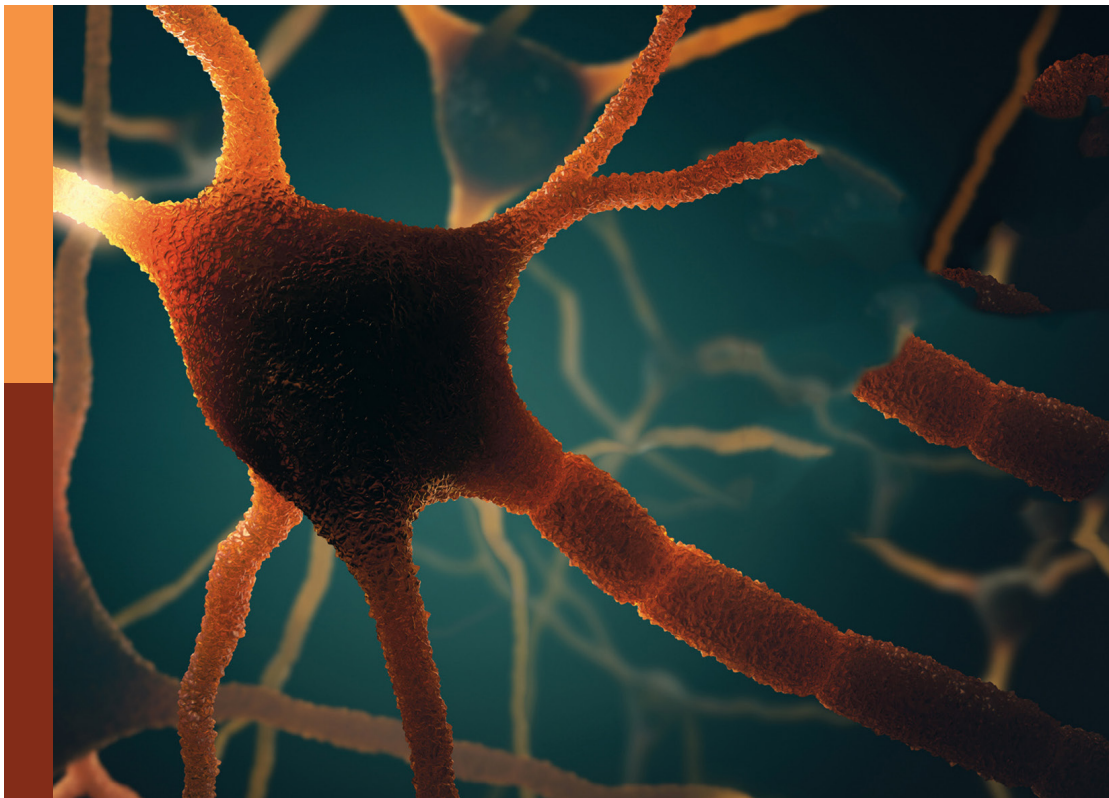
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Physical exercise for age-related neuromusculoskeletal disorders

Edited by
Xue-Qiang Wang, Min Hu, Li Li, Dongsheng Xu and Howe Liu

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Physical exercise for age-related neuromusculoskeletal disorders

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Editorial: Physical exercise for age-related neuromusculoskeletal disorders

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Editorial on the Research Topic
Physical exercise for age-related neuromusculoskeletal disorders

Age-related neurological and musculoskeletal disorders with increasing life expectancy are emerging as major public health problems. Neurological disorders occur when neurons in the brain and spinal cord begin to degenerate such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, spinal stenosis, and amyotrophic lateral sclerosis. In addition, both motor and sensory peripheral nervous pathologies could negatively affect physical activity in the aging population. Meanwhile, musculoskeletal disorders are pathological conditions that affect muscle, bone, cartilage, joint, and connective tissue, thereby leading to physical and functional impairments in patients, including but not limited to, osteoarthritis (OA), intervertebral disc degeneration, rheumatoid arthritis, osteoporosis, sarcopenia, and ankylosing spondylitis. Frailty syndrome, gait abnormality, and balance deficit that are commonly seen in older adults could be combined effects of neural and orthopedic dysfunction. Moreover, neuromusculoskeletal disorders have high rates of prevalence among the aging population and became the primary reason to seek interventions.

Physical exercise has been widely utilized as an effective preventive and interventional measure for patients with neurological and musculoskeletal problems by providing health benefits without side effects. A few key interventional studies have shown clinically meaningful improvements associated with physical exercises among individuals with Parkinson's disease and fibromyalgia, which indicate that further investigations are needed for other types of age-related neuromusculoskeletal disorders. In particular, research to explore the possible mechanisms of the potential beneficial effects of physical exercise is still in its infancy.

Therefore, this Research Topic aims to gather original research, review, and study protocol on physical exercise in the prevention and management of age-related neuromusculoskeletal disorders. We are interested in manuscripts that report the

biomechanical, physiological, and psychological effects as well as the underlying mechanisms of physical exercise for age-related neuromusculoskeletal disorders.

A total of 35 original and review articles have passed the peer review and were finally published. Among these papers, three works explained bone health and osteoporosis, five articles explored muscle diseases, 16 works discussed neurodegenerative diseases, five explored age-related diseases, and other six studies about Chinese traditional exercise. Moreover, we hope this topic will gain new ideas and stimulate available methods for future work in the field. These papers can be categorized into the following sessions.

Bone health and osteoarthritis

Osteoarthritis (OA) is a common chronic irreversible bone disease characterized by the degeneration of articular cartilage and secondary bone hyperplasia. Ning et al. analyzed the production and features of irisin and explained various exercises for irisin to explore the mechanism of osteoarthritis and provide new ideas for the prevention and treatment of osteoarthritis, which is a myohormone released primarily by skeletal muscle, and the synthesis and secretion are induced by exercise-induced muscle contraction to readers. Thus, understanding the importance of exercise in the fight against osteoarthritis will continue to present important references about the treatment and prevention of osteoarthritis. Further studies about the effects of exercise forms and intensity on induced irisin expression, and the regulatory mechanisms of irisin on BMD and cartilage metabolism will implement preventive and therapeutic approaches for osteoarthritis. On that basis, a total of 51 studies were reviewed to elucidate the mechanism of physical activity alleviating the pathological changes of osteoarthritis (Kong H. et al.). Furthermore, they included 59 original articles to explore different types of exercise and parameters that may have different influences on patients with OA. The review expounded on exercise in the prevention and treatment of OA. The paper presented the exercise intervention to treat OA for future patients. Liu et al. conducted similar research that focused on the bone health problem of postmenopausal women.

Muscle diseases

Animal research (Liang et al.) found that during exercise, skeletal muscle exhibits extensive metabolic and energetic remodeling. Thus, exploring the mechanism of exercise-induced acetylation changes in skeletal muscle is helpful to develop scientific exercise prescriptions. Hence, exercise is effective to treat muscle diseases such as sarcopenia, which is a common chronic disease with a loss in muscle strength, muscle mass, and physical abilities. The benefits of vibration training and resistance training on muscle function as a form of exercise have been confirmed by various previous studies. However, the comparison between vibration training and resistance training remains lacking in elderly patients with sarcopenia. In Lu's protocol (Lu et al.), this study conducted a 12-week, three-arm randomized controlled trial. A total of 54 participants were randomized into resistance training, vibration training, and control groups. Moreover, they compared the effect of vibration training and resistance training among old patients with sarcopenia on muscle strength, muscle mass, blood biomarkers, physical abilities, and life quality. Then, they added measurements of upper and lower limb muscle strength and blood biomarkers as compared to previous studies. Another systematic review by Guo et al. included 21 studies and 1,330 participants to explore the effect of traditional Chinese medicine on sarcopenia. They analyzed the present evidence for applying traditional Chinese medicine to treat sarcopenia. The study also suggested that traditional Chinese medicine has a significant effect on body function and muscle strength for people with sarcopenia.

Other types of muscle diseases can also be improved by exercise. Zhuang et al. analyzed 12 studies on physical activity (PA) effects in older people with sarcopenic obesity (SO). Aerobic training decreased body weight and body mass index; resistance training improved body fat, appendicular skeletal muscle mass index, appendicular skeletal muscle mass, handgrip strength, and knee extension strength as compared to a control group without PA. Meanwhile, the aerobic combined with resistance training improved body fat, body mass index, appendicular skeletal muscle mass index, handgrip strength, and PA increased insulin-like growth factor 1 (IGF-1) as compared to a control group without PA. The systematic review and meta-analysis showed that PA is an effective treatment to improve physical performance, muscle strength, muscle mass, body composition, and IGF-1 in SO elderly adults. Zhu et al. included 10 studies to perform a mixed comparison of different exercise interventions on function, respiration, fatigue, and quality of life in adults with amyotrophic lateral sclerosis (ALS). The study concluded that multimodal exercise and rehabilitation programs are more beneficial for patients with ALS. However, its safety and practice guidelines are unclear, which still need to be further confirmed by large samples and high-quality randomized controlled trials.

Neurodegenerative diseases

Herein, neurodegenerative diseases such as stroke, Parkinson's disease (PD), movement disorders, multiple sclerosis, diabetic neuropathic pain, and Alzheimer's disease (AD) are included. Recent research trends in exercise therapy for some kind of neurodegenerative diseases were revealed by four bibliometric articles (Chen B. et al.; Chen J. W. et al.; Dong et al.; Jiang et al.) and provided potential research frontiers. This

provided a useful basis for further research on priority issues, partners, and development trends.

Parkinson's disease is a kind of disease distinguished by bradykinesia, balance disruption, rigidity, and gait impairment. In an animal experimental study, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced Parkinson's disease mice were used to observe their motor ability after 12-week treadmill training (Tong et al.). The results presented that a 12-week treadmill exercise dramatically improved the motor performance of the MPTP-induced PD mouse model, thereby suggesting that substantia nigra and striatum are essential to brain regions that undergo key transcriptional changes, after exercise intervention in the PD model. The effects of traditional Chinese exercise (TCE) on balance, gait outcomes, and motor symptoms in participants with PD were evaluated (Wu et al.). A total of 15 studies and 873 subjects were analyzed in this study. The results revealed significant improvements in balance outcomes and gait outcomes, and motor symptoms compared with control groups. This work presented that TCE is beneficial for motor symptoms, balance function, and gait function among patients with PD. Meanwhile, the additional study focused on aerobic and resistance training also contributed to this conclusion (Zhou et al.).

Stroke is the leading cause of death worldwide and will cause severe sensorimotor dysfunction and limitations. Li L. et al. explore immediate muscle electrical impedance property alterations among chronic stroke patients in the lower extremity instantly after functional electrical stimulation (FES)-assisted cycling training. This report stated that electrical impedance myography can make clear the changes in intrinsic characteristics of paralyzed muscles in chronic stroke patients after FES-assisted cycling training. In another work, 15 RCTs involving 488 participants were included (Li X. et al.). The combined data showed that after 3–12 weeks of intervention, the wearable sensor-based exercise group showed remarkable improvement as compared with the traditional exercise group. This study also showed a statistically significant difference in visual scores between post-assessment and 1-month follow-up assessment. In addition, this study indicated that wearable sensor-based exercise was advantageous in enhancing balance in people with neurodegenerative diseases, as evidenced by the Chen studies on bilateral arm training (Chen S. et al.).

Meanwhile, Alzheimer's disease is a common neurological disease and is the major cause of dementia worldwide. Li et al. researchers provided a comprehensive systematic review of combined exercise and music interventions in participants with Alzheimer's disease. They found that combined physical activity and music interventions are helpful to improve cognitive functioning and wellbeing among AD patients. The study concluded that physical and musical interventions are essential in assisting medical guidance by therapists. The combination of physical activity and music intervention improved gait disorders in PD patients with freezing of gait, thereby improving their comprehensive motor function (Li K.-P. et al.).

The effects of exercise on other different types of neurodegenerative diseases have also been studied (Liao Q. et al.; Luo et al.; Zhang Y. et al.). In addition, Zhang G. et al. included a total of 32 chronic back pain (CBP) patients without depressive symptoms and 30 CBP patients with depressive symptoms. All subjects underwent functional magnetic resonance imaging scans and clinical assessments of depressive symptoms and pain-related manifestations. The research concluded that comorbid depressive symptoms can aggravate the impairment of pain matrix function in CBP patients. However, this impairment cannot directly lead to an increase in pain intensity, which may be related to the fact that some brain regions of the pain matrix are the common neural basis of depression and CBP.

Age-related diseases

Two reviews summarized previous studies showing that exercise can improve chronic pain in middle-aged and older adults. One presented by Wen et al. included 17 studies of the mind-body exercise (MBE) method in middle age people and senior citizens with chronic pain. It indicated that mind-body exercise had a modest effect on relieving pain compared with the non-active and active control group. The results suggested that MBE was a significant method for relieving chronic pain symptoms in middle-aged and older people as compared with the inactive and active groups. Another mini-review included a total of 11 randomized controlled trials with 1,256 middle-aged and elderly patients with chronic low back pain (CLBP) and concluded that traditional Chinese exercise can effectively relieve the pain of middle-aged and elderly patients with CLBP (Wang X.-Q. et al.).

