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Review

The safety of tai chi: A meta-analysis of adverse events in randomized controlled trials☆

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ABSTRACT

Objectives: To review current publications to examine safety of tai chi (TC).
Design: Cochrane Library, EBSCO host and MEDLINE/PubMed were searched for randomized controlled trials (RCTs) including TC as the core intervention and reporting adverse events (AEs). Data were extracted considering active vs. inactive control group comparisons and presence of an AE monitoring protocol. Meta-analyses were conducted for overall results as well as control group and reporting specific conditions.
Results: In 256 RCTs of TC, 24 met eligibility criteria (1794 participants) and were assessed using the Cochrane Risk of Bias tool. The frequency of non-serious, serious and intervention-related AEs were not found to be significantly different between TC and inactive or active control conditions. In studies with an AE monitoring protocol, more non-serious adverse events (RD = 0.05; 95% CI: 0.00, 0.10; $P = 0.05$) were reported for TC compared to inactive interventions. Given the higher overall AE risks related to studies of participants with heart failure, additional analyses examined this set separately. More serious AEs were found for inactive interventions compared with TC in studies with heart failure participants (RD = −0.11; 95% CI: −0.20, −0.03; $P = 0.01$).
Conclusion: Findings indicate that TC does not result in more AEs than active and inactive control conditions, and produces fewer AEs than inactive control conditions for heart failure patients.

1. Introduction

Tai chi (TC) is rooted in Chinese philosophy, and is a low-intensity, mind-body exercise that continues to grow in popularity in the general population and is recognized for various therapeutic applications [1,2]. Currently, TC is generally taken to be a technique which can contribute to physical and mental well-being as a result of practicing a series of physical postures or movements with a focus on rhythmic breathing and meditative states [2–5]. It has been shown to generate multifaceted benefits, including but not limited to improving functional fitness [6], lower extremity muscle strength [7], balance [8], falls prevention [9], cardiorespiratory function [10], sleep [11,12] and mental health [13]. One of the key features that has made TC a promising intervention, especially for older and rehabilitating adults, is its purported safety. Previous reviews on the efficacy and safety of TC generally concluded that TC is as safe as what is used for controlled comparison conditions [14–16].

Despite the long-held reputation and published evidence supporting its safety, TC has recently received challenges in scientific articles as well as the Chinese lay press regarding the safety of TC among practitioners [17–20] and motivated beginners [17]; suggesting a need to systematically evaluate the safety of TC in the body of published research.

An adverse event (AE) is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a treatment, and that does not necessarily have a causal relationship with this treatment” [21]. Reporting AEs during clinical trials presents a vital component of assessing new therapies' safety. Only one systematic review has focused on assessing TC-associated AEs [22]. However, to our knowledge, there has not been a review of the literature that has

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specifically and comprehensively evaluated the reporting of AEs and safety of TC using meta-analysis. In pursuing a comprehensive evaluation and meta-analysis of AEs in TC, there are two trends in the literature to be considered. The recently published review notes the underreporting of specific monitoring protocols in many of the published studies and suggests the importance of implementing and describing such protocols to more dependably reveal AEs [22]. Therefore, in the current review, subgroup analyses of studies that specify the adoption of an AE protocol were conducted. Further, one of the most frequently addressed patient populations for whom TC is tested are patients with heart failure (HF), a group with particularly high risk for engaging in exercise that, along with age and intensity of exercise, places participants at higher risk for AEs, particularly cardiovascular events [23]. While TC is known as a low-intensity activity, it is nevertheless a form of exercise. So, although the low-intensity and generally gentle flowing movements of TC may be seen as ideal for these patients, the present review included a subgroup analysis comparing study participants with and without HF to address the higher risk of AEs in this population.

The purpose of this article was to systematically review and analyze the frequency of AEs in TC RCTs and evaluate these occurrences relative to both active and inactive control conditions. Subgroup analyses were conducted to address potential reporting bias associated with monitoring protocol and examination of any specific HF related AEs. The research hypotheses are:

Hypothesis 1. TC will not produce a significantly different rate of AEs as control interventions (active and inactive).

