45	1 [43]	− 8.870 (− 10.870, − 6.870)	< 0.05	1 [43]	− 7.900 (− 9.894, − 5.906)	< 0.05
> 45	7 [48–54]	− 16.794 (− 22.845, − 10.744)	< 0.05	7 [48–54]	− 7.331 (− 10.067, − 4.595)	< 0.05
Weekly exercise time, min/week						
< 150	0	-	-	0	-	-
150 to 210	1 [48]	− 27.800 (− 32.311, − 23.289)	< 0.05	1 [48]	− 11.000(− 14.119, 7.881)	< 0.05
> 210	7 [47, 49–54]	− 13.809 (− 19.071, − 8.548)	< 0.05	7 [47, 49–54]	− 6.254 (− 8.680, − 3.827)	< 0.05

SBP, systolic blood pressure; *DBP*, diastolic blood pressure

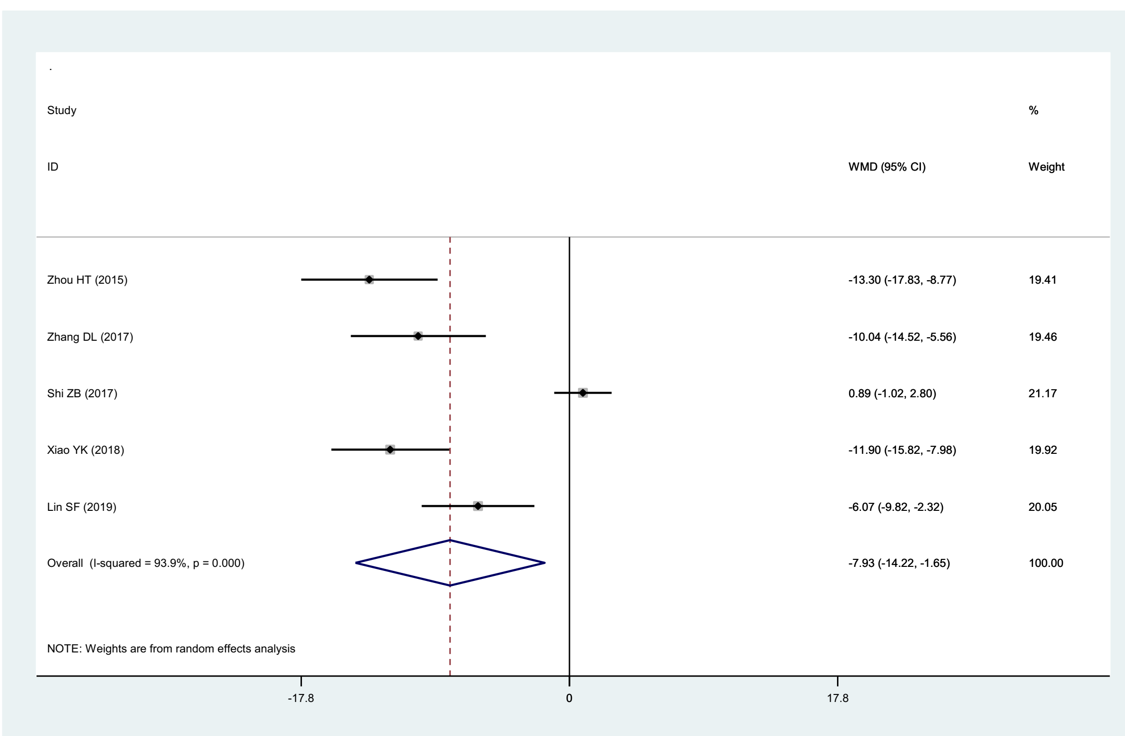

Fig. 4 Forest plot of SBP of Tai Chi vs. other exercise

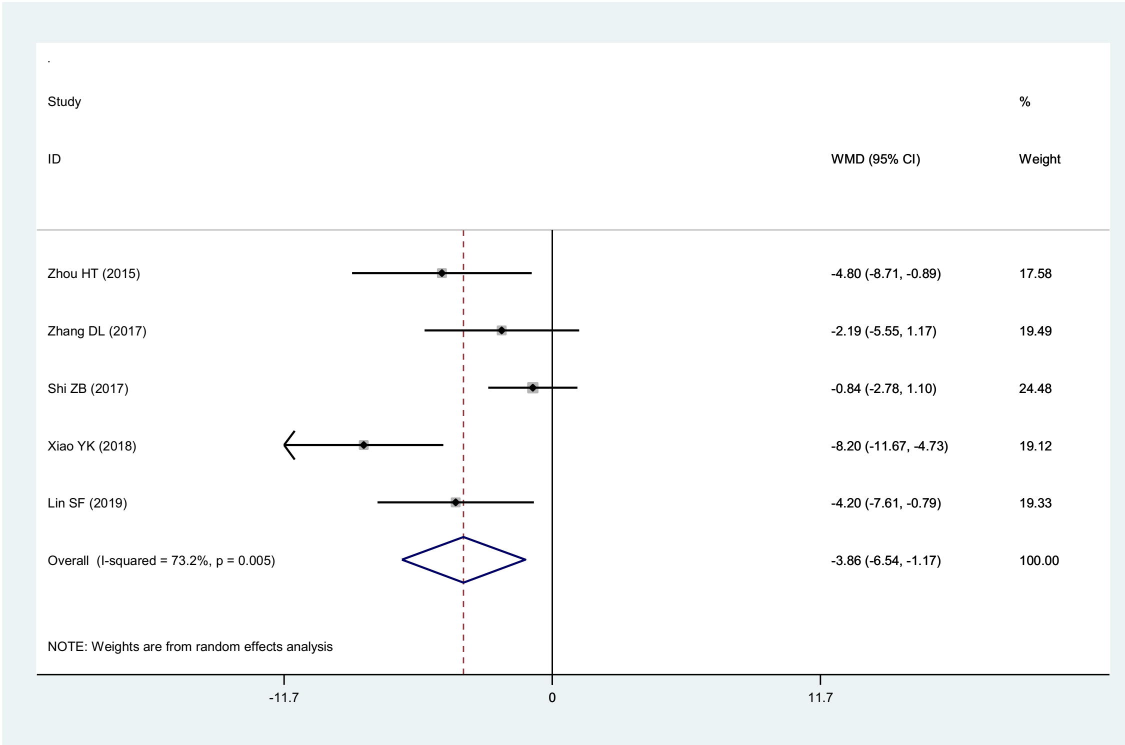

Fig. 5 Forest plot of DBP of Tai Chi vs. other exercise

