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Benefits of Tai Chi Quan on neurodegenerative diseases: A systematic review

Rui Wang [a], Hao Zhou [a], Yu-Chen Wang [a], Xiao-Long Chang [b], Xue-Qiang Wang [a,c,*]

[a] Department of Sports Rehabilitation, Shanghai University of Sport, Shanghai 200438, China
[b] School of Physical Education and Training, Shanghai University of Sport, Shanghai 200438, China
[c] Department of Rehabilitation Medicine, Shanghai Shangti Orthopaedic Hospital, Shanghai 200438, China

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ABSTRACT

Background: Neurodegenerative diseases have become an important concern with the accelerated aging process. Tai Chi Quan (TCQ) has positive benefits for brain health and chronic diseases. The aim of this study was to summarize the protective effects of TCQ for motor function, cognition, quality of life, and mood in patients with neurodegenerative diseases.

Methods: A systematic search was conducted via PubMed database and the Web of Science core collection database until August 20, 2021. The available English systematic reviews, meta-analyses, and clinical trials were included. Two reviewers completed the screening and assessment process independently.

Results: A total of 28 studies on Parkinson's disease, 21 on cognitive impairment, and 9 on multiple sclerosis met the included criteria. The study found that TCQ remarkably improved general motor function and balance, and prevented falls for Parkinson's disease. TCQ significantly improved global cognitive function for cognitive impairment. TCQ was likely safe and beneficial for multiple sclerosis as result of heterogeneous outcomes and small samples.

Conclusion: TCQ exercise can effectively improve the motor function, global cognitive function, and falls in patients with neurodegenerative diseases. However, the positive effects of TCQ on the quality of life and mood of patients with neurodegenerative diseases need further evidence.

1. Introduction

Neurodegenerative diseases are chronic disease states characterized by slow and progressive dysfunction and the loss of neurons and axons in the central nervous system (Heemels, 2016). According to primary clinical features, neurodegenerative disorders can be classified as Alzheimer's disease (AD) or dementia, Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis, spinocerebellar ataxia, spinocerebellar atrophy, and motor neuron disease (Dugger and Dickson, 2017). The prevalence of neurodegenerative diseases is increasing as a result of lifespan extension (Kondo, 1996; Farooqui and Farooqui, 2009). These diseases tend to worsen over time and result in a variety of functional impairments, such as cognitive impairment (CI), motor dysfunction, and loss of self-care (Karlawish, 2014; Doherty et al., 2011). The 2019 Global Burden of Disease Study revealed that people with neurodegenerative diseases are leading contributors to the need for rehabilitation (Cieza et al., 2021). The data from the Global Burden Disease Results Tool showed that the trend in the percentage of people over the age of 55 with years lived with disabilities due to PD and AD globally over the past decade is still increasing (Global burden of disease study 2019, available from: https://vizhub.healthdata.org/gbd-compare/). The global costs for dementia will be US $2.54 trillion in 2030 (Jia et al., 2018). Many patients with PD reported that they paid more than US $500 out of pocket for drugs and assistive devices or rehabilitation therapy annually (Wong et al., 2014). Although these diseases have no cure, physical activity is a crucial allied support in the treatment of neurodegenerative disorders (Keus et al., 2009). Moderate physical activity contributes in delaying brain aging and improves cognition and memory (Di Liegro et al., 2019; Erickson et al., 2019). Physical activity can produce analgesic and antidepression effects and bring a sense of well-being (Koltyn et al., 2014). One of the most popular alternative and complementary methods in the management of neurodegenerative diseases is mind–body exercises, such as Tai Chi Quan (TCQ), yoga, and Qigong.

* Correspondence to: Department of Sports Rehabilitation, Shanghai University of Sport, 399 Changhai RD, Shanghai 200438, China.
E-mail address: wangxueqiang@sus.edu.cn (X.-Q. Wang).

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TCQ is a Chinese traditional exercise that comprises mental concentration, physical balance, muscle relaxation, and breathing (Hong et al., 2000). TCQ is a kind of light- to moderate-intensity exercise depending on duration, style, experience, and posture (Peng, 2012). Many studies have indicated the positive effects of TCQ in various conditions, such as musculoskeletal disorders, (Hall et al., 2009) falls, (Lomas-Vega et al., 2017), brain health, (Liu et al., 2018a) and other chronic diseases (Lan et al., 2002). A bibliometric analysis of TCQ for health promotion from 1980 to 2020 showed that one of the promising fields to focus on is the application of TCQ in neurodegenerative diseases (You et al., 2021). Previous studies supported the efficacy of TCQ in improving clinical features and dysfunction in patients with CI, PD, or MS (Lim et al., 2019; Song et al., 2017; Taylor and Taylor-Piliae, 2017).

In 2021, Yu et al. (2021) released the latest systematic review and meta-analysis of the impact of TCQ in patients with PD, and the pooled results showed that TCQ can bring up gains in motor function and balance. At the same year, Gu et al. (2021) published a systematic review and meta-analysis of the effect of TCQ in elderlies with CI and concluded that TCQ is a relatively safe activity to bring better changes in cognitive function. In 2017, Taylor and Taylor-Piliae (2017). However, these articles only summarized some aspects of TCQ's effectiveness on neurodegenerative diseases. A clear and comprehensive interpretation of the benefits and potential mechanisms of TCQ in neurodegenerative diseases is crucial to project beneficial complementary and adjunctive therapeutic strategies. Therefore, we conducted an integrative review to summarize studies related to the efficacy of TCQ as a supportive therapy for patients with neurodegenerative diseases and discussed the underlying mechanisms of the efficacy of TCQ.

2. Methods

2.1. Data sources and searches

A preliminary search revealed that studies on the efficacy of TCQ on neurodegenerative diseases were concentrated on patients with PD, CI, and MS. The complete search strategy was carried out in the PubMed database and the Web of Science Core Collection database on August 20, 2021. The key words of search strategy were "Tai Chi", "Taiji", "Parkinson's", "dementia", "Alzheimer's disease", "cognitive impairment", and "multiple sclerosis".

2.2. Study selection

The included criteria were 1) the types of studies were limited to systematic reviews, meta-analyses, and clinical trials; 2) all studies should include patients with PD, CI, or MS, regardless of age and disease stage; 3) all clinical trials designed with control groups, such as randomized controlled trials (RCTs) and non-randomized controlled trials; 4) all clinical trials should contain any form of TCQ as one of the interventions for patients with PD, CI, or MS; 5) language was English; 6) the studies were published before August 20, 2021. We excluded reviews, protocols, case reports, letters, comments, and clinical practice guidelines. Irrelevant data and unavailable studies were also excluded. Two reviewers completed the screening process independently. Any controversial studies were decided by discussion.

2.3. Data extraction and quality assessment

Two reviewers separately extracted data on the efficacy of TCQ for patients with neurodegenerative diseases from the included meta-analyses and clinical trials. The two reviewers independently assessed the quality of the included meta-analyses and clinical trials. Inconsistent evaluation scores were resolved by discussion. The quality of meta-analyses was evaluated using a tool called *Assessment of Multiple Systematic Reviews (*Shea et al., 2007*)*. This tool consists of 11 items, and the study with a total score of 7 and above is considered of high quality. The quality of clinical trials was evaluated using the Physiotherapy Evidence Database PEDro scale. This scale consists of random allocation, concealed allocation, baseline comparability, blind subjects, blind therapists, blind assessors, adequate follow-up, intention-to-treat analysis, between-group comparisons, and point estimates and variability. Each item is assigned a value of 1, and a higher score indicates a better quality.

2.4. Data analysis

Considering the differences in disease types, intervention groups and outcome measures in the included studies, we reviewed the efficacy of TCQ categorically according to disease types, namely PD, CI and MS. And then, we reported the effect of TCQ categorically compared to no intervention, usual care, or other active therapies from the included meta-analyses and clinical trials according to clinical features of each disease.

3. Results

In the preliminary search, we obtained 138 records about PD, 85 records about CI, and 20 records for MS. After deduplication, 193 titles and abstracts were screened. 96 full- texts were reviewed. We obtained 28 studies about PD, 21 studies about CI, and 9 studies about MS (Fig. 1). 11 systematic reviews without meta-analyses were used to trace potential clinical trials. Finally, a total of 16 systematic reviews and meta-analyses and 31 clinical trials were evaluated and summarized in Tables 1 and 2, respectively.