Hypothesis 2. Studies that adopt an AE monitoring protocol will result in higher rates of AE reporting than those that do not include an AE reporting protocol.

Hypothesis 3. In patients with HF, TC will not produce a significantly different rate of serious or non-serious AEs than control interventions.

2. Methods

This review was designed and managed according to the Recommendations of the Cochrane Collaboration [24] and PRISMA Guidelines [25].

2.1. Standards of eligibility

Inclusion criteria. Two-arm RCTs with older adults (i.e., more than half of the participants aged ≥50) in which one arm was TC and a comparison group were considered eligible. We included studies that compared TC with active intervention (e.g., endurance training, stretching) or inactive control conditions (e.g. no treatment, usual care, education).

Exclusion criteria. The following conditions were excluded: 1) TC was one component among multi-modal interventions instead of the sole core intervention; 2) comparative studies among different TC forms with exception of a non-TC control group; 3) significant differences in baseline characteristics; 4) AEs were only reported in one group, or not specified. No further limitations were set regarding type of TC, or intervention control, length, frequency, or duration of the program. English or Chinese publications were allowed (as these are the most common two languages used for TC publications and authors were able to review in one or the other native language). No exclusions were made on the basis of population.

Types of outcome measures. Adverse events were defined as any unfavorable health changes experienced by participants that happened during the trial, regardless of whether the changes were likely related to the intervention. To qualify as a reported AE, an incident had to be explicitly referred to as an AE, or studies reporting health-related dropouts were also eligible. AEs which occurred during the intervention period were included, and AEs which occurred during follow-up (non-intervention) period were excluded [26].

AEs were classified into three types: 1) serious; 2) non-serious; and 3) intervention-related. Serious AEs were defined as resulting in death, disability/permanent damage requiring hospitalization or medical intervention [21,27]. AEs of other kinds were considered non-serious. The third category depended upon whether an intervention-related association was assessed or not. Those intervention-related AEs could be either serious or non-serious. Causal association to the intervention was presumed only if the original articles reported it as such.

Falls were not reported as AEs based on the fact that falls were the designated study outcome of interest in many of the studies included, not considered to be secondary to TC, but rather potentially reduced by TC [26,28,29].

2.2. Search methods

MEDLINE/PubMed, EBSCOhost and the Cochrane Library were searched from the beginning to February 29, 2016. Keywords used were “tai chi”, “qigong”, and a filter for retrieving RCTs [24]. Each database search method was adapted as needed. Two review authors (H.C. and Q.W.) independently evaluated the potential abstracts and full articles and were in agreement in determination of eligibility selections.

2.3. Data extraction

Two review authors (H.C. and Q.W.) independently extracted data on country of origin, participants (e.g., number, condition, age), interventions (e.g., TC type, dose), control interventions (e.g., type, dose), and AEs (e.g. AE reporting, having described AE monitoring protocols) using a developed data extraction form. If needed, inconsistencies were presented to a third review author (L.L.) and discussed until consensus was achieved.

2.4. Study quality assessment

The Cochrane risk of bias tool was used to assess the study quality independently [30]. Risk of bias was assessed in the field of: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. For each criterion, risk of bias was designated as low, unclear, or high [30]. A third reviewer (L.L.) checked discrepancies and a consensus was reached under discussion.

2.5. Data analysis

2.5.1. AE analysis and heterogeneity

Although the primary purpose of analysis was to compare AEs in TC intervention groups to control conditions, the non-TC control interventions were grouped into two categories, active interventions and inactive interventions. AEs of TC compared with the two control group categories were analyzed separately because differences in AEs between TC and active controls (higher risk for AEs due to activity) and TC with inactive controls (potentially lower risk for AE in comparison group) may require consideration of the potential differences in results. Meta-analyses were conducted with RevMan version 5.3 software. The preferred estimator was the Mantel–Haenszel risk difference (RD). For the outcomes, 95% confidence intervals (CIs) were set. Statistical heterogeneity was assessed using the I^2 test and χ^2 tests [24]. An $I^2 > 70\%$ indicated heterogeneity. A fixed-effect model was used if provided no significant statistic heterogeneity; when I^2 was > 70%, random-effect model was used [31].