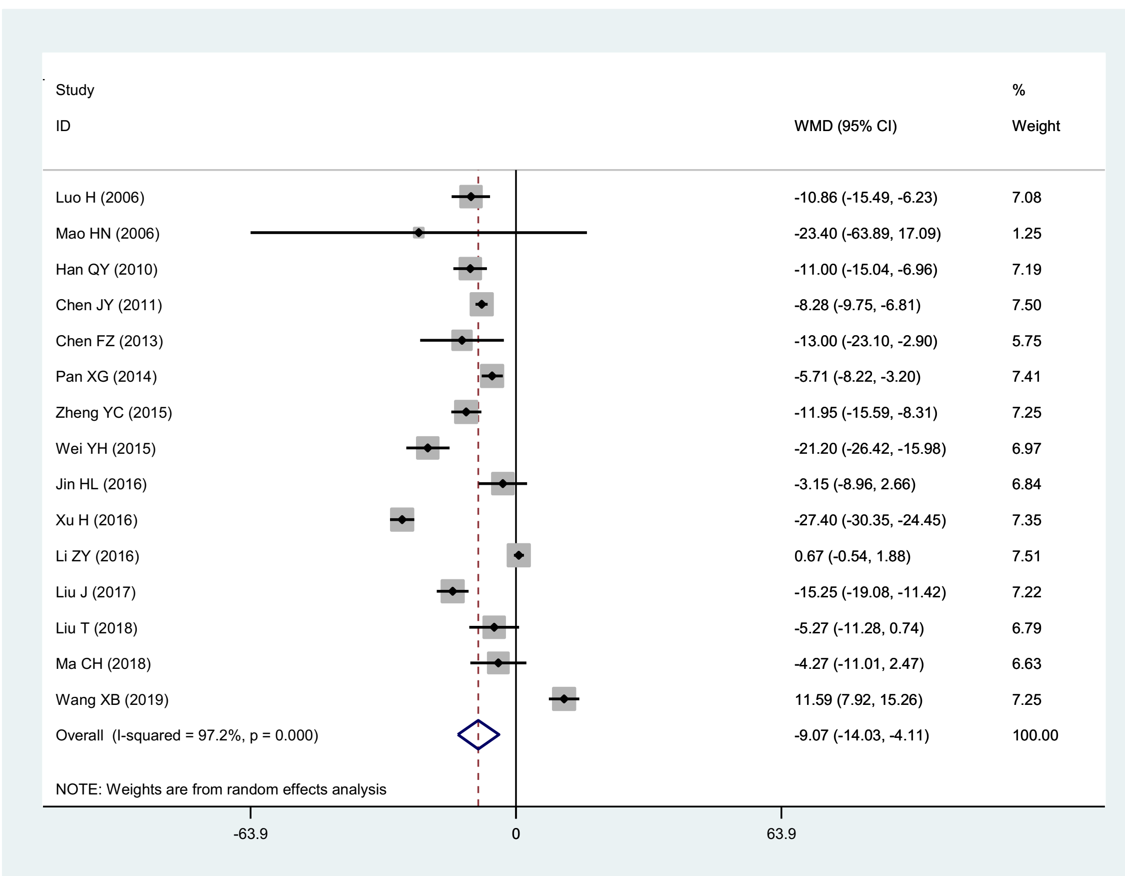

Fig. 6 Forest plot of SBP of Tai Chi vs. AHD

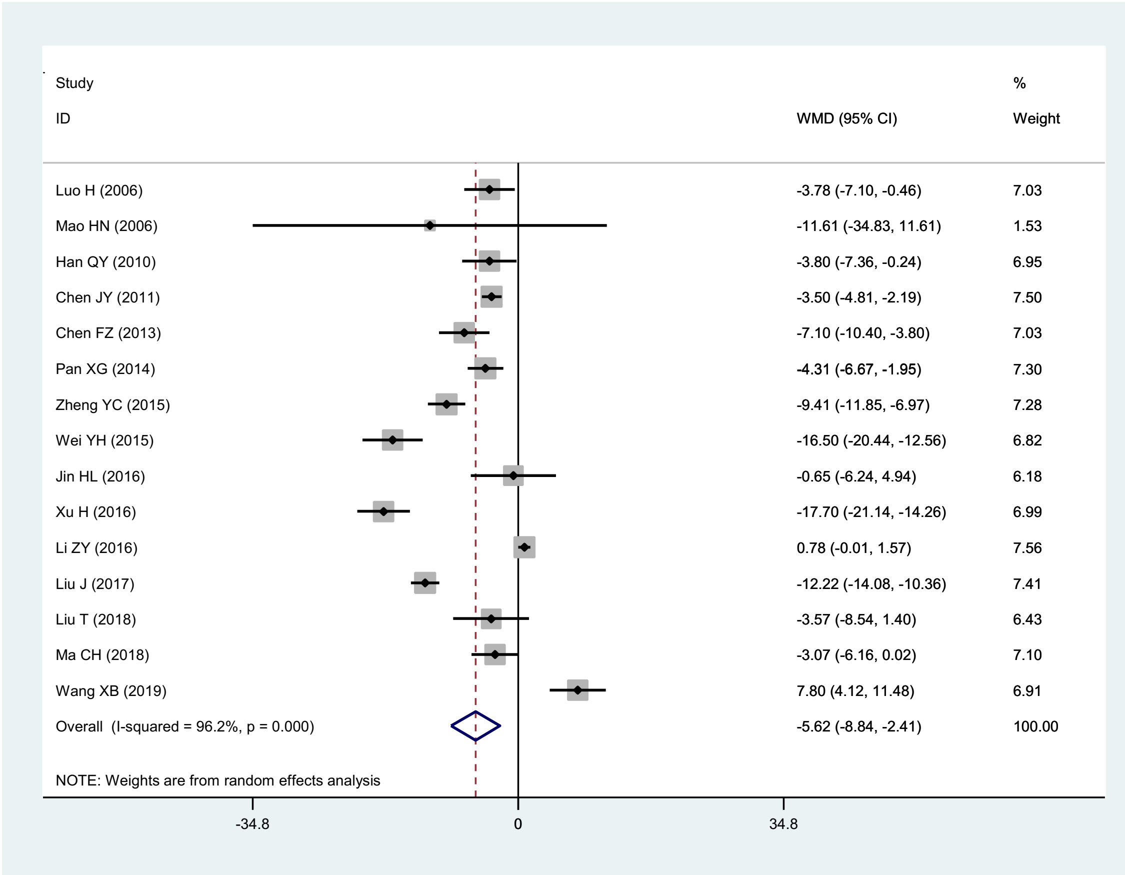

Fig. 7 Forest plot of DBP of Tai Chi vs. AHD

Table 2 Subgroup Analyses of BP of Tai Chi vs. AHD

	SBP			DBP		
	n	Effect size (95% CI)	*P*	*n*	Effect size (95% CI)	*P*
Age, year						
< 50	3 [33, 35, 40]	− 17.947 (− 28.205, − 7.688)	0.001	3 [33, 35, 40]	− 11.239 (− 17.958, − 4.521)	0.001
≥ 50	11 [27, 29–32, 34, 36–39, 41]	− 5.972 (− 10.490, − 1.455)	0.01	11 [27, 29–32, 34, 36–39, 41]	− 3.747 (− 6.816, − 0.678)	0.017
Intervention duration, week						
< 12	4 [31, 32, 36, 40]	− 11.654 (− 30.427, 7.119)	0.224	4 [31, 32, 36, 40]	− 6.656 (− 18.348, 5.037)	0.265