3.1. Tai Chi Quan for Parkinson's disease

3.1.1. The clinical features, prevalence, and impact of Parkinson's disease

PD is characterized by the progressive death of dopaminergic neurons and occurs mostly in the elderly with an increasing prevalence rate (Samii et al., 2004). As of 2019, more than 5 million people worldwide suffer from PD. Patients often have motor dysfunction, such as rest tremor, stiffness, bradykinesia, and postural instability (Li et al., 2012). Nonmotor symptoms, such as underlying psychological problems and sleep disorder, aggravate the process of patients' disabilities (Boland and Stacy, 2012). PD often affect the patients' caregivers and family members. A 2005 report said that almost 70% of indirect costs are related to uncompensated care and productivity loss by family (Huse et al., 2005). More than 55% of patients with PD need inpatient care and long-term care facilities, and the average annual total cost can be as high as $30,000 in a long-term care period (Hermanowicz and Edwards, 2015). The data of 486 patients with PD from six countries showed that the average total cost of each patient for half a year ranged from €2600 to €9800, and the direct cost accounted for 60–70% of the total cost (von Campenhausen and Winter, 2011). Based on the American Academy of Neurology guideline, physical therapy is beneficial for the motor function and quality of life of patients with PD (Pringsheim et al., 2021; Reich and Savitt, 2019; Petzinger et al., 2013). Physical exercise needs to focus on improving gait performance, aerobic capacity, balance, strength, and functional independence for patients with PD.

3.1.2. Effects of TCQ on motor symptoms

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most common tool to assess motor symptoms in patients with PD. Seven meta-analyses (Song et al., 2017; Jin et al., 2019; Kwok et al., 2016; Yang et al., 2015, 2014; Zhou et al., 2015; Ni et al., 2014) reported that UPDRS scores remarkably increased when patients with PD practiced TCQ compared to control group. The TCQ group improved UPDRS scores better than no treatment or medication alone group (standard mean difference [SMD]=−0.57, 95% confidence interval (CI) [− 1.11, − 0.04], P = 0.03) and other exercise plus medication group (SMD=−0.78, 95%CI [−1.46, −0.10], P = 0.02) (Yang et al., 2015,

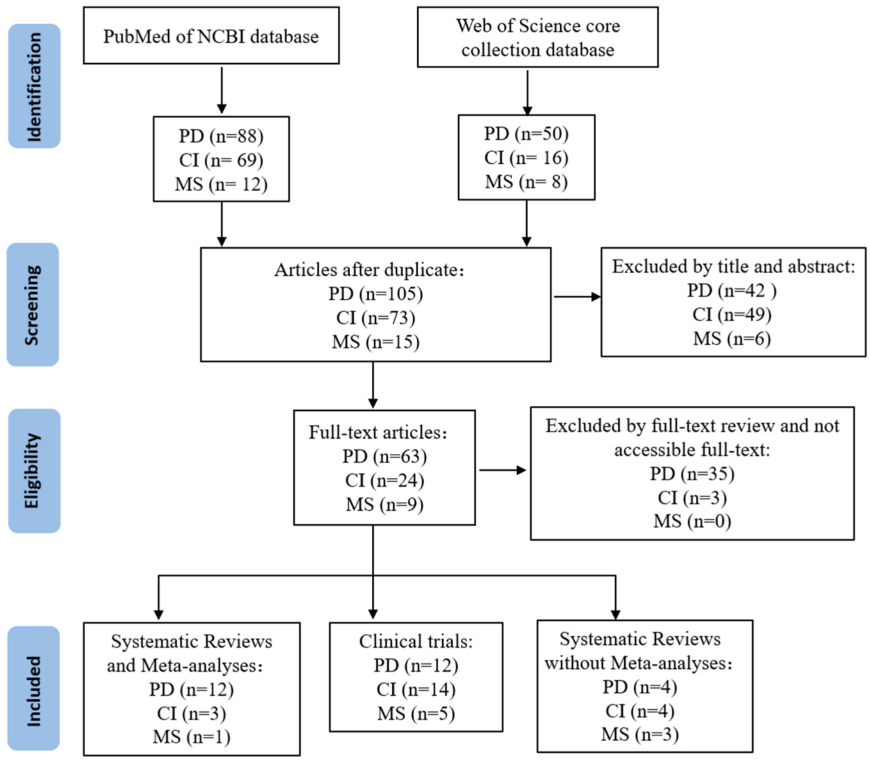

Fig. 1. Flowchart of article search, exclusion, and analyses.

2014). Ni et.al (Ni et al., 2014) showed that TCQ plus medication was also better than medication alone or other exercises plus medication. However, there was no difference between any groups if all patients with PD were not on medication. Besides, two RCTs (Cheon et al., 2013; Li et al., 2012) showed that TCQ had a better improvement on UPDRS scores compared to stretching. A recent meta-analysis (Yu et al., 2021) published by Yu et.al in 2021 showed no significant difference between the TCQ group and the control group. Five RCTs showed the same results (Amano et al., 2013; Gao et al., 2014; Hackney and Earhart, 2009; Vergara-Diaz et al., 2018; Zhang et al., 2015).

The common clinical evaluation tools for balance and falls include the Berg balance scale (BBS), functional reach test (FRT), and timed up and go test (TUGT). Remarkable improvement in BBS was observed in the six meta-analyses (Yu et al., 2021; Liu et al., 2019; Kwok et al., 2016; Yang et al., 2014; Ni et al., 2014). A meta-analysis (Yu et al., 2021) of 17 RCTs concluded that TCQ significantly improved BBS scores (mean difference [MD]=2.74, 95%CI [2.91, 7.26], $P < 0.001$). Three meta-analyses (Liu et al., 2019; Yang et al., 2015; Ni et al., 2014) showed consistent results of significant improvement in FRT in the TCQ group, and TCQ plus medication was better than other active therapies plus medication (SMD=−0.77, 95%CI (−1.51, −0.03), $P = 0.04$). Besides, the effect of TCQ was superior to stretching and resistance training in FRT, maximum excursion, and directional control (Li et al., 2012). However, the effect of TCQ on TUGT is controversial. The results of six meta-analyses (Song et al., 2017; Yu et al., 2021; Kwok et al., 2016; Zhou et al., 2015; Yang et al., 2014) showed that TCQ significantly improve the ability of dynamic balance, but four RCTs (Vergara-Diaz et al., 2018; Choi, 2016; Gao et al., 2014; Hackney and Earhart, 2008) found no significant difference between TCQ group and non-exercise or usual care group. PD stage affects the curative effect of TCQ to some extent. See Tables 1 and 2 for detailed comparisons. Easwaran et al. (2020) appraised 42 meta-analyses on the health promotion of TCQ, and high-quality evidence supported that TCQ had a large effect ($0.80 \leq$SMD < 1.00) on reducing falls in patients with PD. As of October 2019, Zhong et al. (2020) evaluated the quality of systematic reviews on TCQ for improving balance and falls and found that the level of evidence that TCQ improved the fall rate of patients with PD was low. Therefore, definitive conclusions will be acknowledged with more robust evidence.

Patients with PD have poor locomotor control with short steps and rapid speed. In terms of gait performance, four meta-analyses (Yang et al., 2015, 2014; Zhou et al., 2015; Ni et al., 2014) and four RCTs (Vergara-Diaz et al., 2018; Zhang et al., 2015; Amano et al., 2013; Hackney and Earhart, 2008) demonstrated that TCQ had no significant effect on gait velocity and stride length compared to control group. Moderate-quality evidence demonstrated that TCQ has a moderate effect ($0.50 \leq$ SMD < 0.65) on stride length and a small to moderate effect ($0.30 \leq$ SMD < 0.5) on functional mobility in the scoping review of Easwaran et al (Easwaran et al., 2020).

3.1.3. *Effects of TCQ on quality of life*

Moderate-quality evidence showed that TCQ has a small to moderate effect ($0.30 \leq$ SMD < 0.5) on quality of life in the scoping review of Easwaran et al (Easwaran et al., 2020). Previous studies have shown inconsistent results. Like Chen et.al 's study (Chen et al., 2020), Jin et.al (Jin et al., 2019) reported that TCQ significantly improved quality of life in patients with PD (SMD=0.66, 95%CI [0.41, 0.91], $P < 0.001$). At least 12 weeks of TCQ exercise can remarkably improve the quality of life of patients with PD (Chen et al., 2020). The TCQ group had substantially better scores in quality of life compared with stretching training, resistance training, and the no treatment group (Kamieniarz et al., 2021). However, four meta-analyses (Yu et al., 2021; Fidan et al., 2019; Yang et al., 2015; Zhou et al., 2015) reported no significant difference between TCQ group and control group. The differences in results between studies may be due to inconsistencies in PD staging, intervention time, TCQ styles, and control groups.