2.5.2. Subgroup and sensitivity analyses

Two subgroups, AE protocol adoption (articles with AEs protocol vs. those without an AE protocol) and types of participants (participants with heart failure vs. no heart failure), were examined by subgroup

analyses.

In order to evaluate the robustness of the results, sensitivity analyses were conducted for the studies which had low risk of selection bias.

2.6. Risk of publication bias

For meta-analysis which included at least 10 studies, risk of publication bias was evaluated [24]. RevMan version 5.3 software was used to create funnel plots. Publication bias was judged by visual analysis. Asymmetrical funnel plots were considered as representing high risk of publication bias; roughly symmetrical funnel plots were considered as representing low risk [24].

3. Results

3.1. Literature search

The search strategy yielded 2590 records. After removing duplicates, 1380 records were screened for eligibility. Of these, 1110 were excluded for the following reasons: (1) not randomized; (2) not relevant; (3) full article unavailable; or (4) did not use TC interventions. In the remaining 270 full articles, 14 were excluded because comparisons were between different types of TC only, or included three or more arms. Altogether, 256 full-text articles were searched for AEs. In them, 186 full-text articles (72.65%) did not report any information on AE tracking or data, and 44 articles (17.19%) describing 42 studies did not report sufficient AE data. Finally, 26 articles on 24 studies, all in English, were included for reporting and meta-analysis (Supplemental Fig. S1) [8,12,26,28,29,32–53].

3.2. Participant and setting characteristics

A total of 1794 participants were included in the 243 studies. The sample number per study ranged from 10 to 368, with a median of 55 (inter quartile range, 34–75.5). In these 24, 14 were carried out in North America (USA; totally of 1044 participants); 1 in South America (Brazil; 61 participants); 5 in Asia (3 in China, 1 each in Korea and Israel; 510 participants); 3 in Europe (1 each in France, Italy and Turkey; 159 participants); and 1 in Australia (20 participants). Twenty-one studies included participants with a range of physical or mental health problems (1642 participants). The remaining 3 studies were completed with healthy people or those not selected according to a particular health condition (152 participants) (Table 1).

The median age was 65 (inter quartile range, 59.2–72.23) years, ranging from 13.1 to 84.15 years. A total of 1250 women and 544 men were included. The female participant percentage ranged from 11.11–100% with a median of 66.67% (inter quartile range, 43–83.64%). Ethnicity was not reported in 7 studies; in the other studies, the Caucasian participant percentage ranged from 0 to 100% with a median of 77.5% (inter quartile range, 42–86.87%). Body Mass Index (BMI) was not reported in ten studies; for those reporting, BMI ranged from 21.7 to 38 with a median of 27.36 (inter quartile range, 26–29.9).

3.3. Intervention characteristics

Among the 24 included studies, 11 stated that Yang style was used; 2 each stated that Sun style or 24-style was used; 5 studies employed various non-traditional TC styles; the remaining 4 did not mention the TC styles used in the intervention. The median duration of TC interventions was 12 (inter quartile range, 12–22) weeks, ranging from 12 to 48 weeks in length. The TC interventions covered altogether 897 participants. 15 studies compared TC with active interventions (n = 965), and 9 compared with inactive interventions (n = 829) (Table 1).

3.4. Risk of bias in individual studies

The assessment results of risk of bias (24 included studies) are displayed in Supplementary Table S1. Half of studies reported satisfactory random sequence generation and allocation concealment. Five studies (21.74%) reported satisfactory blinding of participants. 17 studies (70.83%) reported satisfactory blinding of outcome assessment (Supplementary Table S1).

3.5. Analyses of adverse events

Table 2 presents the absolute numbers of studies, participants, and AEs of each analysis. Testing of the first hypothesis indicated there was no difference in the frequency of serious, non-serious, or intervention-related AEs when comparing TC with active and inactive control interventions (Table 2). The frequency of serious (Risk Difference = −0.03, 95% CI: [−0.06, 0.00]; P = 0.08) and non-serious (Risk Difference = 0.03, 95% CI: [−0.00, 0.07]; P = 0.07) AEs was not significantly different between TC and inactive controls. Heterogeneity was low in all meta-analysis (I^2 between 0% and 24%). As there was no evidence of heterogeneity, a fixed-effect model was used (Table 2).