In addition to the analgesic effects of exercise in middle-aged and older adults, another three studies examined whether or not exercise improves upper limb, cognitive, and executive functions in older adults. Meanwhile, Liao T. et al. examined a 12-week Wheelchair Tai Chi Ball (WTCB) treatment for older people with a physical disability. The results represented that the WTCB intervention had significant effects on the following domains: daily living activities, physical health, mental health, and maintaining upper limb muscle strength. The study concluded that WTCB could improve upper limb muscle strength in disabled older adults. Wang H. et al. researched to investigate the relationship between walking speed, cognitive impairment, and cognitive functions among elder people. The results showed that walking speed was inversely related to cognitive impairment in males. Apart from that, the relationship between walking speed and impaired orientation was noticeable for both men and women. Zheng et al.'s study about executive function ends up with the same conclusion.

Traditional Chinese exercise

Tai Chi is one of the most common traditional Chinese exercises and has been widely used in clinical studies. Song et al. performed a study of 40 older females with knee osteoarthritis (KOA). In this study, subjects were grouped into a 12 weeks Tai Chi or control group. The results revealed that 12 weeks of Tai Chi was more effective to improve physical function and life quality in elder women with KOA as compared with the control group. Another study related to Tai Chi Chuan (TCC) was conducted (Huang et al.). Herein, a motion capture system was used to measure the three aspects of the motion of the pelvis and lower limbs in 15 elderly patients with TCC and 15 healthy controls. This work showed kinematic changes in the pelvic and lower limb joints and presented a strategy to decrease the risk of trips in long-term TCC trainers while crossing obstacles. Therefore, the protocol reported by Wang R. et al. aimed to conduct a single-blind randomized controlled trial involving older adults with chronic low back pain based on the two studies. They recruited a total of 138 participants and randomly assigned them in a 1:1 ratio (Tai Chi or physical therapy). Then, participants underwent a 40-week long-term impact study. Hence, this work demonstrated the feasibility and effectiveness of Tai Chi to treat low back pain. However, current studies and works on this topic have several limitations based on a comprehensive exploration. First, mechanisms of different physical exercises or activities for age-related neuromusculoskeletal disorders remained inadequate, because current works did not apply either large human samples or animal models. Consequently, their results were unreliable. Second, we did not find any related content about how to connect these basic physical exercises to clinical practice. Shao et al. also contributed to this conclusion.

As for other types of traditional Chinese exercises, in a review conducted by Kong L. et al., they included 21 studies related to neck pain to support the effectiveness of Traditional Chinese Exercises (TCEs). The combined results suggested that TCEs had positive effects on pain relief. Particularly, Baduanjin had a beneficial complementary effect on the improvement of neck flexion and extension. Furthermore, the combined results indicated that TCEs revealed positive influences in the improvement of disability and pain relief as compared with the waiting list. Another research focused on clinical efficacy and electroencephalogram signal characteristics of Yijinjing Qigong intervention on early post-stroke depression was also conducted by Sun et al..

However, there are still several limitations of current studies and works on this topic based on a comprehensive exploration. First, the mechanisms by which different physical exercises or activities contribute to age-related neuromusculoskeletal disorders remain inadequate, as current works do not apply to large human samples or animal models. Consequently, their results are not reliable. Second, we did not find any related content about how to connect these basic physical exercises to clinical practice.

Thus, we hope this work can inspire the interest of scholars researching the effects of physical exercise for age-related neuromusculoskeletal disorders, thereby improving future research studies with new strategies and high-quality design. Current experiments are still in the theoretical stage. Therefore, further work should pay more attention to these research frontiers.

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YW drafted the manuscript. KL reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Effectiveness and Success Factors of Bilateral Arm Training After Stroke: A Systematic Review and Meta-Analysis

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Bilateral arm training (BAT) presents as a promising approach in upper extremity (UE) rehabilitation after a stroke as it may facilitate neuroplasticity. However, the effectiveness of BAT is inconclusive, and no systematic reviews and meta-analyses have investigated the impact of different factors on the outcomes of BAT. This systematic review and meta-analysis aimed to (1) compare the effects of bilateral arm training (BAT) with unilateral arm training (UAT) and conventional therapy (CT) on the upper limb (UL) motor impairments and functional performance post-stroke, and (2) investigate the different contributing factors that may influence the success of BAT. A comprehensive literature search was performed in five databases. Randomized control trials (RCTs) that met inclusion criteria were selected and assessed for methodological qualities. Data relating to outcome measures, characteristics of participants (stroke chronicity and severity), and features of intervention (type of BAT and dose) were extracted for meta-analysis. With 25 RCTs meeting the inclusion criteria, BAT demonstrated significantly greater improvements in motor impairments as measured by Fugl-Meyer Assessment of Upper Extremity (FMA-UE) than CT ($MD = 3.94$, $p =< 0.001$), but not in functional performance as measured by the pooled outcomes of Action Research Arm Test (ARAT), Box and Block Test (BBT), and the time component of Motor Function Test (WMFT-time) ($SMD = 0.28$, $p = 0.313$). The superior motor impairment effects of BAT were associated with recruiting mildly impaired individuals in the chronic phase of stroke ($MD = 6.71$, $p < 0.001$), and applying a higher dose of intervention ($MD = 6.52$, $p < 0.001$). Subgroup analysis showed that bilateral functional task training (BFTT) improves both motor impairments ($MD = 7.84$, $p < 0.001$) and functional performance ($SMD = 1.02$, $p = 0.049$). No significant differences were detected between BAT and UAT for motor impairment ($MD = -0.90$, $p = 0.681$) or functional performance ($SMD = -0.09$, $p = 0.457$). Thus, our meta-analysis indicates that BAT may be more beneficial than CT in addressing post-stroke UL motor impairment, particularly in the chronic phase with mild UL paresis. The success of

BAT may be dose-dependent, and higher doses of intervention may be required. BFTT appears to be a valuable form of BAT that could be integrated into stroke rehabilitation programs. BAT and UAT are generally equivalent in improving UL motor impairments and functional performance.

Keywords: bilateral arm training, stroke, upper extremity, rehabilitation, ICF model, meta-analysis, neuroplasticity

INTRODUCTION

Contralateral hemiparesis is one of the most common deficits following a stroke (Cramer et al., 1997; Van Der Lee et al., 2001). It is estimated that 48–77% of stroke patients encounter contralateral hemiparesis acutely (Lawrence et al., 2001; Held et al., 2019; Simpson et al., 2021), and 40–50% of patients will continue to have it chronically (Jørgensen et al., 1995; Cramer et al., 1997; Broeks et al., 1999). Although the most significant amount of recovery is suggested to happen in the first three months post-stroke (Wade et al., 1983; Kwakkel et al., 2003; Kwakkel and Kollen, 2013), research has supported that upper extremity (UE) recovery can still occur years after (Carey et al., 1993).

Due to the prevalence of UE impairments post-stroke and the importance of recovery for optimal function and performance of activities of daily living (ADLs), different rehabilitation strategies have been identified and studied. It is not surprising that most of the well-studied UE rehabilitation strategies to date are primarily focused on the unilateral arm since hemiparesis is more evident on one side of the body following a stroke (Beer et al., 2000; Wagner et al., 2006; Sathian et al., 2011; Kantak et al., 2017). However, there is evidence that stroke patients have reduced bilateral arm coordination and functional performance in most ADLs compared to the neurologically intact population (Kantak et al., 2017). In fact, most manual tasks in our daily life require the usage of both UEs and interlimb coordination. A relatively recent upper extremity (UE) rehabilitation strategy targeting interlimb coordination post-stroke is bilateral arm training (BAT). It involves incorporating both upper limbs to perform motor tasks simultaneously or sequentially to improve the movement of the affected limb (Mudie and Matyas, 2000; Waller et al., 2008). Several types of BAT have been identified, including bilateral functional task training (BFTT), bilateral arm training with rhythmic auditory cueing (BATRAC), bilateral robot-assisted training (BRAT), bilateral priming, and mirror therapy (Stoykov and Corcos, 2009; Wolf et al., 2014). Several hypotheses have been proposed regarding the positive effects of BAT on motor function. First, BAT may promote positive neural interactions between sensorimotor-related areas in the ipsilesional and contralesional hemispheres to enhance coupling effects post-stroke (Fan et al., 2015, 2016). Second, increased activity in the sensorimotor-related areas following BAT may contribute to functional reorganization and neuroplasticity (Whitall et al., 2011; Waller et al., 2014). Third, BAT may allow restoration of normalized interhemispheric transcallosal inhibition (IHI) and reduce short-interval intracortical inhibition (SICI) in the ipsilesional hemisphere, both of which are associated with recovery of motor function after stroke (Cicinelli et al., 2003; Stinear et al., 2008; Swayne et al., 2008).

Despite the potential for the usage of BAT in the post-stroke population, the effectiveness of BAT is inconsistent across the studies. According to the Guidelines for Adult Stroke Rehabilitation and Recovery for Healthcare Professionals, bilateral training paradigms fall into Class-IIb in which benefits outweigh the risks, but usefulness/efficacy is less well-established, and additional research is needed (Winstein et al., 2016). The level of evidence is graded as "A" with multiple populations evaluated and data derived from multiple RCTs and meta-analyses. A recent meta-analysis (Chen et al., 2019) compared the effect of BAT with unilateral arm training (UAT) in the post-stroke population based upon the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2001). The results revealed that BAT yielded greater improvements in UE motor impairments but not functional performance. Similar findings have also been reported in other systematic reviews (Stewart et al., 2006; Cauraugh et al., 2010; Latimer et al., 2010; Wolf et al., 2014). However, the results should be cautiously interpreted since these reviews included non-RCTs, and some of the included studies did not comprise a comparison group, rendering it difficult to draw robust conclusions. In contrast, other reviews identified contradictory findings, claiming that BAT was similar or inferior to conventional therapy (CT) or UAT (Coupar et al., 2010; Van Delden et al., 2012; Lee et al., 2017b; Richardson et al., 2021). A recently published systematic review highlighted that UAT and BAT improved paretic UE function equivocally in adults with chronic stroke. Van Delden et al. (2012) also reported similar findings based on the categorization of the ICF framework. However, the small number of studies included in these two reviews may limit their generalizability.

Few studies to date have systematically investigated the factors influencing the success of BAT. Van Delden et al. (2012) pointed out that intervention success may depend on the severity of hemiparesis and time of intervention post-stroke. Additionally, (modified) constraint-induced movement therapy [(m)CIMT] has been reported to be more effective than BAT in one systematic review (Lee et al., 2017b). However, considering that (m)CIMT usually involves patients who are mildly impaired or in a later stage of stroke, it is reasonable to assume that the characteristics of participants are important factors when selecting an optimal intervention. Furthermore, different features of treatment within BAT, such as type and dosage of BAT intervention, may also affect the outcomes (Cooke et al., 2010; Pollock et al., 2014; Wolf et al., 2014). Cauraugh et al. (2010) found that BATRAC and coupled BAT with active stimulation are most effective,

whereas Wolf et al. (2014) reported no differences between BFTT, BATRAC, and BRAT. Although the effect of dose of a post-stroke UE treatment has been studied (Kwakkel et al., 1997; Van Peppen et al., 2004; Cooke et al., 2010), no meta-analyses have yet reported the impact of dose on the outcomes of BAT. Therefore, a meta-analysis including high-quality RCTs is urgently needed to systematically investigate the factors influencing the effect of BAT.

Therefore, the purposes of the current systematic review and meta-analysis were twofold: Firstly, to compare the effects of BAT with other interventions in post-stroke UE rehabilitation on motor impairments and functional performance which are two domains of the WHO ICF framework, and secondly, to investigate different determinant factors and their contributions in optimizing comprehensive post-stroke interventions.

METHODS

Literature and Search Strategy

The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) was followed for the present review (Page et al., 2021). A computer-based search of the literature was conducted from the date of inception to June 2021 in the following databases: PubMed, MEDLINE, EMBASE, Cochrane, and Web of Science. The databases were searched using a combination of controlled vocabulary (MeSH) and free-text terms related to the patient type "stroke," body part "upper extremity," intervention type "bilateral arm training," and study type "randomized controlled trial" (see **Appendix 1**). The search strategy was formulated in MEDLINE and modified to the other databases.

Study Selection

The inclusion criteria to identify for qualifying articles were (a) available in English; (b) randomized control trials (RCTs) that included post-stroke adult participants (over the age of 18 years); (c) reported at least one standardized outcome measure; (d) post-stroke duration of the recruited participants was specified; (e) the intervention used for the experimental group was some form of bilateral arm training (BAT); (f) the control group included either unilateral training, conventional rehabilitation, or both. The exclusion criteria were (a) failure to provide relevant data on the outcome measures; (b) the BAT was used not only in one group; (c) the upper limb intervention was not the only focus of the study (i.e. use of virtual reality or electrostimulation in adjunction to UL intervention). Titles and abstracts were screened by two reviewers independently and compared against pre-determined eligibility criteria. All relevant studies were then reviewed in full text to confirm if the inclusion criteria were fulfilled. If any discrepancies arose, a third reviewer was consulted and made the final decision.

Quality Assessment

Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality of each included RCT by two independent reviewers. The PEDro scale is an 11-item scale that has been widely used for rating the methodological quality of RCTs (Sherrington et al., 2000; Maher et al., 2003). Each satisfied item (item 2–11) pertained to internal validity was given one point to the total PEDro scale (maximum score = 10 points), and item 1 related to external validity was rated a YES or NO. Studies scoring four or higher on the PEDro scale were considered of sufficient quality (Van Peppen et al., 2004). Included RCTs were rated by two independent reviewers, and a third reviewer made the final decision if any discrepancies occurred.