12 to 24	7 [27, 28, 33–35, 37, 41]	− 9.477 (− 12.944, − 6.011)	< 0.05	7 [27, 28, 33–35, 37, 41]	− 6.384 (− 9.423, − 3.344)	< 0.05
> 24	4 [29, 30, 38, 39]	− 7.125 (− 18.073, 3.822)	0.202	4 [29, 30, 38, 39]	− 3.966 (− 11.409, 3.478)	0.296
Exercise frequency, times weekly						
< 3	1 [30]	− 11.000 (− 15.040, − 6.960)	< 0.05	1 [30]	− 3.800 (− 7.359, − 0.241)	0.036
3 to 4	1 [38]	11.590 (7.921, 15.259)	< 0.05	1 [38]	7.800 (4.120, 11.480)	< 0.05
> 4	11 [28, 29, 31–37, 39, 40]	− 11.113 (− 16.909, − 5.318)	< 0.05	11 [28, 29, 31–37, 39, 40]	− 6.967 (− 10.857, − 3.077)	< 0.05
Session duration, min/session						
< 30	1 [40]	− 27.400 (− 30.351, − 24.449)	< 0.05	1 [40]	− 17.700 (− 21.145, − 14.255)	< 0.05
30 to 45	5 [28, 31, 32, 35, 39]	− 9.282 (− 18.383, − 0.182)	0.046	5 [28, 31, 32, 35, 39]	− 5.418 (− 11.558, 0.723)	0.084
> 45	5 [27, 29, 30, 36, 37]	− 7.695 (− 9.831, − 5.559)	< 0.05	5 [27, 29, 30, 36, 37]	− 3.647 (− 4.673, − 2.620)	< 0.05
Weekly exercise time, min/week						
< 150	3 [30, 32, 40]	− 12.550 (− 31.247, 6.147)	0.188	3 [30, 32, 40]	− 6.828 (− 17.785, 4.129)	0.222
150 to 210	1 [28]	− 13.000 (− 23.096, − 2.904)	0.012	1 [28]	− 7.100 (− 10.401, − 3.799)	< 0.05
> 210	8 [29, 31, 33–37, 39]	− 10.051 (− 13.629, − 6.474)	< 0.05	8 [29, 31, 33–37, 39]	− 6.610 (− 10.450, − 2.769)	0.001