Among the TC groups, the frequency of serious, non-serious, and intervention-related AEs in individual studies ranged from 0.0–15.385%, 0.0–16.28%, and 0.0–6.45%, respectively. Among them, 2.23% (20 of 897), 5.02% (45 of 897), and 0.46% (4 of 897) of participants in the TC groups reported serious, non-serious and intervention-related AEs.

3.6. Subgroup analyses and sensitivity analyses

There were no group differences when comparing TC and active interventions (Tables 3-4). In addressing Hypothesis 2, more non-serious AEs were found when comparing TC with inactive interventions in studies with adoption of an AE monitoring protocol but not in studies without AE protocol (Table 3). Studies that have adopted an AE monitoring protocol may be inclined to report more AEs [54]. Of the 24 eligible studies that included an AE report, only 11 trials included an explicit monitoring protocol, which provides a more reliable framework for interpreting the validity of AE report.

Regarding Hypothesis 3, more serious AEs were found for inactive intervention groups (IIG) compared with TC group (TCG) in studies with HF participants but not in participants without a heart failure diagnosis (Table 4). Heterogeneity was high in this subgroup differences analysis (I^2 = 82.9%; P = .02). Serious AEs in this analysis included: death (n = 1, TC group; n = 5, inactive intervention group); hospitalized (n = 2, TCG; n = 4, IIG); worsening heart failure (n = 2, TCG; n = 5, IIG); worsening co-morbidities of HF (n = 0, TCG; n = 2, IIG).

In the sensitivity analyses, results remained similar when only including studies having low risk of selection (Table 5). For the test of risk of publication bias, visual inspection revealed that all funnel plots were sufficiently symmetrical, representing low risk of publication bias.

4. Discussion

This systematic review on TC RCTs across a broad range of ages, conditions and intervention protocols showed that TC is not prone to increased incidence of serious, non-serious or intervention-related AEs compared with active or inactive control interventions. Not surprisingly, the odds of non-serious AEs increased with adoption of an AE protocol, possibly due to greater vigilance in detection and reporting of events that might have been neglected in studies without a protocol to guide detection and reporting. The odds of serious AEs (including death, hospitalization, worsening HF, and worsening co-morbidities) decreased with HF participants in the TC condition compared with inactive interventions. That is, with no intervention (e.g., usual care or

Table 1
Characteristics of the included studies.