3.1.4. *Effects of TCQ on mood*

Depression often occurs in patients with PD. According to Easwaran et al.' study, moderate-quality evidence suggested that TCQ had a small to moderate effect ($0.30 \leq$ SMD <0.5) on reducing depression in

Table 1
Summary of systematic reviews and meta-analyses of Tai Chi Quan for neurodegenerative diseases.

First author (year) [ref]	Quality score	Included sample	Patients (number)	Control groups	Outcomes	Main statistical results compared to control groups
Yu et al. (2021)	11, high	17 RCT	PD (951)	Usual care, Qigong, resistance exercise, stretching, routine exercise	(1) Gait velocity (2) UPDRS motor score (3) PDQ-39 score (4) Activities-specific balance confidence (5) TUGT (6) BBS	(1) SMD= 0.47, 95%CI (0.12, 0.83), P = 0.009 (2) NS (P = 0.12) (3) NS (P = 0.06) (4) MD= 5.08, 95%CI (2.91, 7.26), P < 0.001 (5) MD= −1.05, 95%CI (−2.06, −0.05), P = 0.04 (6) MD= 2.74, 95%CI (2.91, 7.26), P < 0.001
(Chen et al., 2020)	9, high	20 studies	PD (1143)	Usual lifestyle with no extra exercise, non-exercise health education	(1) QoL	(1) SMD= −0.24, 95%CI (−0.36, −0.12), P < 0.001
(Liu et al., 2019)	11, high	5 RCT	PD (355)	Regular exercise, resistance training, balance training, strengthening, no treatment	(1) Number of falls (2) BBS (3) FRT (4) TUGT	(1) Greater reductions on falls in the TCG (Odds rate=0.29, 95%CI (0.11, 0.79), P < 0.05). (2) Compared to no intervention: MD= 3.81, 95%CI (2.03, 5.58), P < 0.0001; compared to walking exercise: MD= 3.00, 95%CI (0.88, 5.12), P < 0.05. (3) Compared to resistance training and stretching: MD= 3.55, 95%CI (1.88, 5.23), P < 0.0001. (4) Compared to no interventions: MD= −1.43, 95%CI (−2.38, −0.48), P < 0.05.
(Jin et al., 2019)	11, high	21 RCT 1 non-RCT	PD (1199)	No intervention, placebo, waiting-lists, routine care, non-sports control	(1) UPDRS (2) TUGT (3) Balance function (4) Depression (5) QoL	(1) SMD= −0.61, 95%CI (−0.95, −0.27), P < 0.001 (2) MD= −1.47, 95%CI (−1.80, −1.13), P < 0.001 (3) SMD= 0.79, 95%CI (0.62, 0.97), P < 0.001 (4) SMD= −1.61, 95%CI (−2.65, −0.57), P = 0.002 (5) SMD= 0.66, 95%CI (0.41, 0.91), P < 0.001
(Fidan et al., 2019)	9, high	7 studies	PD (1504)	Different interventions, no intervention	(1) QoL	(1) NS (P = 0.523)
(Winser et al., 2018)	10, high	7 studies	PD (414)	No treatment, usual care	(1) BBS (2) TUGT (3) Number of falls	(1) Compared to usual care: NS (P = 0.18); compared to no treatment: NS (P = 0.20). (2) Compared to usual care: NS (P = 0.81); compared to no treatment: MD= −2.13, 95%CI (−3.26, −1.00), P = 0.0002. (3) Compared to usual care: odds rate= 0.47, 95%CI (0.29, 0.77), P = 0.003; compared to no treatment: odds rate= 0.29, 95%CI (0.11, 0.79), P = 0.02.
(Song et al., 2017)	11, high	15 RCT 6 non-RCT	PD (755)	Other active interventions, no treatment, wait-list control	(1) UPDRS III (2) Balance (3) TUGT (4) 6MWT (5) Number of falls (6) Depression (7) QoL (8) Cognition	(1) P < 0.001 (2) P < 0.001 (3) P = 0.005 (4) NS (P = 0.06) (5) P = 0.004 (6) P = 0.008 (7) P < 0.001 (8) NS (P = 0.477)
(Kwok et al., 2016)	10, high	6 RCT 4 non-RCT	PD (406)	No intervention, placebo, wait-list control, usual care, non-exercise control	(1) UPDRS III (2) BBS (3) TUGT (4) 6MWT	(1) SMD= −0.91, 95%CI (−1.37, −0.45), P < 0.05 (2) SMD= 1.48, 95%CI (0.91, 2.06), P < 0.01 (3) SMD= −0.97, 95%CI (−1.46, −0.47), P < 0.01 (4) SMD= 0.78, 95%CI (0.35, 1.21), P < 0.05
(Yang et al., 2015)	9, high	13 RCT 2 non-RCT	PD (799)	Medication, other exercises	(1) UPDRS III (2) BBS (3) TUGT (4) FRT (5) Gait velocity (6) Step length (7) 6MWT (8) ADL (9) PDQ-39	(1) Compared to medication alone: SMD= −0.57, 95% CI (−1.11, −0.04), P = 0.03; compared to other exercise plus medication: SMD= −0.78, 95%CI (−1.46, −0.10), P = 0.02. (2) TCG plus medication compared to medication alone: SMD= −1.22, 95%CI (−1.65, −0.80), P < 0.00001; TCG plus medication compared to other therapy plus medication: SMD= −0.99, 95%CI (−1.44, −0.54), P < 0.0001. (3) Compared to medication alone: SMD= −1.06, 95% CI (−1.44, −0.68), P < 0.00001; compared to other therapy plus medication: NS (P = 0.24) (4) TCG plus medication compared to other therapy plus medication: SMD= −0.77, 95%CI (−1.51, −0.03), P = 0.04. (5) Compared to medication alone: NS (P = 0.94) (6) Compared to medication alone: NS (P = 0.99) (7) Compared to medication alone: NS (P = 0.08) (8) TCG plus medication compared to medication alone: SMD= −0.81, 95%CI (−1.50, −0.12), P = 0.02. (9) Compared to medication alone: NS (P = 0.95); compared to other therapy plus medication: NS (P = 0.93)

(continued on next page)

Table 1 (*continued*)

First author (year) [ref]	Quality score	Included sample	Patients (number)	Control groups	Outcomes	Main statistical results compared to control groups
(Zhou et al., 2015)	10, high	9 RCT	PD (569)	No intervention, walking, stretching, resistance, tango, qigong, waltz/ foxtrot	(1) UPDRS III (2) TUGT (3) 6MWT (4) Balance (5) Gait velocity (6) Stride length (7) QoL	(1) SMD= −0.75, 95%CI (−1.22, −0.28), P = 0.002 (2) SMD= −0.73, 95%CI (−1.35, −0.10), P = 0.02 (3) SMD= −0.53, 95%CI (−1.12, 0.07), P = 0.08 (4) SMD= 0.85, 95%CI (0.51, 1.20), P < 0.00001 (5) NS (P = 0.11) (6) NS (P = 0.21) (7) NS (P = 0.40)
(Yang et al., 2014)	10, high	7 RCT 1 non-RCT	PD (470)	No intervention, other active therapies	(1) UPDRS III (2) BBS (3) OLST (4) TST (5) Gait velocity (6) Step length (7) 6MWT (8) TUGT	(1) Compared to no treatment: SMD= −0.57, 95%CI (−1.11, −0.04), P = 0.03; compared to other active therapies: NS (P = 0.11). (2) Compared to no treatment: SMD= 1.22, 95%CI (0.80, 1.65), P < 0.00001; compared to other active therapies: SMD= 0.74, 95%CI (0.38, 1.10), P < 0.0001. (3) Compared to no treatment: NS (P = 0.33) (4) Compared to no treatment: NS (P = 0.43) (5) Compared to no treatment: NS (P = 0.94); compared to other active therapies: NS (P = 0.06) (6) Compared to no treatment: NS (P = 0.99); compared to other active therapies: NS (P = 0.27) (7) Compared to no treatment: NS (P = 0.08) (8) Compared to no treatment: SMD= 1.06, 95%CI (0.68, 1.44), P < 0.00001.
(Ni et al., 2014)	10, high	9 studies	PD (409)	Medication alone, walking, routine physical exercise, resistance training, stretching, no intervention, waltz/ foxtrot	(1) UPDRS III (2) BBS (3) FRT (4) TUGT (5) QoL (6) Gait velocity (7) Stride length	(1) TCG plus medication compared to medication alone and other exercises plus medication: MD= −4.34, 95%CI (−6.67, −2.01), P = 0.0003; TCQ compared to no intervention and qigong alone: NS (P = 0.07). (2) TCG plus medication compared to medication alone and other exercises plus medication: MD= 4.25, 95%CI (2.83, 5.66), P < 0.00001; TCQ compared to other exercise alone: MD= 9.33, 95% CI (3.06, 15.60), P = 0.004. (3) TCQ plus medication compared to other exercises plus medication: MD= 3.89, 95%CI (1.73, 6.04), P = 0.0004; TCQ compared to other exercise alone: MD= 3.05, 95%CI (2.04, 4.06), P < 0.00001. (4) TCQ plus medication compared to other exercises plus medication and medicine alone: MD= −0.75, 95%CI (−1.30, −0.21), P = 0.007; TCQ compared to other exercise alone: NS (P = 0.67) (5) TCQ plus medication compared to other exercises plus medication and medicine alone: SMD= −1.10, 95%CI (−1.81, −0.39), P = 0.002; TCQ compared to other exercise alone: NS (P = 0.85) (6) TCG plus medication compared to medication alone and other exercises plus medication: NS (P = 0.30); TCQ compared to no intervention and other exercises alone: NS (P = 0.70). (7) TCQ plus medication compared to other exercises plus medication and medicine alone: SMD= 0.56, 95%CI (0.03, 1.09), P = 0.04; TCQ compared to no intervention and other exercises alone: NS (P = 0.67).
(Gu et al., 2021)	11, high	9 RCT	CI (827)	Education, routine treatments, stretching, relaxation exercises	(1) MMSE (2) MoCA (3) CDR (4) LMDRS (5) DSF (6) DSB	(1) TCG for less than 6 months: MD= 1.81, 95%CI (1.32, 2.30), P < 0.05; TCG for more than 6 months: NS (P = 0.12). (2) MD= 3.5, 95%CI (0.76, 6.24), P < 0.05 (3) MD= −0.55, 95%CI (−0.80, −0.29), P < 0.05 (4) TCG for less than 6 months: MD= 1.53, 95%CI (0.99, 2.08), P < 0.05; TCG for more than 6 months: NS (P = 0.18). (5) NS (P = 0.38) (6) NS (P = 0.50)
(Wang et al., 2018)	9, high	7 studies	CI (827)	Education, usual care, placebo, no intervention	(1) Global cognition (2) Memory (3) Executive function	(1) NS (P = 0.14) (2) NS (P = 0.11) (3) NS (P = 0.46)
(Wayne et al., 2014)	8, high	7 RCT 2 non-RCT	CI (1636)	Usual care, no intervention, education, other active exercises	(1) MMSE	(1) Compared to no intervention: MD= 0.35, 95%CI (0.108, 0.584), P = 0.004; compared to another active intervention: MD= 0.30, 95%CI (0.113, 0.486), P = 0.002.
(Xiang et al., 2017)	10, high	2 studies	MS (103)	Relaxation, conventional therapy, usual care, stretching, education	(1) Fatigue	(1) NS (P = 0.13)