SBP, systolic blood pressure; *DBP*, diastolic blood pressure

Table 3 Meta-analysis of other outcomes

Outcomes	No. of studies	I^2	*P* value	MD	95% CI	*P* value
Tai Chi vs. HE/NT						
TC	3	74.4%	0.02	− 0.753	− 1.161, − 0.345	< 0.05
TG	3	77.2%	0.012	− 0.373	− 0.795, 0.049	0.083
HDL-C	3	80.5%	0.006	0.269	− 0.184, 0.722	0.244
LDL-C	3	87.6%	0.000	− 1.048	− 1.650, − 0.447	0.001
Tai Chi vs. AHD						
TG	4	98.6%	0.000	− 2.238	− 3.889, − 0.587	0.008

Publication Bias

Funnel plot analysis of SBP of Tai Chi vs. antihypertensive drugs (AHD) was shown in Supplemental Figure S5. The Egger's test ($P = 0.224$), Begg's test ($P = 0.621$) did not detect publication bias (Supplemental Figure S6-S7), nor did Duval and Tweedie's trim and fill computation change the results.

Trial Sequential Analysis

A required information size (RIS) of 1013 patients in SBP and 1081 patients in DBP (Tai Chi vs. AHD), 213 patients in SBP and 171 patients in DBP (Tai Chi vs. HE/NT), and 462 patients in SBP and 349 patients in DBP (Tai Chi vs. other exercises) was calculated based on empirical method ($\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power 80%)). The blue cumulative Z-curve was constructed using a random effects model and surpasses the trial sequential monitoring boundary for benefit (etched curve) before the RIS is achieved, indicating that cumulative evidence is conclusive (Supplemental Figure S8-S13).

Safety

In 28 included RCTs, only 2 RCTs [36, 54] reported that no adverse effects occurred in Tai Chi groups.

Quality of Evidence

Using the GRADE summary of evidence, the quality of evidence for the BP of Tai Chi vs. AHD was moderate, and DBP of Tai Chi vs. HE/NT was high. Other outcome indicators were considered low or very low quality. Of the 5 downgrading factors, the inconsistency was the most common downgrading factor, followed by imprecision and publication bias (Table 4).

Discussion

Summary of Findings

In this systematic review of 28 RCTs with a total of 2937 hypertensive participants, the results demonstrated that Tai Chi vs. HE/NT, other exercises, and AHD significantly reduced SBP and DBP. The trial sequential analysis suggested that the evidence in our meta-analysis was reliable and conclusive. Besides, compared with HE/NT, Tai Chi got the largest BP reduction; compared with other exercise, Tai Chi got the smallest BP reduction. Subgroup analyses of Tai Chi vs. AHD suggested that Tai Chi for hypertensive patients < 50 years old showed over three times the reduction of SBP and DBP than patients ≥ 50 years old. Intervention for 12–24 weeks could significantly lower SBP and DBP than intervention < 12 weeks and intervention > 24 weeks.