Reference	Origin	Participants (N; condition; age)	Intervention	Control intervention	Dose (duration/session; session/week; program length)	AE Protocol (Y/N)
TC group vs. active exercise						
Caminiti 2011	Italy	60;chronic heart failure; 73.8	10 move Yang style	Endurance training	30 min; 3 × /week; 12 weeks	N
Deschamps 2009	France	52;sedentary obese women; 80.7	Modified Yang style	Cognition-action	30 min, 4 × /week; 24 weeks	N
Hart 2004	Israel	18;first-stroke survivors; 54.77	TC	Physiotherapy exercises (improvement of balance)	60 min; 2 × /week; 12 weeks	N
Hwang 2016	Taiwan	368;fall-related experience; 72.35	Yang style	Lower Extremity Training	60 min; 1 x/week; 24 weeks	N
Larkey 2015	USA	101;breast cancer survivors; 58.8	TC easy	Sham TC	60 min; 1 x/week; 12 weeks + home practice	Y
Lee 2015	China	59;Functional Ambulation Classification; 84.15	Siting TC	Limbs mobilization exercise	60 min; 3 × /week; 12 weeks	N
Nery 2015	Brazil	61;recent myocardial infarction; 58	Beijin style	full-body stretching exercises	100 min; 3 × /week; 12 weeks	N
Son 2015	Korea	45;seniors; 72.11	Sun style	Otago exercise	60 min; 2 × /week; 12 weeks	N
Tsang2007	USA	38;type 2 diabetes; 65	12 move Sun and Yang style hybrid form	Sham exercise	60 min; 2 × /week; 16 weeks	Y
Tsang 2010	Australia	20;overweight/obese adolescents; 13.1	Yang style	Kung Fu	60 min; 3 × /week; 24 weeks	Y
Wang 2009	USA	40;knee osteoarthritis; 65	10 form Yang style	Wellness education and stretching	60 min; 2 x/week; 12 weeks; +20 min home practice daily	Y
Yeh 2013	USA	16;heart failure with preserved ejection fraction; 66	5 moves form Yang style	Aerobic exercise	60 min, 2 × /week; 12 weeks; + home practice	N
Yildirim 2015	Turkey	47;seniors; 63.65	Yang style	Combined exercise	60 min; 3 × /week; 12 weeks	Y
Zhang 2008	China	20;type 2 diabetes 57.4	24 style short form	Free activity program	60 min; 5 × / week; 14 weeks	N
TC group vs. inactive condition						
Barrow 2007	USA	65;symptomatic heart failure;68	Wu Chian Chuan + Orchid Hand 21 style	Standard medical supervision and drug treatment	55 min; 2 × /week; 16 weeks (intervention only)	N
Irwin 2008	USA	112;Moderate Sleep Complaints; 69.6	TC	Health education	40 min; 3 × /week; 16 weeks	N
Tsai 2013	USA	55;cognitive impairment and osteoarthritic knee; 78.91	12 form Sun style for arthritis	Health education	20-40 min; 3 × /week; 20 weeks	N
Wolf 2003	USA	311;Transitionally Frail; 80	6 out of 24 styles	Wellness education	intervention:60-90 min; 2 × /week; 48 weeks control:60 min; 1 × /week; 48 weeks	Y
Yeh 2011	USA	100;chronic heart failure; 67	Short form Yang style	Heart health education program	60 min; 2 × /week; 12 weeks; + 35 min home practice 3 × /week (intervention only)	Y
Wayne 2012	USA	86;post-menopausal osteopenic women; 59.6	TC	Waitlist	60 min; 2 × /week; 4 weeks; + 1 × /week; 32 weeks; + home practice (intervention only)	Y
Wayne 2014	USA	60;seniors; 64.2	TC	Usual health care	30 min; 2 × /week; 24 weeks (intervention only)	Y
Yeh 2004	USA	30;chronic heart failure; 63.5	5 moves form Yang style	Waitlist, usual care	60 min, 2 × /week; 12 weeks; + home practice (intervention only)	Y
Yeh 2010	USA	10;chronic obstructive pulmonary disease; 65.5	Short form Yang style	Waitlist, usual care	60 min; 2 × /week; 12 weeks; + videotape home practice (intervention only)	Y

Table 2
Adverse events of Tai Chi versus active and inactive interventions.

Type of AE	No. of Studies	Tai Chi Group		Control Group		Risk Differences	95% CI	*P* value	Heterogeneity		
		No. of events	No. of participants	No. of events	No. of participants				I^2	Chi^2	*P*
Tai Chi versus Active Interventions											
Serious	15	6	476	7	489	0.00	[−0.02,0.02]	0.84	0%	6.51	0.95
Non-serious		6		3		0.01	[−0.01,0.03]	0.45	0%	6.41	0.96
Intervention-related		2		1		0.00	[−0.01,0.02]	0.77	0%	1.82	1.00
Tai Chi versus Inactive Interventions											
Serious	9	14	421	25	408	−0.03	[−0.06,0.00]	0.08	21%	10.13	0.26
Non-serious		39		24		0.03	[−0.00,0.07]	0.07	24%	10.50	0.23
Intervention-related		2		0		0.00	[−0.01,0.02]	0.55	0%	2.04	0.98

waitlist) or inactive interventions (e.g., educational control condition), participants more likely progressed to AEs, and those AEs may be related to progression of their disease (deemed to be not associated with the intervention). In contrast, those who were in the TC interventions were less likely to have AEs, possibly due to the health benefits associated with this practice (as indicated in some of the main results of these studies) [32,33,48,50,55,56]. TC generally improved physical performance outcomes (6-min walking distance and knee extensor strength), disease-specific quality of life [15] and vagal activity of autonomic markers (baroreflex sensitivity) [57] of HF patients. Further, blood pressure is frequently found to be significantly reduced in HF and non-HF compromised populations practicing TC [58] suggesting another pathway for HF patients to fare better in the TC arm of studies. Further and larger-scale research is required to better understand how TC may benefit individuals experiencing HF relative to AEs.