Data Collection

The following information was extracted independently by two reviewers from the included studies: (1) baseline characteristics of the study participants (age, gender, side of lesion, post-stroke duration); (2) interventions implemented in experimental and control groups (type, duration, and intensity); (3) the inclusion and exclusion criteria; (4) The outcome measures data; (5) whether the study includes follow-up data and the timeline for data collection. Based upon the WHO ICF framework (World Health Organization, 2001), the outcome measures included in this review primarily focused on two domains: (1) motor impairment associated with body functions and structure and (2) functional performance of upper limb (UL) associated with activities. Fugl-Meyer Assessment of Upper Extremity (FMA-UE) data was collected to represent body functions and structure domain, and Action Research Arm Test (ARAT), Box and Block Test (BBT), and the time component of Motor Function Test (WMFT-time) were extracted to represent activities domain since they measure the same underlying construct (Coupar et al., 2010). Motor Activity Log (MAL) is a self-reported assessment of patients' perspective of arm use and quality of movement in ADLs (Santisteban et al., 2016). The MAL was also extracted to represent patient-perceived UL functional performance if available. If more than one outcome measure was reported for the same domain in the identified article, only one outcome measure's data was extracted. WMFT was pooled first if more than one outcome measures were reported for the ICF activities domain, followed by ARAT, BBT, and MAL. The order was determined based on the reported frequency of use and the level of measurement quality and clinical utility (Alt Murphy et al., 2015; Santisteban et al., 2016). The reviewers reached a consensus through discussion or consulting the third reviewer if disagreement occurred.

To compare the effects of BAT with CT and UAT according to the severity of UL paresis, we adopted and revised the severity classification based upon the previous studies (Van Der Lee et al., 1999; Suputtitada et al., 2004; Morris et al., 2008; Lin et al., 2009; Stoykov et al., 2009; Wu et al., 2011) included in Van Delden and colleagues' work (Van Delden et al., 2012). As shown in **Figure 1**, the hemiparesis severity classification was based on Brunnstrom stage, active range of motion of wrist and finger extension, average baseline FMA-UE score, and ARAT score. The recruited participants in each study were categorized into mild, moderate, and severe UL paresis.

Since another focus of this review was to explore the effects of bilateral training during different phases of stroke in

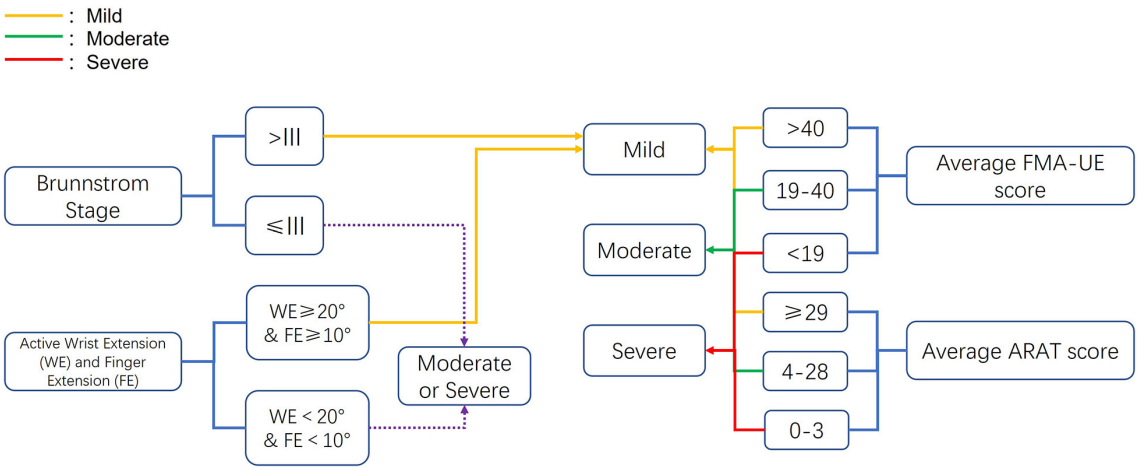


FIGURE 1 | Criteria for the upper extremity paresis severity classification. ARAT, Action Research Arm Test; FMA-UE, Fugl-Meyer Assessment of Upper Extremity.

comparison to other rehabilitation protocols, we classified the included studies into three recovery stages based on the timeline of stroke recovery established in the first Stroke Recovery and Rehabilitation Roundtable (Bernhardt et al., 2017): hyper-acute/acute (0–7 days post-stroke), subacute (7 days−6 months post-stroke) and chronic (>6 months post-stroke).

The type of interventions implemented in the experimental and comparison groups were documented for subgroup analysis. Bilateral arm training involves performing motor tasks with both ULs in a symmetric or asymmetric design. It can be practiced with or without the aid of an external device (Hatem et al., 2016). As described in a previous review, three categories of BAT, including bilateral functional task training (BFTT), bilateral arm training with rhythmic auditory cueing (BATRAC), and bilateral robot-assisted training (BRAT) have been identified (Wolf et al., 2014). In addition to the three categories of BAT mentioned above, mirror therapy (MT) involves the use of a mirror to create a reflective illusion of the non-affected arm as if it were the affected one (Ramachandran et al., 1995). One strategy of MT involves actively synchronizing the affected limb with the mirror reflection of the unaffected limb, thus considering it as a form of BAT (Toh and Fong, 2012). Most of the previous systematic reviews examining the effectiveness of BAT excluded MT (Van Delden et al., 2012; Chen et al., 2019; Richardson et al., 2021). However, MT is cost-friendly, simple, and relatively less labor-intensive, and its effectiveness is of interest to be examined with other types of BAT. Therefore, we included the active form of MT as a type of BAT in the present review. In the case of BRAT and BFTT, if BFTT were used simultaneously in the same experimental therapy protocol, it was considered BRAT since an external robotic device was used.

For the control subgroups, unilateral arm training (UAT) was described as an exercise intervention using the hemiparetic UL while excluding the contralateral UL (Van Delden et al., 2012) as well as conventional therapy (CT), which involved conventional occupational/physical therapy, routine clinical rehabilitation, traditional therapeutic activities, dose-matched therapeutic exercise that did not exclude the use of the non-paretic arm were identified.

Data related to the intervention dose was also extracted to conduct a subgroup analysis. Therapy dose can be described in terms of length of treatment sessions, the number of treatment sessions, and intensity of intervention (Cooke et al., 2010; Pollock et al., 2014). The intervention dose often provides duration-based information in stroke rehabilitation, including minutes or days per week (Lang et al., 2009). Therefore, we determined a criterion to categorize the included studies into higher and lower dose groups. If the treatment hours were ≥7 hours per week or the total treatment hours ≥ 30, it was classified into the higher dose group. Whereas if the treatment hours were <7 h per week or the total treatment hours<30 h, it was categorized into the lower dose group. For the studies reporting the range of training time, the average value was used to calculate the intervention dose.

For the studies with more than 2 groups (e.g., contains BAT, UAT and CT groups), BAT vs. UAT and BAT vs. CT data were extracted separately for meta-analyses. All the extracted data were summarized in the tables.

Statistical Analysis

Data management and meta-analysis were performed by R version 3.6.3 using "metafor" package (Viechtbauer, 2010). Mean difference (MD) and standardized mean difference [SMD, assessed by Hedges' g, $g = 0.2$ for small effect, $g = 0.5$ for medium effect, and $g = 0.8$ for large effect (Cohen, 1988)] between post and pre-intervention was used as the primary outcome for motor impairment measurement and the function performance measurements, respectively. For studies that only reported mean and standard deviation for post and pre-intervention rather than the MD, we calculated the MD or SMD as appropriate. We obtained the sample standard deviation (SD) for MD or SMD using the covariance formula with correlation parameter $\rho = 0.8$ (Chen et al., 2019; Deeks et al., 2021). Finally, the estimated MD

or SMD and the corresponding 95% confidence interval (CI) were reported. The results were visualized using forest plots.

The MD of FMA-UE was used to test motor impairment, while the SMD of ARAT, BBT, and WMFT-time were aggregated for testing function performance. Although MAL is also on the UL functional performance level of the WHO ICF, it represents patient-perceived UL activity performance and was hence analyzed separately as a secondary analysis. SMD was calculated for MAL for easier comparison with other functional outcomes. Two null hypotheses were tested for both motor impairment and functional performance in the meta-analysis: (1). There is no difference in MD or SMD between BAT and CT; and (2). There is no difference in MD or SMD between BAT and UAT. Mixed-effects model was used for the meta-analysis regression. The Higgins I^2 index and Q-statistic were used to test the heterogeneity. The τ^2 (estimated amount of total heterogeneity) and H^2 (total variability divided by sampling variability) were also estimated and reported. A fixed-effects model would be used if $I^2 < 50\%$, indicating a low-to-moderate heterogeneity; otherwise, a random-effects model would be used.

Several subgroup analyses were performed. MD of motor impairment and SMD of function performance were investigated by stroke chronicity (three phases), the severity of UL paresis (three phases), the type of BAT (four types), and the intervention dose (two doses).

Publication bias was evaluated by funnel plot virtually and then tested by rank-correlation test and Egger's test (Begg and Mazumdar, 1994; Egger et al., 1997). For analysis that may have publication bias, the selection models method with step function was performed and tested by likelihood ratio test (LRT) as the sensitivity analysis (Hedges, 1992; Hedges and Vevea, 1996; Mcshane et al., 2016).

RESULTS

Data Retrieval

The initial search resulted in 1,052 articles. Once duplicate articles were excluded, 423 articles remained for further screening. Therefore, 382 articles were removed subsequently based on title and abstract. Forty-one articles were subjected to full-text assessment, of which 17 articles were excluded due to the following reasons: (i) the studies were not RCTs ($n = 8$), (ii) the studies did not provide sufficient data for statistical analysis ($n = 5$), (iii) the bilateral training was included in both experimental and control groups ($n = 2$), (iv) post-stroke duration was not specified in the study ($n = 2$). Finally, a total of 25 studies with 1,103 participants fulfilled the inclusion criteria and were ultimately included in this systematic review (**Figure 2**).

Study Characteristics

One study included participants in the acute phase of stroke (Meng et al., 2018). Eight studies recruited subjects in the subacute phase of stroke (Desrosiers et al., 2005; Lum et al., 2006; Morris et al., 2008; Brunner et al., 2012; Van Delden et al., 2013; Samuelkamaleshkumar et al., 2014; Hsieh et al., 2017; Renner et al., 2020), and the remaining 16 studies included subjects in the chronic phase of stroke (Luft et al., 2004; Waller and Whitall, 2008; Lin et al., 2009, 2010, 2015; Hsieh et al., 2011; Whitall et al., 2011; Wu et al., 2011, 2013a,b; Liao et al., 2012; Yang et al., 2012; Lee et al., 2017a; Sethy et al., 2018; Hsu et al., 2019; Hung et al., 2019).

Based upon the pre-determined criteria for the severity of UL paresis, two studies classified as targeting populations with severe paresis (Samuelkamaleshkumar et al., 2014; Renner et al., 2020), nine studies were considered as including participants with a moderate paresis (Luft et al., 2004; Lum et al., 2006; Morris et al., 2008; Waller and Whitall, 2008; Whitall et al., 2011; Liao et al., 2012; Hsieh et al., 2017; Meng et al., 2018; Hung et al., 2019), and participants recruited in the remaining 14 studies were categorized as having mild UL paresis (Desrosiers et al., 2005; Lin et al., 2009, 2010, 2015; Hsieh et al., 2011; Wu et al., 2011, 2013a,b; Brunner et al., 2012; Yang et al., 2012; Van Delden et al., 2013; Lee et al., 2017a; Sethy et al., 2018; Hsu et al., 2019).

Four categories of BAT were identified in the included studies: (1) bilateral functional task training (BFTT) ($n = 10$) (Desrosiers et al., 2005; Morris et al., 2008; Lin et al., 2009, 2010; Wu et al., 2011; Brunner et al., 2012; Lee et al., 2017a; Meng et al., 2018; Sethy et al., 2018; Renner et al., 2020), (2) bilateral robot-assisted training (BRAT) ($n = 9$) (Lum et al., 2006; Hsieh et al., 2011, 2017; Liao et al., 2012; Yang et al., 2012; Wu et al., 2013b; Lin et al., 2015; Hsu et al., 2019; Hung et al., 2019), (3) mirror therapy (MT) ($n = 2$) (Wu et al., 2013a; Samuelkamaleshkumar et al., 2014), and (4) bilateral training with rhythmic auditory cueing (BATRAC) ($n = 4$) (Luft et al., 2004; Waller and Whitall, 2008; Whitall et al., 2011; Van Delden et al., 2013). One study implemented a hybrid therapy protocol (participants received an equal amount of time in BFTT and BRAT in the experimental groups) was classified into the BRAT group since an external robotic device was used (Hung et al., 2019).

Two studies were excluded from the subgroup analysis for the intervention dose due to the unequal amount of therapy received in the experimental and control groups (Brunner et al., 2012; Samuelkamaleshkumar et al., 2014), yielding 23 total studies available for further investigation. According to the previously described criteria, 13 studies were classified into the higher dose group (Lin et al., 2009, 2010; Hsieh et al., 2011, 2017; Wu et al., 2011, 2013a,b; Liao et al., 2012; Yang et al., 2012; Lee et al., 2017a; Meng et al., 2018; Sethy et al., 2018; Renner et al., 2020), while 10 were categorized into the lower dose group (Luft et al., 2004; Desrosiers et al., 2005; Lum et al., 2006; Morris et al., 2008; Waller and Whitall, 2008; Whitall et al., 2011; Van Delden et al., 2013; Lin et al., 2015; Hsu et al., 2019; Hung et al., 2019).