Table 4 Results of GRADE

Tai Chi vs. control	Outcome indicators	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Tai Chi vs. HE/NT	SBP	0	− 1[a]	0	− 1[b]	0	Low
	DBP	0	0	0	0	0	High
Tai Chi vs. other exercises	SBP	0	− 1[a]	0	− 1[b]	− 1[c]	Very low
	DBP	0	0	0	− 1[②]	− 1[c]	Low
Tai Chi vs. AHD	SBP	0	− 1[a]	0	0	0	Moderate
	DBP	0	− 1[a]	0	0	0	Moderate

[a] I^2 value of the combined results was large and high heterogeneity

[b] The confidence intervals were wide or not match the optimal information size

[c] There was a suspicion of publishing bias

Comparison with Other Systematic Reviews

Although previous 6 systematic reviews (SRs) [15–20] have already been conducted to investigate the effectiveness of Tai Chi on hypertension, there are still a lot of room for improvement when we used AMSTAR 2 to assess the methodological quality. All SRs were considered "critically low" quality owing to the absence of the key items. Absence of protocol in advance, incomprehensive search strategy, no gray literature searching or experts in relevant fields consulting, no list of excluded studies with reasons, no sources of funding reporting were the most common methodological problems (Supplementary Table S3). Wang et al. [15] included undiagnosed patients and Zhang et al. [19] only searched Chinese databases; other meta-analyses included non-RCTs or involving non-hypertensive patients, which may increase the risk of bias and lead to false results. Owing to the flaws of previous SRs, we conducted this SR and meta-analysis strictly in accordance with the items in AMSTAR 2, PRISMA, and explored whether cumulative data were adequately powered to evaluate outcomes by performing TSA.

Implication for Future Study

Based on our research, we found that Tai Chi for hypertension patients < 50 years old showed more than three times the reduction of SBP and DBP in patients ≥ 50 years old. With the growth of age, the elasticity of the blood vessel wall and the blood volume is reduced. One possible explanation might be that patients ≥ 50 years old may have serious underlying diseases besides hypertension, which may be difficult to lower BP and affect the effectiveness of Tai Chi. However, due to small sample size, the relationship between age and effectiveness of Tai Chi needs further confirmation. Besides, our systematic review found that intervention for 12–24 weeks could significantly lower SBP and DBP than intervention < 12 weeks and intervention > 24 weeks, which was consistent with the findings of Cornelissen et al. [55••]. This finding may be explained by unsupervised exercise sessions, longer treatment durations are often associated with worse adherence, especially in exercise programs without facility. Previous study [55••] showed that > 210 min of weekly exercise produced the smallest reductions in BP, similar to trends in BP observed in our study. Whether there is a dose–response relationship between Tai Chi and BP reduction, more high-quality studies are required.

To enhance the quality of evidence, the quality of the original RCTs should be improved. The random sequence generation and allocation concealment should be correctly used. Due to the particularity of Tai Chi, blind methods are difficult to implement. Future studies could separate researchers, outcome assessors, and data collectors, or use objective outcome indicators to minimize the impact of subjective factors and to ensure the authenticity of the results. Besides, few included RCTs had published protocol in advance, which concerns that statistically non-significant results might not be published.

Strengths and Limitations

This is the latest systematic review of Tai Chi for hypertension, we have registered on the PROSPERO in advance, conducted and reported this study in strict accordance with the AMSTAR 2 and PRISMA statement guidelines. Besides, we performed TSA to explore whether the evidence in our meta-analysis was reliable and conclusive. However, potential limitations should be considered. Firstly, some of the included studies involving prehypertensive patients, which may be sensitive to exercise, thus the effectiveness of Tai Chi may be exaggerated. Secondly, some included RCTs were with high risk of bias. Furthermore, we only included studies published in Chinese and English, language bias may exist.

Conclusions

Tai Chi could be recommended as an adjuvant treatment for hypertension, especially for patients less than 50 years old. However, due to poor methodological qualities of included RCTs and high heterogeneity, this conclusion warrants further investigation.

Author Contributions Dongling Zhong, Juan Li, Han Yang contributed equally to this work.

Conceptualization: Juan Li, Rongjiang Jin
Data curation: Yuxi Li, Yijie Huang
Methodology: Tianyu Liu
Writing—original draft: Dongling Zhong, Juan Li, Han Yang
Writing—review & editing: Qiwei Xiao, Yuxi Li

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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