Abbreviations
RCT = randomized controlled trial; PD = Parkinson's disease; UPDRS = unified Parkinson's Disease rating scale; TUGT = Timed Up and Go test; BBS = Berg balance scale; SMD = standard mean difference; CI = confidence interval; MD = mean difference; TCG = Tai Chi group; QoL = quality of life; FRT = functional reach test; 6MWT = 6-minute Walk Test; ADL = activities of daily living; PDQ-39 = Parkinson's disease questionnaire-39; OLST=One leg stance test; TST=Tandem stance test; TCQ = Tai Chi Quan; CI = cognitive impairment; MMSE = mini-mental state examination; MoCA = Montreal cognitive assessment; CDR = clinical dementia rating; LMDRS=Logical Memory Delayed Recall Score; DSF = digit span forward; DSB = digit span backward; MS = multiple sclerosis.

patients with PD (Easwaran et al., 2020). Two high-quality systematic review and meta-analyses (Song et al., 2017; Jin et al., 2019) demonstrated that TCQ was beneficial for PD patients with depression.

3.2. Tai Chi Quan for cognitive impairment

3.2.1. The clinical features, prevalence, and impact of cognitive impairment

Cognitive decline is one of the main manifestations of human aging and can sometimes turn into a medical condition, such as mild CI, AD, or dementia (Morley, 2018). As of 2019, more than 50 million people, including more than 32 million women, have AD or other forms of dementia. AD is the most common form of dementia worldwide and makes up to 60–80% of all dementia cases (Lane et al., 2018). The prevalence of AD increases with aging, particularly between 65 and 85 years of age (Mayeux and Stern, 2012). The most common clinical features of AD are progressive memory decline, executive dysfunction, personality and behavioral changes, and loss of functional independence (Erkkinen et al., 2018). Approximately 50% of patients are unaware and diagnosed late because of the insidiousness of initial symptoms. In 2020, the total cost of care for AD is up to $300 billion, and out-of-pocket costs for patients account for about 22% of the total cost ($author1$ et al., 87]</id>). In China, the annual expenses for dementia increased to $47.2 billion in 2010 and would reach $114.2 billion in 2030 (Xu et al., 2017). Global costs, including consultation, hospitalization, and rehabilitation for AD and other dementias, would be up to $1 trillion by 2050 with the progression of population aging (Wong, 2020). Therefore, countries need to exert efforts in decreasing the risk factors for AD and other dementias because of the rising numbers, heavy economic costs, and the incurable nature of these diseases. Notably, mild CI is an intermediate stage between normal aging and dementia and is a key reversible stage in the prevention of dementia (Anderson, 2019). Timely intervention at this stage can reduce the incidence of dementia. Long-term cognitive training and physical exercise are beneficial in delaying cognitive decline in older adults (Brasure et al., 2018).

3.2.2. Effect of TCQ on global cognitive function

The mini-mental state examination (MMSE), montreal cognitive assessment (MoCA), and clinical dementia rating (CDR) are used to screen patients with CI. A total of three systematic review and meta-analyses reported the efficacy of TCQ in patients with CI. Gu et.al reported that TCQ for less than 6 months might improve MMSE scores (MD=1.81, 95%CI [1.32, 2.30], $P < 0.05$), MoCA scores (MD=3.5, 95% CI [0.76, 6.24], $P < 0.05$), and CDR scores (MD=−0.55, 95%CI [−0.80, −0.29], $P < 0.05$) (Gu et al., 2021). Lam et al. (2014) concluded that TCQ provided a remarkable improvement on the CDR scores but not MMSE scores for patients with mild CI after one year of intervention. Although the pooled result of Wu et al.'s study indicated that TCQ had a small effect on improving global cognition of healthy elderlies aged 60 years or above, (Chan et al., 2019) TCQ had a remarkable effect on cognitive function in patients with CI compared to other active intervention or no intervention group (Wayne et al., 2014). Several RCTs (Huang et al., 2019; Chan et al., 2016; Lam et al., 2012, 2011) reported no significant difference in MMSE between the TCQ group and the control group. Overall, TCQ has the potential to improve global cognitive function in the early stages of dementia and in elderlies at risk of cognitive decline.

3.2.3. Effect of TCQ on memory and executive function

Results were inconsistent on memory and executive function in patients with CI due to different assessment tools. Two meta-analyses (Gu et al., 2021; Wang et al., 2018) showed that TCQ had no remarkable effect on memory and executive function compared to no intervention, education, or usual care. A systematic review also demonstrated that TCQ has no substantial effect on the memory and executive function of patients with CI (Farhang et al., 2019). Several clinical trials showed the similar results (Hsieh et al., 2018; Sungkarat et al., 2017; Chan et al., 2016; Fogarty et al., 2016; Cheng et al., 2014; Lam et al., 2011). However, three RCTs (Young, 2020; Sungkarat et al., 2017; Cheng et al., 2014) reported that the TCQ group had a considerably positive effect on memory compared to the non-exercise group. The efficacy of TCQ is related to the intervention time to some extent. Lim et al. (2019) suggested that TCQ training 3 times a week, 30 min each time for at least 12 weeks might improve working memory and executive function. Related studies in Table 2 varied in the type of control group and the duration of the intervention.

3.2.4. Effect of TCQ on falls and quality of life

Four clinical trials (Williams and Nyman, 2021; Nyman et al., 2019; Hsieh et al., 2018; Liu et al., 2018b) reported no remarkable differences in TUGT between groups. Only two clinical trials (Hsieh et al., 2018; Liu et al., 2018b) reported statistically significant improvement in FRT and two clinical trials (Lam et al., 2012, 2011) reported statistically significant improvement in BBS. Evidence that TCQ can reduce depression symptoms in patients with dementia was insufficient, and no remarkable intergroup differences in quality of life existed (Table 2).