The rehabilitation protocols used in the control groups included conventional therapy (CT) ($n = 21$) and unilateral arm training (UAT) ($n = 10$). The reported protocols of UAT consisted of (modified) constraint-induced movement therapy (m)CIMT ($n = 2$) (Brunner et al., 2012; Van Delden et al., 2013) distributed constraint-induced therapy (dCIT) ($n = 2$) (Lin et al., 2009; Wu et al., 2011) unilateral robotic-assisted therapy (URAT) ($n = 4$), (Lum et al., 2006; Yang et al., 2012; Wu et al., 2013b; Hung et al., 2019), and dose-matched unilateral functional task training (UFTT) ($n = 2$) (Morris et al., 2008; Renner et al., 2020). Twenty-one studies had conventional therapy as a

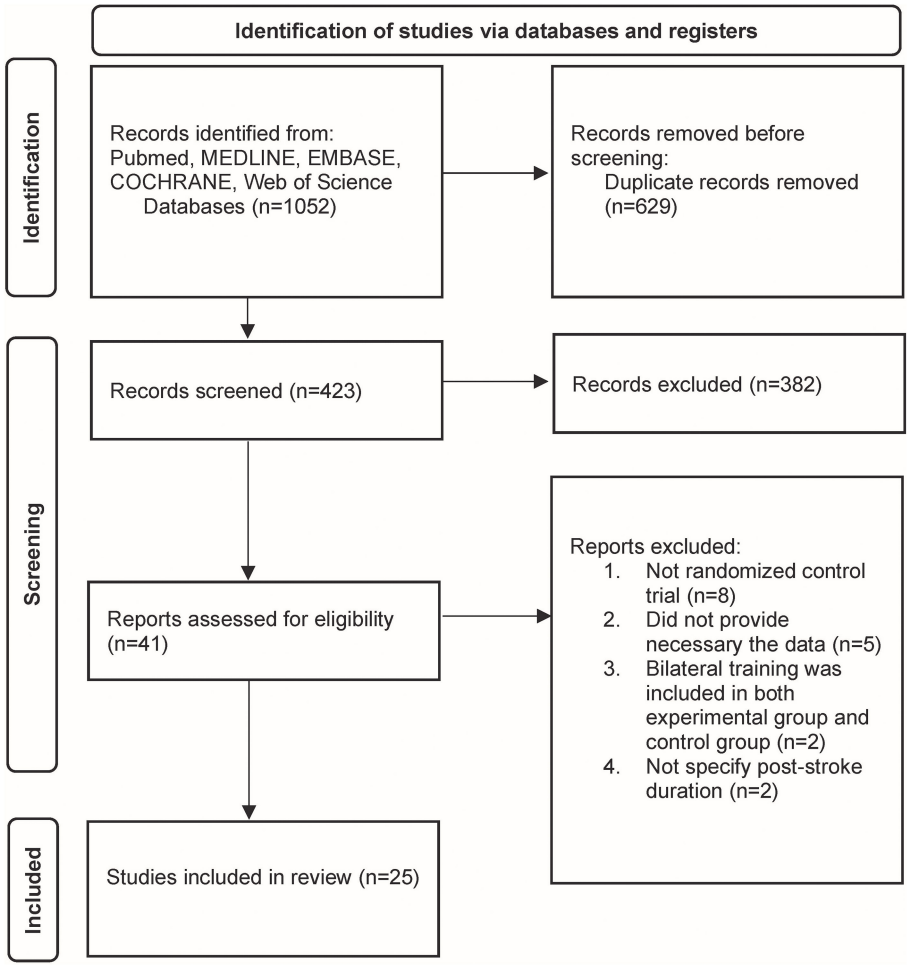


FIGURE 2 | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study identification.

comparison group that included multidisciplinary rehabilitation programs, sensorimotor stimulation program, task-oriented approach, routine occupational therapy, or physical therapy.

The baseline information of participants and the characteristics of included studies are present in **Tables 1**, **2**.

Quality Assessment

Table 3 presents the methodological quality assessment of the included studies as evaluated using the PEDro scale. All studies scored more than 4 points on the PEDdro scale, indicating sufficient quality among the included studies. The mean score of PEDro was 6.36 points ($SD = 0.91$), ranging from 5 to 8 points.

Meta-Analysis Results

BAT vs. CT

Nineteen studies assessed motor impairment of the UL using the FMA-UE (Luft et al., 2004; Desrosiers et al., 2005; Lum et al., 2006; Waller and Whitall, 2008; Lin et al., 2009, 2010, 2015; Hsieh et al., 2011, 2017; Whitall et al., 2011; Liao et al., 2012; Yang et al., 2012; Van Delden et al., 2013; Wu et al., 2013a; Samuelkamaleshkumar et al., 2014; Lee et al., 2017a; Meng et al., 2018; Sethy et al., 2018; Hsu et al., 2019). **Figure 3A** shows the descriptive and meta-regression results for the motor impairment between BAT and CT. The meta-analysis fixed-effects model found that BAT demonstrated significantly greater UE motor impairments improvements than the CT group ($MD = 3.94$, 95% CI: [1.73, 6.15], $p < 0.001$).

In terms of the time post-stroke, 13 out of the 19 studies recruited participants in the chronic phase of stroke (Luft et al., 2004; Waller and Whitall, 2008; Lin et al., 2010, 2015; Hsieh et al., 2011; Whitall et al., 2011; Liao et al., 2012; Yang et al., 2012; Wu et al., 2013a; Lee et al., 2017a; Sethy et al., 2018; Hsu et al., 2019), and the remaining six studies included subjects in the acute and subacute phases of stroke (Desrosiers et al., 2005; Lum et al., 2006; Van Delden et al., 2013; Samuelkamaleshkumar et al., 2014; Hsieh et al., 2017; Meng et al., 2018). Since only one article was identified in the acute phase, only subacute and chronic phases were considered here. Greater improvements were shown in the chronic phase of stroke with the BAT in FMA-UE compared to the CT ($MD = 4.59$, 95% CI: [2.00, 7.19], $p < 0.001$). However, such differences were not observed in the subacute phase ($MD = -0.74$, 95% CI: [−5.94, 4.46], $p = 0.780$).

TABLE 1 | Characteristics of recruited participants included in this meta-analysis.

References	Total N	Age (years) [Mean (SD)]	Gender [Male (%)]	Time post stroke [Mean (SD)]	Lesion side [Right (%)]	Phase	Severity
Brunner et al. (2012)	30	BAT = 64.8 (12.8); UAT = 61.0 (10.0)	BAT = 8 (50.0%); UAT = 11 (78.6%)	BAT = 36.9 d (25.1); UAT = 48.43 d (39.3)	BAT = 10 (62.5%); UAT = 8 (57.1%)	Subacute	Mild
Desrosiers et al. (2005)	41	BAT = 72.2 (10.8); CT = 74.3 (10.1)	BAT = 9 (45.0%); CT = 10 (47.6%)	BAT = 34.2 d (34.4); CT = 35.4 d (33.7)	BAT = 7 (35.0%); CT = 11 (52.4%)	Subacute	Mild
Hsieh et al. (2011)	18	BAT = 54.6 (10.5); CT = 54.0 (8.05)	BAT = 8 (66.7%); CT = 5 (83.3%)	BAT = 18.0 mo (8.0); CT = 28.33 mo (19.9)	BAT = 6 (50.0%); CT = 2 (33.3%)	Chronic	Mild
Hsieh et al. (2017)	31	BAT = 49.28 (10.9); CT = 52.87 (10.40)	BAT = 11 (68.8%); CT = 7 (46.7%)	BAT = 2.5 mo (1.69); CT = 2.21 mo (1.11)	BAT = 8 (50.0%); CT = 11 (73.3%)	Subacute	Moderate
Hsu et al. (2019)	43	BAT = 53.1 (13.9); CT = 52.6(12.5)	BAT = 11 (50.0%); CT = 9 (42.9%)	BAT = 13.7 mo (8.6); CT = 14.7 mo (13.2)	NR	Chronic	Mild
Hung et al. (2019)	29	BAT = 58.45 (13.11); UAT = 53.17 (12.28)	BAT = 10 (66.7%); UAT = 9 (64.3%)	BAT = 29.33 mo (28.44); UAT = 37.86 mo (34.77)	BAT = 6 (40.0%); UAT = 8 (57.1%)	Chronic	Moderate
Lee et al. (2017a)	30	BAT = 57.33 (9.88); CT = 54.60 (16.03)	BAT = 9 (60.0%); CT = 10 (66.7%)	NR	BAT = 7 (46.7%); CT = 6 (40.0%)	Chronic	Mild
Liao et al. (2012)	20	BAT = 55.51 (11.17); CT = 54.56 (8.20)	BAT = 6 (60.0%); CT = 7 (70.0%)	BAT = 23.9 mo (13.39); CT = 22.20 mo (17.47)	BAT = 6 (60.0%); CT = 7 (70.0%)	Chronic	Moderate
Lin et al. (2009)	60	BAT = 51.58 (8.67); UAT = 55.28 (9.34); CT = 50.70 (13.93)	BAT = 12 (60.0%); UAT = 11 (55.0%); CT = 11 (55.0%)	BAT = 18.50 mo (17.40); UAT = 21.25 mo (21.59); CT = 21.90 mo (20.51)	BAT = 11 (55.0%); UAT = 8 (40.0%); CT = 12 (60.0%)	Chronic	Mild
Lin et al. (2010)	33	BAT = 52.08 (9.60); CT = 55.50 (13.17)	BAT = 10 (62.5%); CT = 9 (52.9%)	BAT = 13.94 mo (12.73); CT = 13.12 mo (8.13)	BAT = 7 (43.8%); CT = 9 (52.9%)	Chronic	Mild
Lin et al. (2015)	33	BAT = 52.63 (10.49); CT = 57.47 (10.29)	BAT = 12 (75.0%); CT = 16 (94.1%)	BAT = 27.75 mo (19.04); CT = 21.82 mo (21.66)	BAT = 8 (50.0%); CT = 8 (47.1%)	Chronic	Mild
Luft et al. (2004)	21	BAT = 63.5 (15.3); CT = 59.6 (10.5)	BAT = 7 (77.8%); CT = 4 (36.4%)	*BAT = 75 mo (NR); *CT = 45.5 mo (NR)	BAT = 6 (66.7%); CT = 7 (63.6%)	Chronic	Moderate
Lum et al. (2006)	20	BAT = 72.2 (11.7); UAT = 69.8 (4.0); CT = 59.9 (5.5)	BAT = 2 (40.0%); UAT = 5 (55.6%); CT = 4 (66.7%)	BAT = 6.2 wk (1.0); UAT = 10.0 wk (1.9); CT = 10.6 wk (2.7)	BAT = 3 (60.0%); UAT = 5 (55.6%); CT = 4 (66.7%)	Subacute	Moderate
Meng et al. (2018)	128	BAT = 55.38 (6.97); CT = 55.19 (7.82)	BAT = 34 (53.1%); CT = 31 (48.4%)	BAT = 8.87 hr (2.69); CT = 9.08 hr (2.35)	BAT = 35 (54.7%); CT = 33 (51.6%)	Acute	Moderate
Morris et al. (2008)	106	BAT = 67.9 (13.1); UAT = 67.8 (9.9)	BAT = 34 (60.7%); UAT = 27 (54.0%)	BAT = 22.6 d (5.6); UAT = 23.2 d (5.7)	BAT = 29 (51.8%); UAT = 23 (46.0%)	Subacute	Moderate
Renner et al. (2020)	69	BAT = 63.7(12.39); UAT = 63.3 (12.50)	BAT = 16 (45.7%); UAT = 16 (47.1%)	BAT = 35.2d(11.03); UAT = 37.2d (13.6)	BAT = 19 (54.3%); UAT = 22 (64.7%)	Subacute	Severe
Samuelkamaleshkumar et al. (2014)	20	BAT = 48.4 (15.58); CT = 53.9 (11.57)	BAT = 8 (80.0%); CT = 8 (80.0%)	BAT = 3.7 wk (1.1); CT = 4.4 wk (1.4)	BAT = 6 (60.0%); CT = 4 (40.0%)	Subacute	Severe
Sethy et al. (2018)	28	BAT = 57.34 (11.92); CT = 57.59 (11.03)	BAT = 10 (71.4%); CT = 9 (64.3%)	BAT = 13.09 mo (2.86); CT = 13.82 mo(3.01)	BAT = 5 (35.7%); CT = 4 (28.6%)	Chronic	Mild
Van Delden et al. (2013)	60	BAT = 62.6 (9.8); UAT = 59.8 (13.8); CT = 56.9 (12.7)	BAT = 11 (57.9%); UAT = 14 (63.6%); CT = 16 (84.2%)	BAT = 7.8 wk (4.9); UAT = 9.2 wk (6.8); CT = 11.1 wk (6.8)	BAT = 11 (57.9%); UAT = 12 (54.5%); CT = 11 (57.9%)	Subacute	Moderate
Waller and Whitall (2008)	18	BAT = 57.95 (13.11); CT = 54.06 (9.11)	BAT = 5 (55.6%); CT = 2 (22.2%)	BAT = 73.53 mo (73.97); CT = 31.55 mo (23.52)	BAT = 4 (44.4%); CT = 4 (44.4%)	Chronic	Moderate
Whitall et al. (2011)	92	BAT = 59.8 (9.9); CT = 57.7 (12.5)	BAT = 26 (61.9%); CT = 24 (48.0%)	BAT = 4.5 yr (4.1); CT = 4.1 yr (5.2)	BT = 23 (56.1%); CT = 25 (50.0%)	Chronic	Moderate