This is the first meta-analysis on AEs in RCTs of TC. In the present meta-analysis, the rate of AEs was somewhat higher than indicated in a prior review of the safety of TC [22]. Wayne and colleagues (2014) reported AEs in 15 of 50 (30%) of included studies, while ours showed AEs in 14 of 24 (58.3%). This difference may be explained through a different search strategy and inclusion standard, along with newer studies being added since that earlier publication. In the present study, only two-arm RCTs with TC alone as one of the two interventions and AE reports were included with a larger proportion of newer studies including an AE monitoring protocol. Wayne and colleagues accepted all TC studies that reported AEs. Previous systematic and meta-reviews on the specific health conditions largely revealed that TC is safe for musculoskeletal conditions [14], cardiorespiratory conditions [15], rheumatoid arthritis [59], fibromyalgia syndrome [16], osteoarthritis [60], Parkinson's disease [61], type 2 diabetes [62] and cancer [63], with further illustration that insufficient reporting prevented definite conclusions. No safety data were included in reviews of several other medical conditions [64–66].

Among 24 studies included in our final meta-analysis, we found underreporting of AE monitoring protocols; half did not include an explicitly described protocol. Three articles [26,40,41] included reports of health-related dropouts in the CONSORT diagram or publication text, however reported no AEs in either group, suggesting that potential AEs were not specifically tracked or reported as AEs. Only 11 of the 24 trials included in Table 1 (representing < 4.3% of all 256 trials) reported both an AE monitoring protocol and explicit AE reports, and the quality of reporting in these studies was variable, with only a small proportion of studies adequately meeting important CONSORT recommendations for reporting harms in RCTs [67]. The less-biased studies included monitoring protocols applied repeatedly throughout the study (e.g. weekly, monthly), solicited information from multiple sources (e.g. patient self-reports, instructor reports), and monitored and documented AEs in both the intervention and control groups [22]. Additionally, reports of AEs in more reliable studies were more comprehensive, not limited to intervention-related events, and provided quantitative data (e.g. frequency of event types) [22].

Overall, random sequence generation and blinding of outcome assessment were applied in most studies. Moreover, risk of bias was lower than in other meta-reviews on RCTs of TC [14,16,59,68]. This result suggests that safety data are more likely to be adequately reported in TC trials with overall better quality of reporting.

Based on the present study, there were no reports of serious AEs that were determined to be attributable to TC or control conditions (active or inactive); rather, AEs were deemed as unrelated to study interventions. Those AEs that were reported as related to the TC or active control interventions were minor, such as musculoskeletal aches and pains.

The frequency of minor musculoskeletal impairment in TC groups (21 of 45) was higher than that in control groups (7 of 27). Reports of minor musculoskeletal events in TC training are consistent with AEs reported in studies of other meditative movement therapies (e.g. yoga) [69,70], but lower than AEs reported in martial arts oriented studies [71,72]. Musculoskeletal events, especially lower extremity pain was reported in six trials [8,28,43,45–47] of the 24 listed in Table 1. Three lower extremity pain reports (including knee [45], wrist and ankle [46] pain) were determined to be related to the TC intervention. Compared with natural walking, biomechanical studies support that practitioners experience higher sheer force and frontal plane torques at the ankle, knee, and hip joints during TC training [73]. It is difficult to draw clear

Table 3
Sensitivity analysis of adverse events of Tai Chi versus controls when only studies with low risk of selection bias were included.