3.3. Tai Chi Quan for multiple sclerosis

3.3.1. The clinical features, prevalence, and impact of multiple sclerosis

MS is a chronic autoimmune disease characterized by neurodegeneration and axonal damage (Thompson et al., 2018). It is more common among adults aged 20–49 years, and its prevalence rate is on the rise globally (Howard et al., 2016). Prevalence estimates were 577 cases per 100,000 people, and the number of female patients was more than twice that of males in Canada (Gilmour et al., 2018). Patients with MS suffer from pain, mobility impairment, limitations of gait and social activities, depression, and other symptoms (Oh et al., 2018; Koch-Henriksen and Sørensen, 2010). These patients often live with the condition for an average of 15 years (Gilmour et al., 2018). In Europe, the average annual cost per patient is €40,300, and patients with severe disability spend more money on treatment (Paz-Zulueta et al., 2020). Direct costs accounts for 77% of total costs, and indirect cost has the largest relative increase at the stage of earlier mobility impairment (Paz-Zulueta et al., 2020; Naci et al., 2010). Therefore, interventions aimed at delaying MS progression may relieve economic burden. Physical activity can be neuroprotective in MS.

3.3.2. Effects of TCQ on balance and mobility

Two clinical trials found that a 12-week TCQ intervention can remarkably improve the BBS score of patients with MS compared with the baseline (Azimzadeh et al., 2015; Nourozi et al., 2014b). Burschka et al. (2014) showed that 6-month TCQ training remarkably improved the balance and coordination performance of patients with MS. The results of a systematic review was consistent (Charron et al., 2018). Kaur (2013) reported that patients with MS had significant improvement in

Table 2
Summary of clinical trials of Tai Chi Quan for neurodegenerative diseases.

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			Tai Chi group (regimen)	Control group (regimen)		
(Khuzema et al., 2020)	RCT (5/ 10)	PD (27)	Six movements of Tai Chi (30–40 min, 5 times/week, 8 weeks)	CG 1: Six poses of yoga (30–40 min, 5 times/ week, 8 weeks) CG 2: Six conventional balance exercises (40–45 min, 5 times/week, 8 weeks)	(1) BBS (2) TUGT (3) 10-m Walk test (4) compliance	(1) P < 0.05 (increased by 26.41%, 8.19%, and 14.34% in the TCG, CG1, and CG2, respectively.) (2) P < 0.05 (decreased by 22.70%, 7.19%, and 8.90% in the TCG, CG1, and CG2, respectively.) (3) P < 0.05 (decreased by 24.47%, 5.91% and 8.99% in the TCG, CG1, and CG2, respectively) (4) 92.78% , 70.28% , 71.94% in the TCG, CG1, and CG2, respectively.
(Vergara-Diaz et al., 2018)	RCT (5/ 10)	PD (32)	PD-Specific Tai Chi (60 min, 3 times/week, 6 months)	Usual healthcare	(1) Compliance and adverse events (2) Gait-related outcomes (3) UPDRS III motor score (4) PDQ-39 (5) TMT-A and TMT-B (6) ABC (7) TUGT	(1) 75% in the TCG vs 94% in the CG. (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) NS (intergroup difference) (7) NS (intergroup difference)
(Choi, 2016)	RCT (5/ 10)	PD (20)	Therapeutic Tai Chi (60 min, twice/week, 12 weeks)	Non-exercise control	(1) ACT (rep/30 s) (2) Stand-up and sit-down from a chair (rep/30 s) (3) TUGT (4) FRT (5) Stand on foot with eyes opened (6) 6MWT (7) ADL	(1) P < 0.01 (2) NS (intergroup difference) (3) NS (intergroup difference) (4) P < 0.05 (5) P < 0.05 (6) NS (intergroup difference) (7) P < 0.05
(Zhang et al., 2015)	RCT (7/ 10)	PD (40)	Yang style 24-posture short-form Tai Chi (60 min, 12 weeks)	Multimodal exercise training (60 min, 12 weeks)	(1) BBS (2) UPDRS III (3) Stride length (4) Gait velocity (5) TUGT	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference)
(Gao et al., 2014)	RCT (6/ 10)	PD (76)	Yang style 24-form Tai Chi (60 min, 3 times/ week, 12 weeks)	No intervention	(1) BBS (2) UPDRS III (3) TUGT (4) Occurrences of falls	(1) P < 0.05 (2) NS (intergroup difference) (3) NS (intergroup difference) (4) P < 0.05 (TCG vs CG: 21.6% vs 48.7%)
(Amano et al., 2013)	RCT (5/ 10)	PD (45)	TCG 1: The first eight movements of the Yang-style short form (60 min, twice/week, 16 weeks) TCG 2: The first eight movements of the Yang-style short form (60 min, 3 times/week, 16 weeks)	CG 1: Qi-Gong meditation (60 min, twice/week, 16 weeks) CG 2: no intervention	(1) Gait initiation S1 DisAP (cm) S1 DisML (cm) S1 VelAP (cm/s) S1 VelML (cm/s) (2) Gait Length Duration (3) UPDRS III	(1) TCG 1 VS CG 1: P = 0.01 (-S1 DisML); TCG 2 VS CG 2: NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference)
(Nocera et al., 2013)	RCT (5/ 10)	PD (21)	Yang style short form Tai Chi (60 min, 3 times/week, 16 weeks)	Non-contact group	(1) PDQ-39 total score (2) Executive function measures (TMT-A, TMT-B, stroop color word, digits backwards, category verbal fluency, letter verbal fluency)	(1) P = 0.04 (2) NS (intergroup difference)
(Li et al., 2014a)	RCT (7/ 10)	PD (195)	Six Tai Chi movements (60 min, twice/week, 24 weeks)	CG 1: resistance training (60 min, twice/week, 24 weeks) CG 2: stretching (60 min, twice/week, 24 weeks)	(1) PDQ-8 score (2) VPS	(1) TCG vs CG 1: P = 0.014; TCG VS CG 2: P < 0.001 (2) TCG vs CG 1: NS; TCG VS CG 2: P = 0.003
(Cheon et al., 2013)	Non-RCT (3/10)	PD (23)	12 movements in the Sun style (50–65 min, 3 times/week, 8 weeks)	CG 1: stretching-strengthening exercise (50–65 min, 3 times/ week, 8 weeks) CG 2: No intervention	(1) UPDRS (2) De Bore's PD QoL (3) SES (4) BDI (5) Strength (Chair-stand test, Arm-curl test) Upper limbs Lower limbs (6) Flexibility (Back-scratch and chair sit-and-reach tests)	(1) TCG vs CG 1: P < 0.05; TCG vs CG 2: P < 0.05 (2) TCG vs CG 2: P < 0.05 (3) NS (intergroup difference) (4) TCG vs CG 2: P < 0.05 (5) Upper limbs: (TCG vs CG 2: P < 0.05; CG 1 vs CG 2: P < 0.05) ; Lower limbs: (CG 1 vs CG 2: P < 0.05) (6) NS (intergroup difference)

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Table 2 (*continued*)