(Continued)

TABLE 1 | Continued

References	Total N	Age (years) [Mean (SD)]	Gender [Male (%)]	Time post stroke [Mean (SD)]	Lesion side [Right (%)]	Phase	Severity
Wu et al. (2011)	66	BAT = 52.22 (10.72); UAT = 51.91 (11.93); CT = 55.19 (2.50)	BAT = 18 (81.8%); UAT = 15 (68.2%); CT = 16 (72.7%)	BAT = 15.92 mo (13.74); UAT = 14.91 mo (12.41); CT = 17.77 mo (12.45)	BAT = 12 (54.5%); UAT = 8 (36.4%); CT = 10 (45.5%)	Chronic	Mild
Wu et al. (2013a)	33	BAT = 54.77 (11.66); CT = 53.59 (10.21)	BAT = 11 (68.8%); CT = 12 (70.6%)	BAT = 19.31 mo (12.57); CT = 21.88 mo (15.55)	BAT = 8 (50.0%); CT = 10 (58.8%)	Chronic	Mild
Wu et al. (2013a)	53	BAT = 52.21 (12.20); UAT = 54.95 (9.90); CT = 54.22 (9.78)	BAT = 13 (72.2%); UAT = 10 (55.6%); CT = 12 (70.6%)	BAT = 23.28 mo (15.37); UAT = 19.00 mo (15.51); CT = 23.41 mo (15.24)	BAT = 9 (50.0%); UAT = 12 (66.7%); CT = 8 (47.1%)	Chronic	Mild
Yang et al. (2012)	21	BAT = 51.4 (10.9); UAT = 50.8 (6.1); CT = 51.6 (7.6)	BAT = 4 (57.1%); UAT = 5 (71.4%); CT = 5 (71.4%)	BAT = 14.7 mo (5.7); UAT = 12.3 mo (4.4); CT = 14.3 mo (6.8)	BAT = 4 (57.1%); UAT = 4 (57.1%); CT = 3 (42.9%)	Chronic	Mild

**Data are presented as median; BAT, bilateral arm training; CT, conventional therapy; d, days; hr, hours; mo, months; NR, not reported; SD, standard deviation; UAT, unilateral arm training; wk, weeks; yr, years.*

Eleven of 19 studies included subjects with mild UL paresis (Lin et al., 2009, 2010, 2015; Hsieh et al., 2011; Yang et al., 2012; Van Delden et al., 2013; Wu et al., 2013a; Lee et al., 2017a; Sethy et al., 2018; Hsu et al., 2019), and eight studies recruited subjects with moderate to severe UL paresis (Luft et al., 2004; Lum et al., 2006; Waller and Whitall, 2008; Whitall et al., 2011; Liao et al., 2012; Samuelkamaleshkumar et al., 2014; Hsieh et al., 2017; Meng et al., 2018). Compared with CT, we found a significant MD in favor of BAT with the mild UL paresis ($MD = 6.28$, 95% CI: [3.15, 9.40], $p < 0.001$), but this effect was not detected in participants with moderate to severe UL paresis ($MD = 1.60$, 95% CI: [−1.53, 4.73], $p = 0.316$). Furthermore, as shown in **Figure 3A**, the effect size increased if patients were in the chronic phase with the mild UL paresis ($MD = 6.71$, 95% CI: [3.47, 9.94], $p < 0.001$), which is 4.27 times the $MD = 1.57$ of the CT group with chronic phase and mild UL paresis.

The impacts of BAT types on UL motor impairment post-stroke were also investigated. Six of 19 studies applied BFTT (Desrosiers et al., 2005; Lin et al., 2009, 2010; Lee et al., 2017b; Meng et al., 2018; Sethy et al., 2018), BRAT was used in seven studies (Lum et al., 2006; Hsieh et al., 2011, 2017; Liao et al., 2012; Yang et al., 2012; Lin et al., 2015; Hsu et al., 2019), MT was implemented in two studies (Wu et al., 2013a; Samuelkamaleshkumar et al., 2014), and the remaining four studies used (m)BATRAC as a type of BAT (Luft et al., 2004; Waller and Whitall, 2008; Whitall et al., 2011; Van Delden et al., 2013). Only the BFTT group demonstrated significantly greater gains in UL motor impairment than the CT group ($MD = 7.84$, 95% CI: [4.37, 11.30], $p < 0.001$) (**Supplementary Figure 1A**), whereas the other types of BAT did not illustrate a superior effect.

Data from 18 studies assessed FMA-UE were available for the intervention dose subgroup analysis. Ten studies were categorized into the higher dose group (Lin et al., 2009, 2010; Hsieh et al., 2011, 2017; Liao et al., 2012; Yang et al., 2012; Wu et al., 2013a; Lee et al., 2017a; Meng et al., 2018; Sethy et al., 2018), while eight studies were classified into the lower dose group based on the pre-determined criteria (Luft et al., 2004; Desrosiers et al., 2005; Lum et al., 2006; Waller and Whitall, 2008; Whitall et al., 2011; Van Delden et al., 2013; Lin et al., 2015; Hsu et al., 2019). As shown in **Figure 4A**, significant improvements in motor impairment were observed in the BAT group than the CT group, when the dose of intervention was high ($MD = 6.52$, 95% CI: [3.48, 9.57], $p < 0.001$). However, the differential effect of BAT and CT was not observed with the lower dose training ($MD = 0.82$, 95% CI: [−2.42, 4.06], $p = 0.620$).

Thirteen studies reported UL functional performance outcomes using ARAT, BBT, and WMFT-time (Luft et al., 2004; Desrosiers et al., 2005; Waller and Whitall, 2008; Whitall et al., 2011; Wu et al., 2011, 2013b; Van Delden et al., 2013; Samuelkamaleshkumar et al., 2014; Lin et al., 2015; Hsieh et al., 2017; Lee et al., 2017a; Meng et al., 2018; Sethy et al., 2018). MAL data reported from five studies were available for secondary analysis (Lin et al., 2009; Liao et al., 2012; Wu et al., 2013a; Hsu et al., 2019). No differential effect of BAT and CT was found either in the UL functional performance ($SMD = 0.28$, 95% CI: [−0.26, 0.82], $p = 0.313$) (**Figure 5A**) or in the patient-perceived arm use ($SMD = 0.02$, 95% CI: [−0.28, 0.32], $p = 0.916$) (**Supplementary Figure 2A**) and quality of movement ($SMD = 0.08$, 95% CI: [−0.22, 0.38], $p = 0.604$) (**Supplementary Figure 3A**). However, in the subgroup analysis by type of BAT, the results showed that BFTT ($n = 5$) significantly improved UL functional performance as measured by ARAT, BBT and WMFT with a substantially large effect size ($SMD = 1.02$, 95% CI: [0.01, 2.02], $p = 0.049$) (**Supplementary Figure 1B**). The superior effect was not observed in other types of BAT [$SMD = -0.72$ in BRAT, 0.85 in MT, −0.09 in (m)BATRAC]. No differential effect was noted in the subgroup analysis stratified by intervention dose (**Figure 6A**).

TABLE 2 | Characteristics of the included studies in this meta-analysis.

References	Type of BAT	Comparison group	BAT intervention dose	Outcome measures
Brunner et al. (2012)	BFTT	UAT: (m)CIMT	4 hr/wk with an OT/PT, daily self-training exercise 2–3 hours/d, 4 wk Total: 86 hrs	ARAT, 9HPT, MAL
Desrosiers et al. (2005)	BFTT	CT: functional activities and exercises	45 min/session, 4 d/wk, 15–20 total sessions, 5 wk Total: 13.125 hrs	FMA, vigorimeter, BBT, Purdue Pegboard Test, FTNT, TEMPA, FIM, AMPS
Hsieh et al. (2011)	BRAT	CT: conventional OT	90–105 min/session, 5 d/wk, 4 wk Total: 32.5 hrs	FMA, MRC scale, MAL, the ABILHAND scale, urinary 8-OHdG, MFSI
Hsieh et al. (2017)	BRAT	CT: task-oriented approach followed by functional and real-life tasks	90 min/session, 5 d/wk, 4 wk Total: 30 hrs	FMA, dynamometer, BBT, modified Rankin Scale, FIM, actigraphy, SIS, self-reported fatigue scale
Hsu et al. (2019)	BRAT	CT: sensorimotor stimulation program followed by therapist-facilitated task-specific training	50 min/session 3 d/wk, 4 wk Total: 10 hrs	MAL,FMA,sEMG
Hung et al. (2019)	BRAT + BFTT	UAT: URAT + (m)CIMT	90 min/session, 3 d/wk, 6 wk Total: 27 hrs	FMA, SIS, WMFT, NEADL
Lee et al. (2017a)	BFTT	CT: OT incorporated the Bobath approach	60 min/session, 5 d/wk, 8 wk Total: 40 hrs	FMA, BBT, MBI
Liao et al. (2012)	BRAT	CT: OT training	90-105 min/session, 5 d/wk, 4wk Total: 32.5 hrs	arm activity ratio, FMA, FIM, MAL, ABILHAND questionnaire
Lin et al. (2009)	BFTT	UAT: dCIT CT: conventional exercises	120 min/session, 5 d/wk, 3 wk Total: 30 hrs	FMA, FIM, MAL, SIS
Lin et al. (2010)	BFTT	CT: OT incorporated NDT	120 min/session, 5 d/wk, 3 wk Total: 30 hrs	Kinematic analyses, FMA, FIM, MAL
Lin et al. (2015)	BRAT	CT: routine clinical rehabilitation	30 min/session, 3 d/wk, 4 wk Total: 6 hrs	BI, FMA, MAS, WMFT
Luft et al. (2004)	BATRAC	CT: based on NDT principles	60 min/session, 3 d/wk, 6 wk Total: 18 hrs	FMA, WMAT, UMAQS, dynamometry, fMRI
Lum et al. (2006)	BRAT	UAT: UFTT CT: conventional therapy based on NDT	60 min/session, 15 total sessions, 4 wk Total: 15 hrs	modified Ashworth scale, FMA, FIM, MSS, motor power examination
Meng et al. (2018)	BFTT	CT: conventional rehabilitation program	60 min/session, 2 session/d, 5 d/wk, 2 wk Total: 20 hrs	FMA, ARAT, AMP, RMT, CMCT
Morris et al. (2008)	BFTT	UAT: UFTT	20 min/session, 5 d/wk, 6 wk Total: 10 hrs	ARAT, RMA UL scale, 9HPT, MBI, Hospital Anxiety and Depression Scale, Nottingham Health Profile
Renner et al. (2020)	BFTT	UAT: UFTT	arm cycle: 20 min/session, 2 sessions/d+ progressive BT/UT session: 20 min/session, 1 session/d. 5 d/wk, 6 wk Total: 30 hrs	FMA, biomechanical parameters measuring isometric force and rate of force generation
Samuelkamaleshkumar et al. (2014)	MT	CT: multidisciplinary rehabilitation program	30 min/session, 2 sessions/d, 5 d/wk, 3 wk Total: 15 hrs	FMA, Brunnstrom stages of motor recovery, BBT, modified Ashworth Scale
Sethy et al. (2018)	BFTT	CT: conventional OT based on Bobath approach.	60 min/session, 5 d/wk, 6 wk Total: 30 hrs	FMA, ARAT, MAL
Van Delden et al. (2013)	mBATRAC	UAT: (m)CIMT CT: exercise therapy based on Royal Dutch Society of Physical Therapy and Dutch Society of Occupational Therapy	60 min/session, 3 d/wk, 6 wk Total: 18 hrs	ARAT, MI, FMA, 9HPT, Erasmus modifications of the Nottingham Sensory Assessment, MAL, SIS
Waller and Whitall (2008)	BATRAC	CT: based on NDT principles	60 min/session, 3 d/wk, 6 wk Total:18 hrs	FMA, WMFT
Whitall et al. (2011)	BATRAC	CT: based on NDT principles	60 min/session, 3 d/wk, 6wk Total:18 hrs	FMA, WMFT, SIS, dynamometer, ROM, 5-point Likert scale, fMRI

(Continued)

TABLE 2 | Continued

References	Type of BAT	Comparison group	BAT intervention dose	Outcome measures
Wu et al. (2011)	BFTT	UAT: dCIIT CT: based on NDT principles	120 min/session, 5 d/wk, 3 wk Total: 30 hrs	kinematic variables, WMFT, MAL
Wu et al. (2013a)	MT	CT: traditional therapeutic activities base on task-oriented treatment principles	90 min/session, 3 d/wk, 4 wk Total: 30 hrs	FMA, kinematic variables, the Revised Nottingham Sensory Assessment, MAL, the ABILHAND questionnaire
Wu et al. (2013b)	BRAT	UAT: URAT CT: conventional therapeutic activities	90–105 min/session, 5 d/wk, 4 wk Total: 32.5 hrs	Kinematic variables, WMFT, MAL, ABILHAND Questionnaire
Yang et al. (2012)	BRAT	UAT: URAT CT: conventional therapeutic activities	90–105 min/session, 5 d/wk, 4 wk Total: 32.5 hrs	FMA, MRC instrument, grip strength, Modified Ashworth Scale