Type of AE	No. of Studies	Tai Chi Group		Control Group		Risk Differences	95% CI	*P* value	Heterogeneity		
		No. of events	No. of participants	No. of events	No. of participants				I^2	Chi^2	*P*
Tai Chi versus Active Interventions											
Serious	9	2	371	5	377	−0.01	[−0.03,0.01]	0.42	0%	0.72	1.00
Non-serious		5		1		0.01	[−0.01,0.03]	0.27	0%	7.59	0.47
Intervention-related		2		0		0.01	[−0.01,0.02]	0.54	0%	2.01	0.98
Tai Chi versus Inactive Interventions											
Serious	3	1	105	4	97	−0.03	[−0.08,0.02]	0.21	63%	5.43	0.07
Non-serious		4		1		0.03	[−0.02,0.08]	0.29	67%	6.00	0.05
Intervention-related		2		0		0.02	[−0.02,0.06]	0.37	1%	2.03	0.36

Table 4
Subgroup analyses by type of adoption of monitoring protocol (articles with AE protocol versus without AE protocol).

Type of AE	No. of studies	Tai Chi group		Active group		Risk differences	95% CI	*P* value	Heterogeneity I^2;Chi^2;*P*	Test for subgroup differences I^2;Chi^2;*P*
		No. of events	No. of participants	No. of events	No. of participants					
Tai Chi vs. Active Interventions										
Serious										
Protocol	5	1	117	1	129	0.00	[−0.04,0.04]	1.00	0%;0.00;1.00	0%;0.01;0.90
No-protocol	10	5	359	6	360	−0.00	[−0.03,0.02]	0.82	0%;6.38;0.70	
Non-serious										
Protocol	5	3	117	2	129	0.01	[−0.03,0.06]	0.63	0%;1.75;0.78	0%;0.04;0.84
No-protocol	10	3	359	1	360	0.01	[−0.01,0.03]	0.56	0%;4.23;0.90	
Intervention-related										
Protocol	5	1	117	1	129	0.00	[−0.04,0.04]	0.94	0%;1.09;0.90	0%;0.00;0.96
No-protocol	10	1	359	0	360	0.00	[−0.01,0.02]	0.76	0%;0.78;1.00	
Tai Chi vs. Inactive Interventions										
Serious										
Protocol	6	12	302	20	295	−0.03	[−0.06,0.01]	0.14	24%;6.62;0.25	0%;0.01;0.93
No-protocol	3	2	119	5	113	−0.02	[−0.07,0.02]	0.31	39%;3.26;0.20	
Non-serious										
Protocol	6	36	302	21	295	0.05	[0.00,0.10]	0.05	0%;4.94;0.42	51.9%;2.081.67;0.15
No-protocol	3	3	119	3	113	0.00	[−0.05,0.05]	0.78	0%;0.69;0.71	
Intervention-related										
Protocol	6	2	302	0	295	0.01	[−0.01,0.02]	0.48	0%;2.44;0.79	0%;0.14;0.71
No-protocol	3	0	119	0	113	0.00	[−0.03,0.03]	1.00	0%;0.00;1.00	

conclusions about these observations because prevalence of these complaints or injuries in age-matched individuals in the same population is not known, but these observations reflect the concerns that are expressed about the safety of TC for knees and other musculoskeletal conditions.

Finally, our review found two incidences of participant reports of psychological AEs such as depression [28]. Similar reports have been found in related mind-body exercises, including qigong and meditation [74,75].

Given the variability in the reporting of monitoring systems and the findings that AE reporting appears to be higher in those studies with monitoring protocols (especially non-serious reporting), we suggest there is a need to more rigorously apply such protocols in future studies. Although the non-serious AEs may be more reliably reported in those studies with monitoring protocols, the proportions of AEs overall when comparing TC with control conditions is similar with or without the protocols. This lends to the idea that even with possible underreporting, TC still poses less or the same risks in general for most populations compared to standard, inactive, or active lifestyles.