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			Tai Chi group (regimen)	Control group (regimen)		
					Upper limbs Lower limbs (7) Agility (8-foot TUGT) (8) 6MWT	(7) TCG vs CG 1: P < 0.05; TCG vs CG 2: P < 0.05 (8) TCG vs CG 1 (better): P < 0.05
(Li et al., 2012)	RCT (7/10)	PD (195)	Six Tai Chi movements (60 min, twice/week, 24 weeks)	CG 1: resistance training (60 min, twice/week, 24 weeks) CG 2: stretching (60 min, twice/week, 24 weeks)	(1) Maximum excursion (%) (2) Directional control (%) (3) Gait- Stride length (4) Gait- Walking velocity (5) FRT (6) TUGT (7) UPDRS III (8) Peak torque knee extension (9) Peak torque knee flexion (10) Falls-rate ratio	(1) TCG vs CG 1: P = 0.01; TCG VS CG 2: P < 0.001 (2) TCG vs CG 1: P = 0.002; TCG VS CG 2: P < 0.001 (3) TCG vs CG 1: P = 0.01; TCG VS CG 2: P < 0.001 (4) TCG vs CG 1: NS; TCG VS CG 2: P < 0.001 (5) TCG vs CG 1: P = 0.01; TCG VS CG 2: P < 0.001 (6) TCG vs CG 1: NS; TCG VS CG 2: P < 0.001 (7) TCG vs CG 1: NS; TCG VS CG 2: P < 0.001 (8) TCG vs CG 1: NS; TCG VS CG 2: P = 0.01 (9) TCG vs CG 1: NS; TCG VS CG 2: P = 0.01 (10) TCG vs CG 1: NS; TCG VS CG 2: P = 0.005
(Hackney and Earhart, 2009)	RCT (5/10)	PD (61)	37 postures of the Yang Short Style (60 min/lesson, twice/week, 20 lessons)	CG 1: Tango lessons (60 min/lesson, twice/week, 20 lessons) CG 2: Waltz and Foxtrot lessons (60 min/lesson, twice/week, 20 lessons) CG 3: No intervention	(1) UPDRS III (2) PDQ-39 Mobility ADL Emotional well being Stigma Social support Cognitive impairment Communication Bodily discomfort (3) PDQ-39 summary index	(1) TCG by time interaction, NS (2) TCG vs other groups in the better mobility and social, P < 0.05 (3) TCG vs other groups, P < 0.05
(Hackney and Earhart, 2008)	RCT (5/10)	PD (33)	Yang style short form Tai Chi (60 min/lesson, twice/week, 20 lessons)	No intervention	(1) UPDRS III (2) BBS (3) TUGT (4) Tandem stance (5) One leg stance (6) Backward FAP (7) Backward stride length (8) Backward velocity (9) Forward FAP (10) Forward stride length (11) Forward velocity (12) Six Minute Walk	(1) P = 0.025 (2) P = 0.001 (3) NS (intergroup difference) (4) P = 0.018 (5) NS (intergroup difference) (6) NS (intergroup difference) (7) NS (intergroup difference) (8) NS (intergroup difference) (9) NS (intergroup difference) (10) NS (intergroup difference) (11) NS (intergroup difference) (12) P = 0.046
(Williams and Nyman, 2021)	RCT (7/10)	Dementia (67)	45 mins Tai Chi with 45 mins informal discussion + usual care (90 min, once/week, 20 weeks)	Usual care	(1) Instrumented TUGT (follow-up at 6 month)	(1) NS (intergroup difference); a reduction in turning velocity for the second turn in the TCG (P = 0.002) at flow-up, compared with baseline.
(Young, 2020)	RCT (7/10)	Dementia (80)	Cognitive stimulation therapy and Tai Chi (15–20 min, twice/week, 7 weeks) + usual care	Usual care	(1) DRS overall DRS attention DRS verbal initiation DRS construction DRS conceptualization DRS memory (2) MMSE (3) DQoL overall	(1) P = 0.008 P < 0.001 on attention NS (intergroup difference) P = 0.001 on construction NS (intergroup difference) P < 0.001 on memory (2) P = 0.002 (3) NS (intergroup difference)
(Nyman et al., 2019)	RCT (7/10)	Dementia (85)	45 mins Tai Chi with 45 mins informal discussion + usual care	Usual care	(1) TUGT (2) BBS (3) Postural sway standing on foam	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference)

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Table 2 (*continued*)

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			Tai Chi group (regimen)	Control group (regimen)		
			(90 min, once/week, 20 weeks)		(4) Iconographical falls efficacy scale (5) ICECAP-O (6) MACE	(5) NS (intergroup difference) (6) NS (intergroup difference)
(Huang et al., 2019)	RCT (6/10)	Dementia (80)	Tai Chi classes (20 min, 3 times/week, 10 months)	Routine treatments and personalized daily care	(1) WHO-UCLA-AVLT score (2) TMT score (3) MMSE score (4) MoCA score (5) GDS score (6) NPI score (7) BI score	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) $P < 0.05$ (6) $P < 0.05$ (7) NS (intergroup difference)
(Hsieh et al., 2018)	Non-RCT (5/10)	MCI (60)	Tai Chi based on virtual reality (60 min, twice/week, 24 weeks)	No exercise or specific behavioral management Training and keep usual daily physical activities	(1) 6MWT (2) 30-s STST (3) 30-s ACT (4) TUGT (5) FRT (6) Sit and reach test (7) Drop ruler test (8) 5-m gait speed (9) Long-term memory (10) Short-term memory (11) Attention (12) Mental manipulation (13) Orientation (14) Abstract thinking and judgment (15) Language (16) Drawing (17) Animal name fluency (18) Cognitive abilities screening instrument (19) GDS score	(1) $P = 0.001$ (2) $P = 0.002$ (3) NS (intergroup difference) (4) NS (intergroup difference) (5) $P = 0.000$ (6) NS (intergroup difference) (7) NS (intergroup difference) (8) $P = 0.009$ (9) NS (intergroup difference) (10) NS (intergroup difference) (11) NS (intergroup difference) (12) NS (intergroup difference) (13) NS (intergroup difference) (14) $P = 0.002$ (15) NS (intergroup difference) (16) NS (intergroup difference) (17) NS (intergroup difference) (18) NS (intergroup difference) (19) NS (intergroup difference)
(Liu et al., 2018b)	RCT (6/10)	Dementia (26)	10-step simplified Tai-chi training (60 min, twice/week, 16 weeks)	Recreational activities (60 min, twice/week, 16 weeks)	(1) TUGT (2) TCST (3) FRT (4) STEP	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) $P < 0.05$ (4) $P < 0.05$
(Siu and Lee, 2018)	Non-RCT (3/10)	MCI (160)	Yang style of Tai Chi (60 min, twice/week, 16 weeks)	Usual recreational activities	(1) Chinese MMSE (2) Chinese version of LADL	(1) No report (2) No report
(Sungkarat et al., 2017)	RCT (8/10)	MCI (66)	10-form Tai Chi (50 min, 3 times/week, 15 weeks) + education	Educational information	(1) Logical memory delayed recall score (2) DSF (3) Block design (4) TMT (5) Edge-contrast sensitivity (6) Knee proprioception (7) Knee extension strength (8) Hand reaction (9) Postural sway (10) PPA fall risk index	(1) $P = 0.006$ (2) NS (intergroup difference) (3) $P = 0.01$ (4) $P = 0.005$ (5) NS (intergroup difference) (6) $P = 0.002$ (7) $P = 0.008$ (8) $P = 0.04$ (9) $P = 0.009$ (10) $P = 0.015$
(Chan et al., 2016)	RCT (6/10)	CI (52)	Tai Chi qigong (60 min, twice/week, 2 months)	Health talk and usual activities (nonactive attention placebo)	(1) Chinese PSQI (2) SF-12 Physical component Mental health component (3) MMSE (4) Chinese memory inventory	At 2 months: (1) NS (intergroup difference) (2) NS (intergroup difference) in the physical component; $P < 0.001$ in the mental health component. (3) NS (intergroup difference) (4) NS (intergroup difference) At 6 months: (1) $P = 0.004$

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Table 2 (*continued*)

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			Tai Chi group (regimen)	Control group (regimen)		
						(2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference)
(Fogarty et al., 2016)	RCT (4/10)	MCI (48)	Tai Chi (90 min, twice/week, 10 weeks) + memory intervention program	Memory intervention program	(1) MAC-SR Ability Frequency Strategies Situation (2) Digit symbol (3) RMBT	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference)
(Li et al., 2014b)	Non-RCT (4/10)	CI (46)	Tai Ji Quan: Moving for Better Balance (60 min, twice/week, 14 weeks)	Usual daily physical activities	(1) MMSE (2) 50-feet speed walk (3) TUGT (4) ABC	(1) P < 0.001 (2) P = 0.02 (3) P = 0.01 (4) P < 0.001
(Cheng et al., 2014)	RCT (6/10)	Dementia (110)	Tai Chi of 12-form Yang style (60 min, 3 times/week, 12 weeks)	CG 1: Mahjong (60 min, 3 times/week, 12 weeks) CG 2: Handicraft group (60 min, 3 times/week, 12 weeks)	(1) MMSE (2) Verbal immediate recall (3) Verbal delayed recall (4) Categorical fluency (5) DSF (6) Digit forward sequence (7) DSB (8) Digit backward sequence	(1) TCG vs CG 2: P < 0.05 at 6 months, P < 0.01 at 9 months; CG 1 vs CG 2: P < 0.01 at 6 months; P < 0.001 at 9 months. (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) TCG vs CG 2: P < 0.05 at 9 months; CG 1 vs CG 2: P < 0.01 at 6 months; P < 0.001 at 9 months. (6) CG 1 vs CG 2: P < 0.01 at 6 months; P < 0.001 at 9 months. (7) NS (intergroup difference) (8) NS (intergroup difference)
(Lam et al., 2012)	RCT (6/10)	MCI (389)	24-forms simplified Tai Chi (≥30 min/day, ≥3 days/week, 12 months)	Muscle stretching and toning exercise (≥30 min/day, ≥3 days/week, 12 months)	(1) MMSE (2) ADAS-Cog (3) Category verbal fluency (4) Delay recall (5) DSF (6) DSB (7) Visual forward span (8) Visual backward span (9) TMT A (10) TMT B (11) BBS (12) Subjective cognitive complaints (13) Cornell depression score (14) Neuropsychiatric inventory (15) CDR sum of boxes	At 12 months: (1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) NS (intergroup difference) (7) NS (intergroup difference) (8) NS (intergroup difference) (9) NS (intergroup difference) (10) NS (intergroup difference) (11) P < 0.05 (12) NS (intergroup difference) (13) NS (intergroup difference) (14) NS (intergroup difference) (15) P < 0.05
(Lam et al., 2011)	RCT (7/10)	MCI (389)	24-forms simplified Tai Chi (≥30 min/day, ≥3 days/week, 8–12 weeks; exercise with a video CD for 5 months)	Muscle stretching and toning exercise (≥30 min/day, ≥3 days/week, 8–12 weeks; exercise with a video CD for 5 months)	(1) MMSE (2) ADAS-Cog (3) Category verbal fluency (4) Delay recall (5) Visual forward span (6) Visual backward span (7) Chinese trail A (8) BBS (9) Subjective cognitive complaints (10) CDR sum of boxes	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) P < 0.01 (7) NS (intergroup difference)