AMAT, Arm Motor Ability Test; AMP, motor-evoked potential amplitude; AMPS, Assessment of Motor and Process Skills; ARAT, Action Research Arm Test; BAT, bilateral arm training; BATRAC, bilateral training with rhythmic auditory cueing; BBT, Box & Block Test; BFTT, bilateral functional task training; BI, The Barthel Index; BRAT, bilateral robot-assisted training; CAHAI-9, Chedoke Arm & Hand Activity Index-9; CMCT, central motor conduction time; COPM, Canadian Occupational Performance Measure; CT, conventional therapy; UAT, unilateral arm training; dCIT, distributed constraint-induced therapy; FIM, Functional Independence Measure; fMRI, Functional magnetic resonance imaging; FTNT, finger to nose test; MAL, Motor Activity Log; (m)CIMT, (modified) constrain-induced movement therapy; MAS, Motor Assessment Score; mBATRAC, modified bilateral training with rhythmic auditory cueing MBI, modified Barthel Index; MFSI, Multidimensional Fatigue Symptom Inventory; MI, Motricity Index; MRC, Medical Research Council; MSS, Motor Status Scale; NDT, Neurodevelopmental Treatment; NEADL, Nottingham Extended Activities of Daily Living; NIHSS, National Institutes of Health Stroke Scale; OT, Occupational Therapy; RMA UL scale, Rivermead Motor Assessment upper-limb scale; RMT, resting motion threshold; sEMG, surface Electromyography; TEMPA, Test d'Evaluation des Membres Supe'rieurs de Personnes Age'es; TMS, Transcranial Magnetic Stimulation; UFTT, unilateral functional task training; UMAQS, University of Maryland Arm Questionnaire for Stroke; URAT, unilateral robot-assisted therapy; SIS, Stroke Impact Scale; WMFT, Wolf Motor Function Test; Y-BAT, Yonsei-Bilateral Activity Test; 9HPT, Nine-Hole Peg Test.

BAT vs. UAT

Six studies in total reported UL motor impairment outcomes using FMA-UE (Lum et al., 2006; Yang et al., 2012; Van Delden et al., 2013; Hung et al., 2019; Renner et al., 2020). No statistically significant difference was found between BAT and UAT in motor impairment ($MD = -0.90$, 95% CI: [−5.17, 3.38], $p = 0.681$) (**Figure 3B**) or in any subgroup analyses (**Figures 3B**, **4B**).

Six studies assessed the UL functional performance using ARAT, and WMFT-time (Morris et al., 2008; Wu et al., 2011, 2013b; Brunner et al., 2012; Van Delden et al., 2013; Hung et al., 2019). Only one study reported MAL (Lin et al., 2009); the perceived UL functional performance would not be discussed below due to insufficient power (**Supplementary Figures 2B**, **3B**). No significant differences were observed between UAT and BAT regarding the UL functional performance post-stroke in general ($SMD = -0.09$, 95% CI: [−0.32, 0.14], $p = 0.457$) (**Figure 5B**) or in the subgroup analyses (**Figures 5B**, **6B**).

Publication Bias and Sensitivity Analyses

To detect publication bias, **Figure 7** shows the funnel plots for BAT compared with CT and UAT, in both motor impairment and functional performance. The red regression line indicates Egger's test for each comparison. There was no publication bias detected as indicated by Egger's test and rank-correlation test.

DISCUSSION

The purpose of this systematic review and meta-analysis was to evaluate the effectiveness of bilateral arm training (BAT) compared to unilateral arm training (UAT) and conventional therapy (CT), respectively, in changing upper extremity (UE) motor impairments and functional performance in the post-stroke population who have experienced UE hemiparesis. Furthermore, we also aimed to explore different contributing factors in determining optimal intervention post-stroke systematically.

The current meta-analysis revealed that BAT is overall more effective in improving UL motor impairment than CT. However, no differential effects of BAT and CT were observed in terms of enhancing UL functional performance. A review article by Coupar et al. (2010) also reported a favorable effect of BAT in improving motor impairment as measured by FMA-UE based on four studies comparing the effectiveness of bilateral training with usual care. A total of 19 RCTs were included in our current meta-analysis to compare the differential effects of BAT and CT on motor impairment outcome, which greatly improved the robustness of current findings. Additionally, the minimal clinically important difference (MCID) is used as an index to determine whether changes in outcome scores resulting from interventions indicate meaningful and clinically important improvements for patients (Copay et al., 2007; Revicki et al., 2008). The estimated MCID for FMA-UE scores ranged from 4.25 to 7.25 (Page et al., 2012). Our findings showed that while the CT group ($MD = 4.32$) has just reached the lower bound of MCID, the BAT group ($MD = 8.55$) has exceeded the upper bound. The differences between BAT and CT in improving FMA-UE scores were even more substantial in the subgroup analysis.

Few studies to date have examined the effectiveness of different types of BAT in comparison to CT. A previous systematic review based on two studies found that the BFTT group showed greater gains in FMA-UE scores than the CT group but not in the activity measures (Wolf et al., 2014). With more RCTs ($n = 7$), our results were partially consistent with their findings, indicating that implementing BFTT not only

TABLE 3 | Methodological quality of included studies assessed by Physiotherapy Evidence Database (PEDro) scale.

References	Eligibility criteria specified (Yes/No)	Random allocation	Concealed allocation	Comparable at baseline	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between group comparisons	Point estimates and variability	PEDro total score (0–10)
Brunner et al. (2012)	Yes	1	1	1	0	0	1	1	0	1	1	7
Desrosiers et al. (2005)	Yes	1	1	1	0	0	1	1	0	1	1	7
Hsieh et al. (2011)	Yes	1	1	1	0	0	1	1	1	1	1	8
Hsieh et al. (2017)	Yes	1	1	1	0	0	1	1	0	1	1	7
Hsu et al. (2019)	Yes	1	1	1	0	0	1	1	0	1	1	7
Hung et al. (2019)	Yes	1	0	0	0	0	1	1	1	1	1	6
Lee et al. (2017a)	Yes	1	0	1	0	0	1	1	0	1	1	6
Liao et al. (2012)	Yes	1	1	1	0	0	1	1	0	1	1	7
Lin et al. (2009)	Yes	1	1	1	0	0	1	1	0	1	1	7
Lin et al. (2010)	Yes	1	0	0	0	0	1	1	0	1	1	5
Lin et al. (2015)	Yes	1	0	1	0	0	1	1	0	1	1	6
Luft et al. (2004)	Yes	1	0	1	0	0	1	0	0	1	1	5
Lum et al. (2006)	Yes	1	0	0	0	0	1	1	0	1	1	5
Meng et al. (2018)	Yes	1	1	1	0	0	1	1	0	1	1	7
Morris et al. (2008)	Yes	1	1	1	0	0	1	1	1	1	1	8
Renner et al. (2020)	Yes	1	0	1	0	0	1	0	0	1	1	5
Samuelkamaleshkumar et al. (2014)	Yes	1	0	1	0	0	1	1	0	1	1	6
Sethy et al. (2018)	Yes	1	1	1	0	0	1	1	0	1	1	7
Van Delden et al. (2013)	Yes	1	1	1	0	0	1	1	0	1	1	7
Waller and Whitall (2008)	Yes	1	0	0	0	0	1	1	0	1	1	5
Whitall et al. (2011)	Yes	1	0	1	0	0	1	0	1	1	1	6
Wu et al. (2011)	Yes	1	0	1	0	0	1	1	0	1	1	6
Wu et al. (2013a)	Yes	1	1	1	0	0	1	0	0	1	1	6
Wu et al. (2013b)	Yes	1	0	1	0	0	1	1	1	1	1	7
Yang et al. (2012)	Yes	1	0	1	0	0	1	1	0	1	1	6

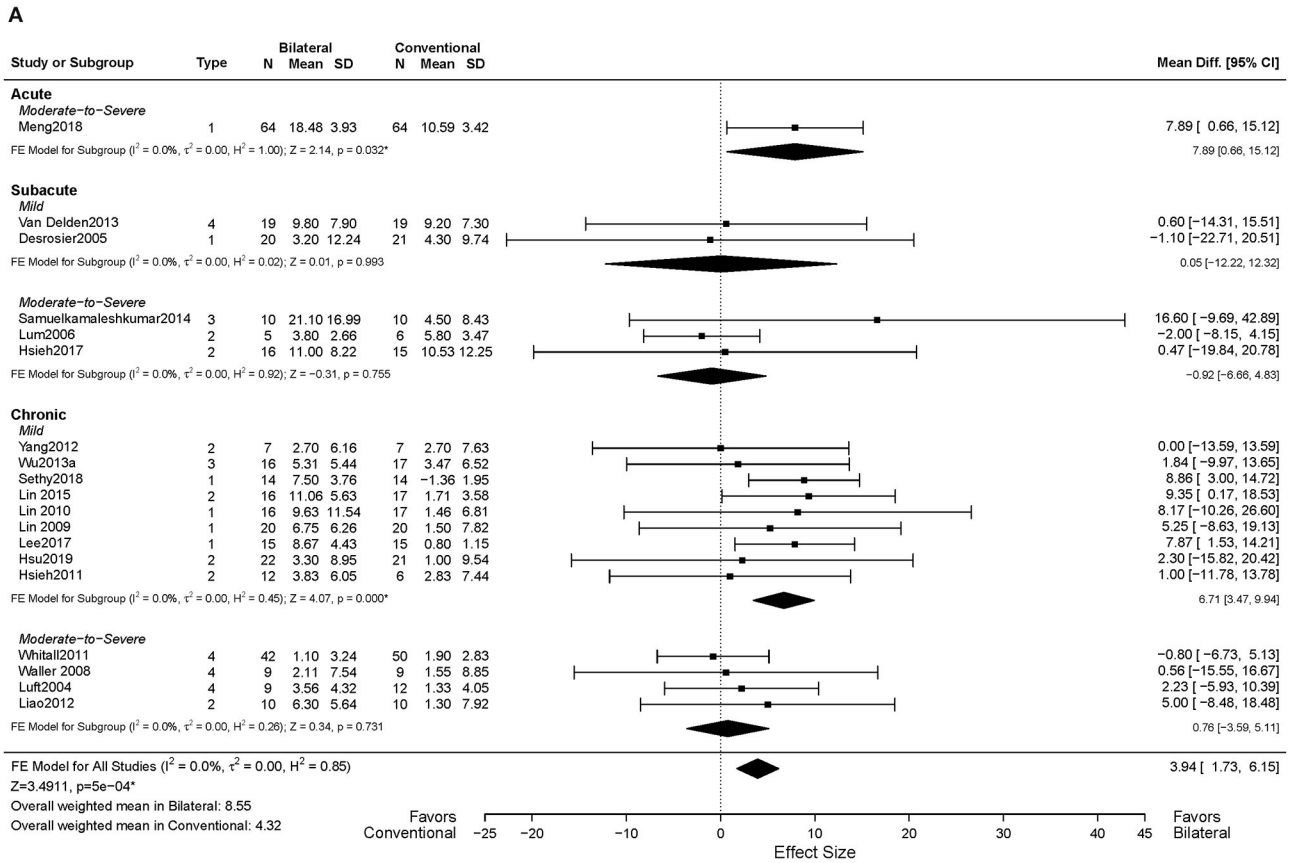


FIGURE 3 | Forest plots comparing the effects of **(A)** BAT vs. CT and **(B)** BAT vs. UAT on the upper extremity motor impairment. 1 = bilateral functional training Test (BFTT); 2 = bilateral robot-assisted training (BRAT); 3 = bilateral arm training with rhythmic auditory cueing (BATRAC); 4 = mirror therapy (MT); BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference; UAT, unilateral arm training; * indicates statistically significant ($p < 0.05$).

resulted in improved motor impairment but also UL functional performance. BFTT typically involves repetitions of various bilateral UL activities with complex interlimb coordination. Repeated attempts to achieve functional task goals associated with BFTT increase ipsilesional hemisphere excitability and help restore balanced IHI (Harris-Love et al., 2011), both of