There were limitations to our meta-analysis. One of the limitations is the heterogeneity of participants and interventions. The heterogeneity and risk bias of the included studies were low suggesting that bias was acceptable. Subgroup analyses presented differences in only a small number of comparisons. The second limitation is the insufficient reporting of AEs in the RCTs. Since 72.66% (186 of 256) of the trials reported no safety data and 17.19% (44 of 256) of the trials only reported data in one intervention group or no specification, the findings can only be considered as approximate. Alongside this concern is the recognition that with the variation in reporting and the lack of having AEs consistently reported across studies, we are examining an "outcome" that cannot be reported as if initially hypothesized and examined across the studies. In this sense, although we include counts of reports, this is not at all a traditional continuous variable. Thirdly, the present research included studies from randomized trials only. Data from audits and cross-sectional studies, especially of longer-term practitioners, and uncontrolled longitudinal studies may better inform long-term effects in the community. Finally, it is worth noting that half of the included trials did not report adequate allocation concealment which is the most important bias source in randomized trials [76], and significantly restricts the interpretability of the research findings (although the potential bias is more likely to present itself in the end points designated as study outcome, less so for the outcomes of AEs as non-targets of study goals). The sensitivity analyses also indicted low risk of selection bias. With the sources of bias taken into account, we suggest that the quality of the evidence, while robust, may be considered with caution.

5. Conclusion

The present results suggest that the frequency and severity of AEs related to TC RCTs are not significantly different from levels associated with other interventions used for control condition purposes (including active and inactive). Regardless of the limitations of the current evidence available, TC appears to be a generally safe intervention. For HF patients, TC may be viewed as particularly safe, contributing more to improvements in the conditions that define HF than to the risks. Recommending TC practice to those living with health conditions or healthy individuals should not be discouraged out of safety concerns. Reporting adequate safety data and adopting internationally accepted guidelines [77] of AEs are strongly suggested in future TC studies.

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Conflict of interests

The authors have no conflicts of interest to declare.

Author contributions

HC contributed to the conceptualization of the study, analysis and writing of the manuscript. QW[2,] MP and DJ contributed to the writing/editing of the manuscript. QW [1] contributed to the analysis. SL contributed to the conceptualization of the study. LL contributed to the

Table 5
Subgroup analyses by type of participants (participants with heart failure versus those without heart failure).

Type of AE	No. of studies	Tai Chi group		Control group		Risk differences	95% CI	*P* value	Heterogeneity I^2;Chi^2;*P*	Test for subgroup differences I^2;Chi^2;*P*
		No. of events	No. of participants	No. of events	No. of participants					
Tai Chi vs. Active Interventions										
Serious										
Heart failure participants	2	0	38	1	38	−0.03	[−0.11,0.06]	0.55	0% ; 0.08 ; 0.77	0% ; 0.33 ; 0.57
Others	13	6	438	6	451	0.00	[−0.02,0.02]	1.00	0% ; 6.33 ; 0.90	
Non-serious										
Heart failure participants	2	0	38	0	38	0.00	[−0.07,0.07]	1.00	0% ; 1.00 ; 0.00	0% ; 0.00 ; 0.97
Others	13	6	438	6	451	0.00	[−0.02,0.02]	0.88	0% ; 6.52 ; 0.89	
Intervention-related										
Heart failure participants	2	0	38	0	38	0.00	[−0.07,0.07]	1.00	0% ; 1.00 ; 0.00	0% ; 0.01 ; 0.94
Others	13	2	438	1	451	0.00	[−0.01,0.02]	0.75	0% ; 1.85 ; 1.00	
Tai Chi vs. Inactive Interventions										
Serious										
Heart failure participants	3	5	97	16	98	−0.11	[−0.20,-0.03]	0.01	0% ; 0.59 ; 0.75	82.9% ; 5.86 ; 0.02
Others	6	9	324	9	310	−0.00	[−0.03,0.03]	0.95	0% ; 0.01 ; 1.00	
Non-serious										
Heart failure participants	3	2	97	2	98	0.00	[−0.05,0.05]	1.00	0% ; 0.00 ; 1.00	41.9% ; 1.72 ; 0.19
Others	6	37	324	22	310	0.04	[−0.00,0.09]	0.06	46% ; 9.34 ; 0.10	
Intervention-related										
Heart failure participants	3	0	97	0	98	0.00	[−0.03,0.03]	1.00	0% ; 0.00 ; 1.00	0% ; 0.10 ; 0.76
Others	6	2	324	0	310	0.01	[−0.01,0.02]	0.48	0% ; 2.36 ; 0.80	

conceptualization of the study and writing of the manuscript.

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