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Table 2 (*continued*)

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			Tai Chi group (regimen)	Control group (regimen)		
						(8) P < 0.05 (9) NS (intergroup difference) (10) P < 0.001
(Azimzadeh et al., 2015)	Non-RCT (4/10)	MS (36)	6-form of Yang style of Tai Chi (45–60 min, twice/week, 12 weeks)	Usual care	(1) BBS	Within TCG: (1) P = 0.003
(Nourozi et al., 2014a)	Non-RCT (4/10)	MS (34)	Yang style of Tai Chi (45–60 min, twice/ week, 12 weeks)	Usual care	(1) BBS (2) QoL-54 scale global score	Within TCG: (1) P = 0.03 (2) P < 0.001
(Burschka et al., 2014)	Non-RCT (4/10)	MS (32)	10-form of Yang-style of Tai Chi (90 min, twice/week, 6 months)	Usual care	(1) Balance test (2) Coordination test (3) CES-D (4) FSMC (5) QLS	(1) P = 0.031 (2) P = 0.003 (3) P = 0.007 (4) P = 0.01 (5) P = 0.012
(Kaur, 2013)	Non-RCT (3/10)	MS (16)	6-form of Tai Chi (40 min/session, 20 sessions, 10–12 weeks)	6-form of Tai Chi + mental practice (60 min/ session, 20 sessions, 10–12 weeks)	(1) Dynamic gait index (2) FRT (3) TUGT (4) ABC	Within TCG: (1) P < 0.05 (2) P < 0.05 (3) P < 0.05 (4) P < 0.05
(Mills and Allen, 2000)	Non-RCT (4/10)	MS (24)	Tai Chi (6 sessions)	Usual care	(1) Single leg standing test (2) Symptom rating questionnaire	At 3 months follow-up within TCG: (1) P < 0.05 (2) P < 0.05

Abbreviations：
RCT = randomized controlled trial; PD = Parkinson's disease; CG = control group; TCG = Tai Chi group; BBS = Berg balance scale; TUGT = Timed Up and Go test; NS = no statistical significance; UPDRS = unified Parkinson's Disease rating scale; PDQ-39 = Parkinson's disease questionnaire-39; TMT = trial making test; ABC = activities-specific balance confidence; FRT = functional reach test; 6MWT = 6-minute Walk Test; ADL = activities of daily living; S1 DisAP = posterior center of foot pressure displacement toward the initial swing limb during S1 phase; S1DisML = lateral center of foot pressure displacement during S1 phase; S1VelAP = the mean center of foot pressure velocity in posterior direction during S1 phase; S1VelML = the mean center of foot pressure velocity in lateral direction toward the initial swing limb during S1 phase; VPS = vitality plus scale; QoL = quality of life; SES = Schwab and England scale; BDI = Beck's depression inventory; FAP = functional ambulation profile; DRS = Mattis dementia rating scale; MMSE = mini-mental state examination; DQoL = dementia quality of life; BBS = Berg balance scale; ICECAP-O = ICEpop CAPability measure for Older people; MACE = Mini Addenbrooke's Cognitive Examination; WHO-UCLA-AVLT = WHO University of California Los Angeles-Auditory verbal learning; MoCA = Montreal cognitive assessment; GDS = geriatric depression scale; NPI = neuropsychiatric inventory; BI = Barthel index; MCI = mild cognitive impairment; STST = sit- to- stand test; ACT = arm curl test; FRT = functional reach test; TCST = timed-chair-stand test; STEP = step test; LADL = Lawton instrumental activities of daily living scale; NR = no report; DSF = digit span forward; PPA = physiological profile assessment; CI = cognitive impairment; PSQI = Pittsburgh sleep quality index; SF-12 = Short-form 12 health survey; MAC-SR = memory assessment clinic scale; RMBT = Rivermead behavioral memory test; ABC = activities-specific balance confidence; ADAS-Cog = Alzheimer's disease assessment scale-cognitive subscale; DSB = digit span backward; CDR = clinical dementia rating; MS = multiple sclerosis; CES-D = center for epidemiolog-ical studies depression scale; FSMC = fatigue scale of motor and cognitive functions; QLS = questionnaire of life satisfaction.

dynamic balance after 20 sessions of TCQ with each session of 40 min.

3.3.3. Effects of TCQ on fatigue, depression, and quality of life

The results of different studies as to whether TCQ relieves fatigue are inconsistent (Zou et al., 2017). Moderate evidence suggested that TCQ did not remarkably improve MS-related fatigue compared with conventional therapy (Xiang et al., 2017). Only two studies reported that TCQ can help relieve depression symptoms in patients with MS (Taylor and Taylor-Piliae, 2017; Burschka et al., 2014). A review reported that patients with MS had a better quality of life after TCQ intervention (Zou et al., 2017).

4. Discussion

4.1. Benefits of Tai Chi Quan on neurodegenerative diseases

Sports rehabilitation can offer many benefits to patients with neurodegenerative diseases. TCQ combines many elements, such as cognition, breath, strength, and stability, and it can be practiced by groups or individuals. TCQ is widely recommended for the management of chronic conditions (Huston and McFarlane, 2016). Currently, studies on the efficacy of TCQ in the intervention of neurodegenerative diseases mainly focus on patients with PD, CI, or MS. The updated Canadian guideline recommends early physical exercise, cognitive activities, and social activities to slow down the progression of PD, and existing evidence shows that these methods have clear benefits (Grimes et al., 2019). In this systematic review, we summarized that long-term TCQ remarkably improves general motor function and balance and prevents falls in patients with PD. Notably, few studies used objective indicators to collect motor function data. Therefore, more objective evaluation is needed to improve the reliability of the efficacy of TCQ on motor symptoms for PD. The 2019 World Health Organization guideline recommended conditional aerobic exercise, multimodal exercise, and cognitive training to reduce the risk of CI. According to our findings, low-to-moderate-intensity TCQ is an appropriate exercise for patients with mild CI and/or dementia to improve global cognitive function. Easy-to- follow Tai Chi-like exercises rather than traditional TCQ are more feasible for patients with AD. Adjusting the goals and strategies of TCQ intervention for patients with PD and CI by stage of disease is also vital for the completion and quality of the study. The included clinical trials on MS had small sample sizes and insufficient follow-up without hidden allocation and blindness. Therefore, TCQ is likely safe and beneficial for patients with MS. TCQ can be considered an adjunct treatment for MS. Future research on the effects of TCQ on MS requires more comprehensive study protocols and stricter execution. Overall, TCQ exercise is a promising and effective therapy for patients with neurodegenerative diseases.

4.2. Potential therapeutic mechanisms of Tai Chi Quan on neurodegenerative diseases

4.2.1. Benefits to the motor system

The connection between different TCQ movements is smooth and accompanied by hand–eye coordination, which can fully mobilize the coordination of limbs. TCQ movements vary and include step forward, step backward, step oblique, and alternating standing on one leg or two legs (Wayne and Kaptchuk, 2008). The junction of these movements requires delicate joint control and muscle coordination. Repeated practice can enhance this kind of coordination. The muscle strength of the lower extremities, which is an important factor of gait velocity, can be increased by TCQ (Penn et al., 2019). In addition, TCQ focuses on the shifting of the center of gravity and the adjustment of hip–ankle stabilization mechanism to contribute to the control of posture and gait function (Li et al., 2012). This mechanism indicates that TCQ enhances the neuromuscular regulatory effect and is suitable for clinical functional rehabilitation. Tremors in patients with PD can be improved by increasing the synergistic contraction of active and antagonist muscles during the TCQ intervention. Based on the above factors, TCQ is helpful to the motor function performance of neurodegenerative diseases (Fig. 2).