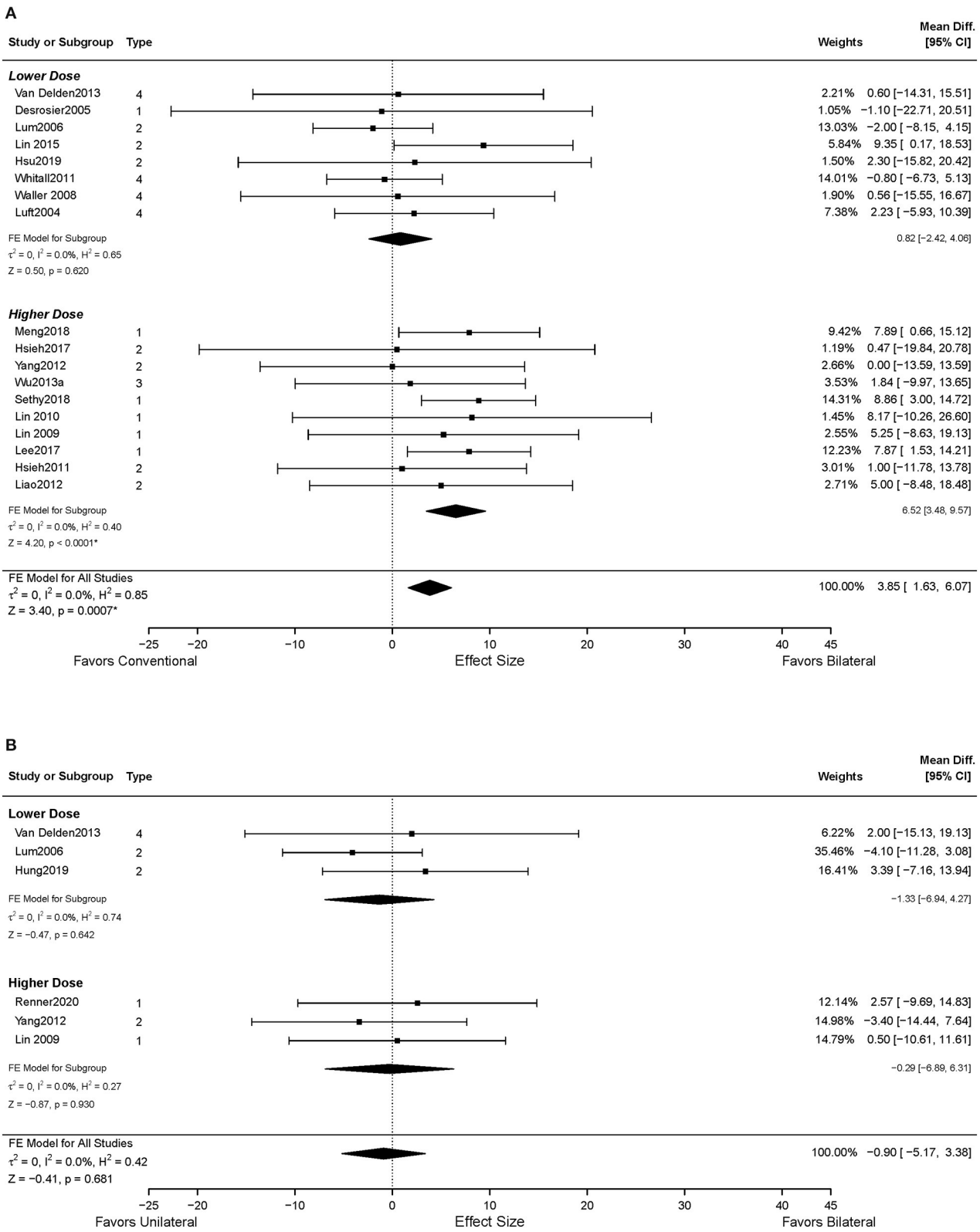


FIGURE 4 | The effects of intervention dose on the UE motor impairment. **(A)** BAT vs. CT; **(B)** BAT vs. UAT. 1 = bilateral functional training Test (BFTT); 2 = bilateral robot-assisted training (BRAT); 3 = bilateral arm training with rhythmic auditory cueing (BATRAC); 4 = mirror therapy (MT); BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference; UAT, unilateral arm training; * indicates statistically significant ($p < 0.05$).

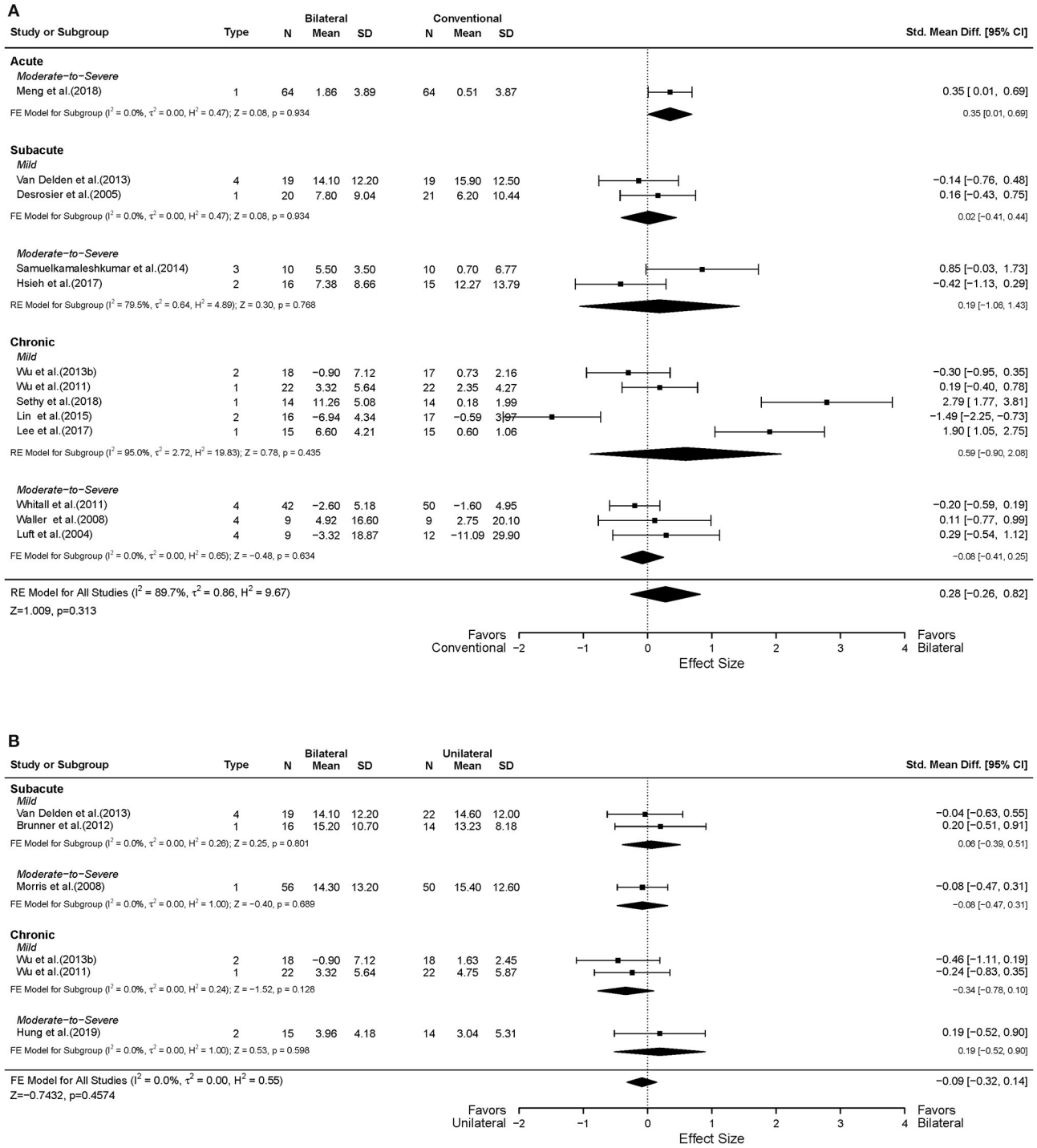


FIGURE 5 | Forest plots comparing the effects of **(A)** BAT vs. CT and **(B)** BAT vs. UAT on the upper extremity functional performance. 1 = bilateral functional training Test (BFTT); 2 = bilateral robot-assisted training (BRAT); 3 = bilateral arm training with rhythmic auditory cueing (BATRAC); 4 = mirror therapy (MT); BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference; UAT, unilateral arm training.

which are associated with better functional recovery post-stroke (Cicinelli et al., 2003; Koski et al., 2004; Murase et al., 2004; Calautti et al., 2007). Moreover, as previously stated in the literature, repetitive practice of functional tasks and asymmetrical movements involves a problem-solving process. It requires greater brain activation in the motor-related cortical areas that may facilitate learning-dependent neuroplasticity (Sadato et al., 1997; Guadagnoli and Lee, 2004; Timmermans et al., 2010;

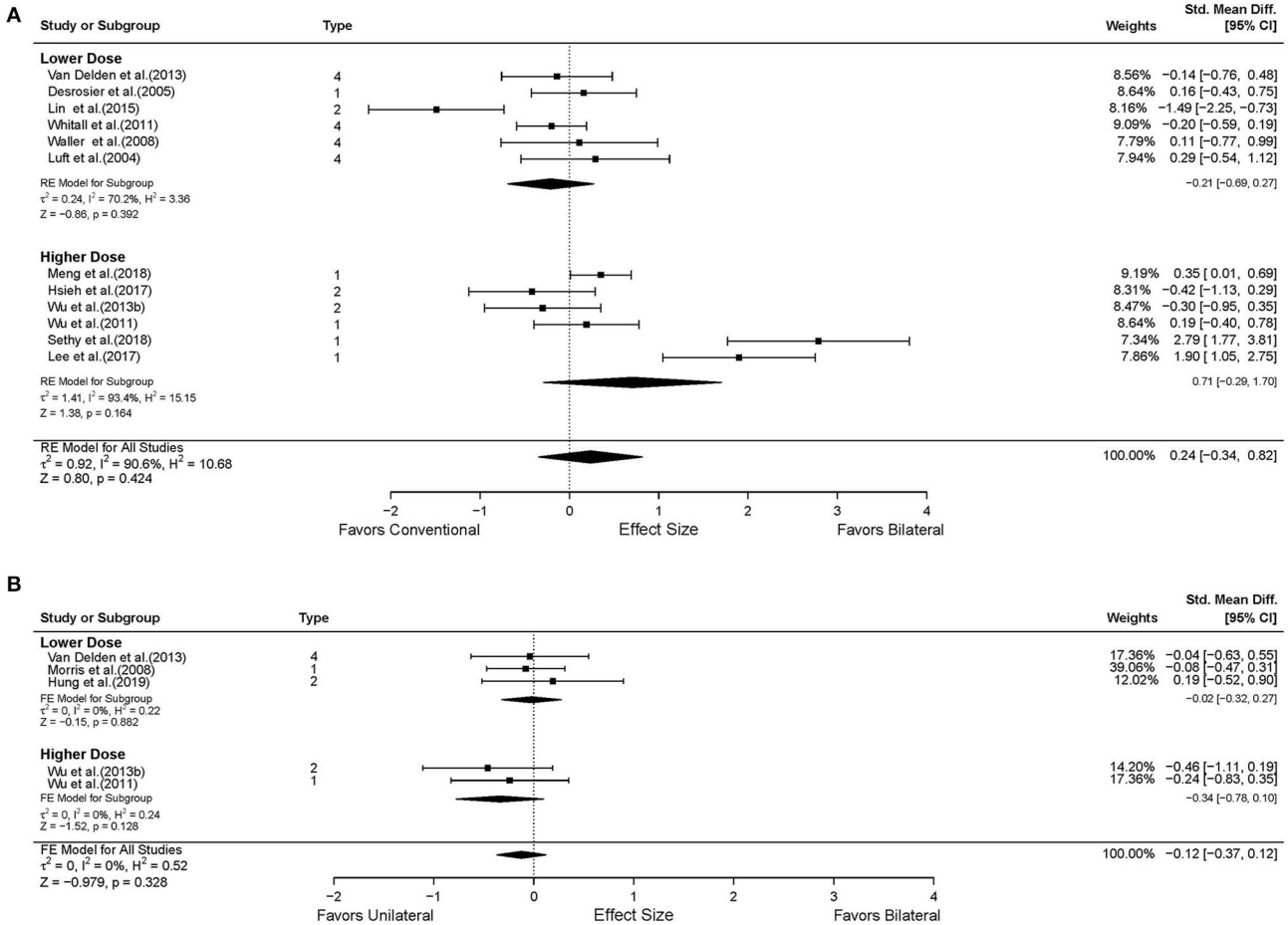


FIGURE 6 | The effects of intervention dose on the UE functional performance. **(A)** BAT vs. CT; **(B)** BAT vs. UAT. 1 = bilateral functional training Test (BFTT); 2 = bilateral robot-assisted training (BRAT); 3 = bilateral arm training with rhythmic auditory cueing (BATRAC); 4 = mirror therapy (MT); BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference; UAT, unilateral arm training.

Tazoe et al., 2013). Thus, increased activation in the ipsilesional hemisphere, restoration of normalized IHI, and promotion of learning-based neuroplasticity might explain the improvements in motor impairment and functional performance in BFTT. Interestingly, although functional performance was improved according to laboratory-based outcome measures, no significant differences were reported in patient-perceived functioning as measured by MAL. Previous evidence suggested that patients' perceptions of functional changes reflect rehabilitation outcomes as effectively as laboratory-based functional measures; however, the former may require larger sample sizes to overcome measurement errors (Simpson and Eng, 2013). Thus, the limited studies reporting MAL in the BFTT group ($n = 2$) might explain the differences between patient-perceived functional performance and other pooled functional outcomes in the current meta-analysis. Nevertheless, some practice tasks in the BFTT protocol and test items in the outcome measures are overlapped; the learning effects could not be ruled out in our study; thus, the results should be interpreted with caution. No significant improvements in motor impairments or functional performance were found with BRAT, BATRAC, or MT in this meta-analysis. Conversely, Cauraugh et al. (2010) reported that BATRAC and coupled bilateral training protocols are the most effective in improving motor capabilities. It is noted that most of the studies included in their review were non-RCTs with diverse comparison groups, and the outcome measures utilized to represent motor recovery were not under the same construction based on the ICF framework. Thus, these limitations might contribute to the observed discrepancy with our findings. Unlike BRAT and BATRAC, BFTT is low-cost, does not require the assistance of an external device, and contains more diversity of UL activities. Our findings encourage rehabilitation professionals to incorporate BFTT into their stroke motor recovery clinical practice.