4.2.2. Benefits to brain systems

TCQ has a potential impact on cognition. From the neuroimaging perspective, TCQ brings several positive changes to the brain structure and function. The cortical thicknesses of the left superior temporal gyrus, medial occipitotemporal sulcus, right middle frontal sulcus, precentral gyrus, and circular sulcus of the insula were larger in the TCQ group than in the non-TCQ group (Wei et al., 2013). TCQ remarkably improved the neuropsychological measures and increased brain volume in elderlies, and 10 months of TCQ increased brain volume by more than 40% (Mortimer et al., 2012). Although neurogenesis diminishes with age, exercise can reverse this decline (Kronenberg et al., 2006). The functional connectivity and homogeneities among some brain regions and the resting-state amplitude of the low-frequency fluctuations in the gyrus and cerebellar lobes were altered after TCQ training (Yu et al., 2018). These changes are related to the improvement of individual cognitive performance. Second, TCQ plays a positive role in pain perception and psychological status. Moderate evidence showed that TCQ is more effective than usual care or no treatment on pain (Hall et al., 2017). The inhibition of anterior cingulate cortex involved in the registration of pain and the increase in the cortical thickness of the insula involved in the sensory and emotional discriminative dimensions of pain after long-term TCQ intervention may contribute to better pain perception and modulation (Wei et al., 2013, 2014). More brain activities are generated during TCQ practice than during usual physical activities (Tsang et al., 2019). The medial prefrontal cortex, anterior cingulate cortex, hippocampus, and insula play roles in increasing positive emotions and suppressing fear and anxiety (Etkin et al., 2011). TCQ might alleviate mood by modulating the functional connectivity between these brain regions. Based on the above evidence, TCQ has a positive effect on the brain systems related to cognition, emotion, and pain perception.

4.2.3. Benefits to the endocrine system

Exercise may contribute to enhanced brain health by regulating brain-derived neurotrophic factor, insulin-like growth factor-1, and vascular endothelial growth factor (Kramer and Erickson, 2007; Flöel et al., 2010). Exercise also exerts beneficial effects on neurodegenerative

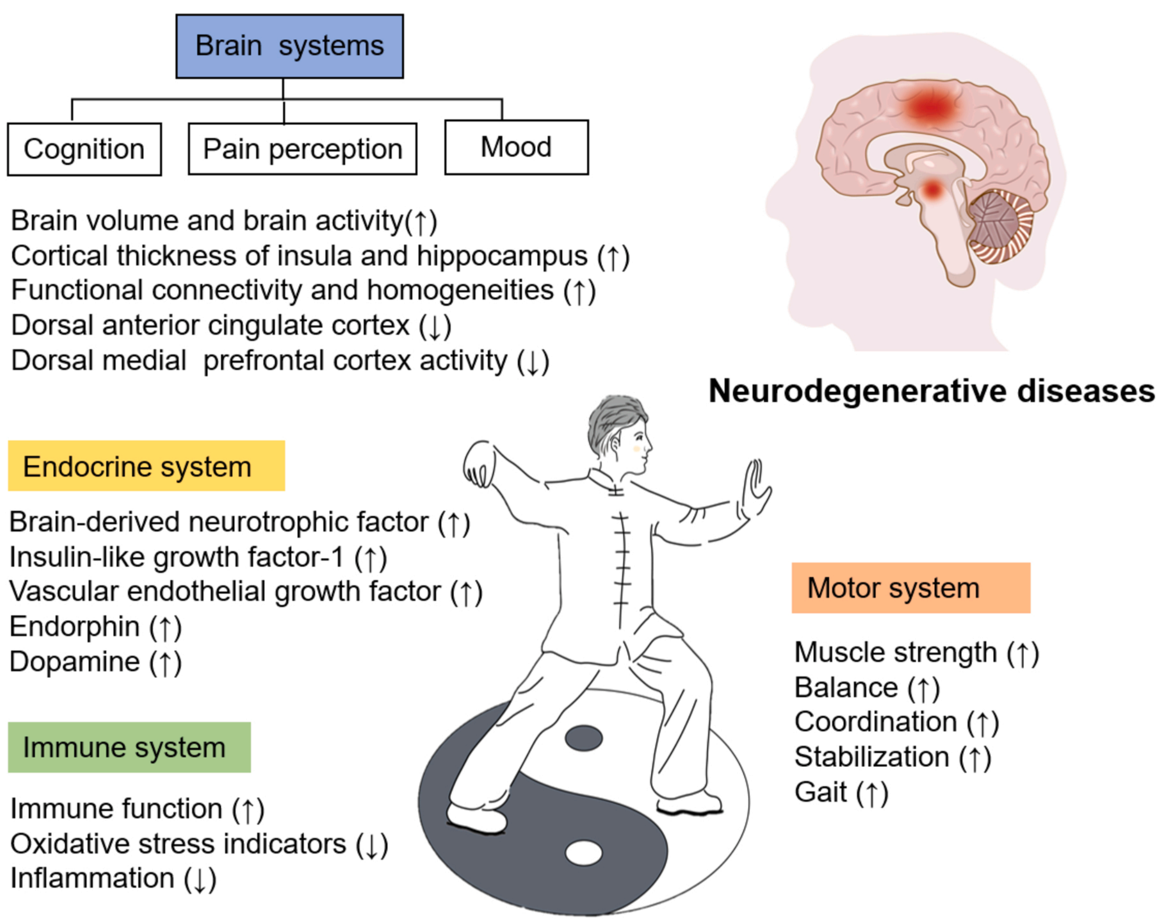

Fig. 2. Potential therapeutic mechanisms of Tai Chi Quan on neurodegenerative diseases.

diseases by releasing some protective substances, such as endorphin and dopamine (Feng et al., 2020). Dopamine is vital for neural processes involved in dynamic balance control in PD, as well as in mood regulation (Kuhman et al., 2020). Meditation can help increase striatal dopamine release (Kjaer et al., 2002). TCQ movements also embody meditation and can be a complementary therapy for PD (Deuel and Seeberger, 2020).

4.2.4. Benefits to the immune system

Neuroinflammation mediated by microglia and astrocyte plays an important role in the occurrence and progress of neurodegenerative diseases. For example, tumor necrosis factor-α-induced protein are positively associated with the severity of PD (Kouchaki et al., 2018). Glial priming, pro-inflammatory factors, and neuronal damage form a vicious circle in the early AD stage (Calsolaro and Edison, 2016). Moreover, 90% of patients with MS have cerebrospinal fluid inflammatory markers (Yamout et al., 2020). Reports found that TCQ favorably affects immune function, oxidative stress indicators, and inflammation (You and Ogawa, 2019; Chen et al., 2010; Morgan et al., 2014). Besides, TCQ promotes cerebral blood flow and arousal, which can speed up the metabolism of inflammatory products (Bower and Irwin, 2016). Therefore, TCQ may relieve the symptoms of neurodegenerative diseases through these ways.

4.3. Limitations and future directions

Clinical trials on the application of TCQ in neurodegenerative diseases are increasing, but the viewpoints of this article are still limited by some factors. First, the efficacy of TCQ may vary as a result of different disease stages, and early TCQ training may have better improvement on functional performance. Moreover, low-quality clinical trials made the pooled results of the meta-analyses not convincing enough. Second, the styles, time, frequency, and total exercise volume of TCQ are different in the clinical trials mentioned above. The short-form Yang style of TCQ or reprogrammed movements are performed for at least 12 weeks. Designing personalized TCQ protocols for patients with PD or AD and other dementias will be promising and valuable in the future. Third, only studies in English were included, which may lead to publication bias. Fourth, current studies do not provide sufficient evidence to explain the whole therapeutic mechanisms of TCQ. Future research can explore the health benefits of TCQ from the perspectives of the cellular level, molecular level, and neuroimaging technology.

5. Conclusions

Studies on the effectiveness of TCQ in neurodegenerative diseases, especially PD, CI, and MS, are increasing. Long-term and regular TCQ exercise can effectively improve the motor function, balance, global cognitive function, and prevent falls in patients with neurodegenerative diseases. In view of the different types of TCQ, the time of interventions, and the different outcomes of specific disease, the positive effects of TCQ on the quality of life and mood of patients with neurodegenerative diseases need further evidence. Meanwhile, the therapeutic mechanism of TCQ will be continuously supplemented.

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CRediT authorship contribution statement

Xue-Qiang Wang: Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Rui Wang:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Hao Zhou:** Formal analysis, Writing – review & editing, Visualization. **Yu-Chen Wang:** Formal analysis, Writing – review & editing, Visualization. **Xiao-Long Chang:** Writing – review & editing, Visualization.

Competing interests

The authors declare that they have no competing interests.

Data Availability

No data was used for the research described in the article.

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