In the subgroup analysis by phase and severity of the stroke, we found that compared to CT, BAT is the most efficacious in improving motor impairment when applied to subjects with mild UL paresis in the chronic phase of stroke. Although motor improvements were shown in the subacute stage, no differences between BAT and CT were detected.

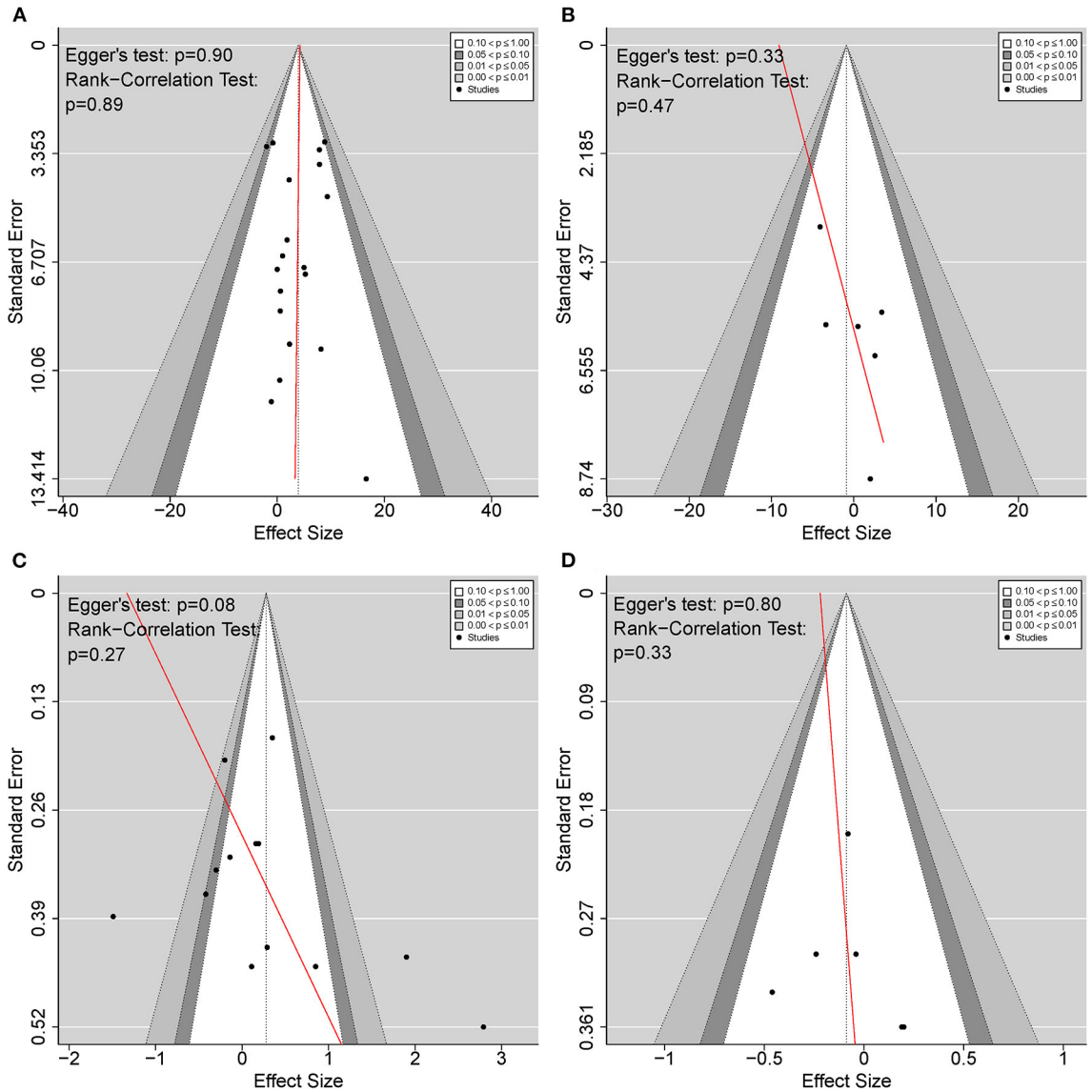


FIGURE 7 | Funnel plots detecting publication bias. **(A)** BAT vs. CT on the upper extremity motor impairment; **(B)** BAT vs. UAT on the upper extremity motor impairment; **(C)** BAT vs. CT on the upper extremity functional performance; **(D)** BAT vs. UAT on the upper extremity functional performance. BAT, bilateral arm training; CT, conventional therapy; UAT, unilateral arm training.

Previous research stated that the neurological recovery does not display a linear pattern, with most patients experiencing some degree of spontaneous recovery post-stroke (Kwakkel et al., 2006; Langhorne et al., 2011). Evidence has supported that the majority of spontaneous recovery of motor function occurs in the first three months post-stroke (Wade et al., 1983; Kwakkel et al., 2003; Kwakkel and Kollen, 2013). Thus, in the subacute stages of recovery, motor function gains may not be so closely related to rehabilitative interventions (BAT or CT) but rather to spontaneous neurological recovery, which might explain the observed equivalent effects of BAT and CT. Additionally, among the five studies with the largest effect size, four applied BFTT as a form of BAT intervention. In this phase, relatively high-functioning individuals with stroke usually show persistent deficits in fine motor dexterity, finger strength, and force control (Patel et al., 2020). Most BFTT protocols involve training that requires fine motor dexterity, such as buttoning, reaching and grasping small objects, tracing, etc. As stated above, higher levels of brain activation in the motor-related cortex have been reported when performing fine tasks with asymmetrical movements (Sadato et al., 1997; Tazoe et al., 2013). Therefore, interventions to improve fine motor dexterity to induce a greater brain activation for favorable effects of BAT in clinical practice may require in individuals with mild UL paresis in the chronic phase of stroke.

Additionally, although it is generally supported by previous studies that higher doses of exercise therapy are somewhat associated with improved motor outcome post-stroke (Kwakkel et al., 1997; Van Peppen et al., 2004; Cooke et al., 2010), no meta-analyses to date have investigated the impact of dose of BAT on motor recovery post-stroke. Based on the included 18 RCTs in the subgroup analysis, BAT significantly improved motor impairments compared with dose-matched CT in the higher dose group. However, BAT and CT did not demonstrate any differences in gaining motor function in the lower dose group. Our current finding indicated that the effects of BAT are dose-dependent and that the beneficial effects of BAT may only be seen with doses of intervention after stroke. Therefore, the intervention dose should be carefully considered when incorporating BAT into clinical practice.

Consistent with the findings of previous reviews (Coupar et al., 2010; Van Delden et al., 2012; Hatem et al., 2016; Lee et al., 2017b), our results indicated that BAT and UAT showed equivocal effects either in improving UL motor impairment or functional performance post-stroke in general. However, the present review did not support the reported superior effect of BAT in improving motor impairment post-stroke as indicated by FMA-UE compared to UAT in Chen et al.'s study (Chen et al., 2019). It should be noted that protocols such as conventional training and routine clinical rehabilitation program were categorized into the UAT group in their review, rendering it challenging to make an accurate comparison between BAT and UAT. In fact, most CT and dose-matched therapeutic exercises protocols were based on neurodevelopmental techniques or multidisciplinary rehabilitation programs consisting of compensatory practice or a small component of bilateral functional task training, both of which include using the unaffected arm. Our results also reported different findings when examining the efficacy of BAT in comparison to CT and UAT, respectively. Therefore, distinguishing CT and UAT into two different comparison groups is necessary for future studies to precisely capture the effects of different types of intervention.

Publication bias was not found in the included studies. However, a potential asymmetry appeared in **Figure 6C** with Egger's test reporting a p-value > 0.05 but < 0.1. To be extra cautious, we further investigated the three identified studies that primarily accounted for the asymmetry (Lin et al., 2015; Lee et al., 2017a; Sethy et al., 2018). A common problem across all three studies was the small sample size, insufficient power, and the effect size was either too high or too low, rendering the results less reliable. However, after excluding the above studies, the heterogeneity disappeared, and the sensitivity analysis results were consistent with the current results. Therefore, these three studies did not affect our findings of the current meta-analysis.

Limitations

The present systematic review and meta-analysis had some limitations. First, we only extracted data related to UL motor impairment and functional performance immediately after the intervention. The long-term efficacy of BAT compared to UAT and CT was not evaluated because the limited studies ($n = 9$) provided follow-up data and the period for follow-up data collection varied largely among these studies. The long-term effectiveness of BAT should be investigated in future studies since it holds significant value in clinical practice. Second, due to largely varied inclusion and exclusion criteria and outcome measures utilized in the included studies, categorizing the severity of UL paresis was difficult. According to our pre-defined criteria, the studies were classified into different severity levels based on the mean values of baseline outcome measures. However, the severity differences within each study may have been overlooked. Third, in contrast to the number of studies included in BAT vs. CT, the number of studies comparing the efficacy of BAT with UAT and subgroup analyses were relatively small, which makes the generalization of the results in BAT vs. UAT less reliable. Fourth, although the use of random-effects model, heterogeneity may still potentially interfere with the interpretation of BAT and CT findings on functional performance after stroke. Fifth, the inclusion criteria were limited to include studies published in English. Not having reviewed the Chinese literature systematically may have potentially missed relevant studies.

CONCLUSION

In conclusion, the present systematic review and meta-analysis suggested that BAT might be more beneficial than conventional therapy CT to improve upper limb (UL) motor impairment post-stroke. The current study also highlighted stroke chronicity, the severity of impairment, type of treatment, and intervention dose were critical factors in choosing an optimal rehabilitation program for restoring UE motor function. BAT might be especially more efficacious than CT in addressing motor impairment if a higher dose of intervention was applied or recruited patients in the chronic phase post-stroke had mild UL paresis. It is also suggested that BFTT may be a valuable form of BAT as it may facilitate both motor and functional recovery; therefore, due to its low cost, simplicity, and variety of activities, it is highly recommended to be integrated into stroke rehabilitation programs. BAT and UAT are generally equivalent in improving UL motor impairments and functional performance post-stroke. However, future comparisons based on a larger number of high-quality studies are needed to precisely capture the differential effects of UAT and BAT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

SC and YQ conceived the idea for the manuscript and participated in the study design. SC, YQ, and AL participated in the literature search and data acquisition. YQ and RC performed data and statistical analysis. SC, CB, AL, YQ, and

DX were involved in manuscript preparation, editing, and review. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.875794/full#supplementary-material

Appendix 1 | Search strategies for meta-analysis.

Supplementary Figure 1 | The effects of bilateral functional task training (BFTT) on the upper extremity **(A)** motor impairments and **(B)** functional performance. BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference. *indicates statistically significant ($p < 0.05$).

Supplementary Figure 2 | Forest plots comparing the effects of **(A)** BAT vs. CT and **(B)** BAT vs. UAT on the MAL-amount of use. 1 = bilateral functional training Test (BFTT); 2 = bilateral robot-assisted training (BRAT); 3 = bilateral arm training with rhythmic auditory cueing (BATRAC); 4 = mirror therapy (MT); BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference; UAT, unilateral arm training; *indicates statistically significant ($p < 0.05$).

Supplementary Figure 3 | Forest plots comparing the effects of **(A)** BAT vs. CT and **(B)** BAT vs. UAT on the MAL-quality of movement. 1 = bilateral functional training Test (BFTT); 2 = bilateral robot-assisted training (BRAT); 3 = bilateral arm training with rhythmic auditory cueing (BATRAC); 4 = mirror therapy (MT); BAT, bilateral arm training; CI, confidence interval; CT, conventional therapy; FE, fixed-effects; RE, random-effects; Std. Mean Diff., standardized mean difference; UAT, unilateral arm training; *indicates statistically significant ($p < 0.05$).

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Alterations of Lysine Acetylation Profile in Murine Skeletal Muscles Upon Exercise

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Objective: Regular exercise is a powerful tool that enhances skeletal muscle mass and strength. Lysine acetylation is an important post-translational modification (PTM) involved in a broad array of cellular functions. Skeletal muscle protein contains a considerable number of lysine-acetylated (Kac) sites, so we aimed to investigate the effects of exercise-induced lysine acetylation on skeletal muscle proteins.

Methods: We randomly divided 20 male C57BL/6 mice into exercise and control groups. After 6 weeks of treadmill exercise, a lysine acetylation proteomics analysis of the gastrocnemius muscles of mice was performed.

Results: A total of 2,254 lysine acetylation sites in 693 protein groups were identified, among which 1,916 sites in 528 proteins were quantified. The enrichment analysis suggested that protein acetylation could influence both structural and functional muscle protein properties. Moreover, molecular docking revealed that mimicking protein deacetylation primarily influenced the interaction between substrates and enzymes.

Conclusion: Exercise-induced lysine acetylation appears to be a crucial contributor to the alteration of skeletal muscle protein binding free energy, suggesting that its modulation is a potential approach for improving exercise performance.

Keywords: aerobic exercise, bioinformatics analysis, lysine acetylation, muscle, proteins

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INTRODUCTION

Protein lysine acetylation is an indispensable and conserved post-translational modification (PTM) that occurs in prokaryotic and eukaryotic cells (Xing and Poirier, 2012). Acetylation is involved in energy metabolism, gene expression, and cell signaling in both animals and bacteria (Xing and Poirier, 2012; Fukushima and Lopaschuk, 2016; Narita et al., 2019). In recent years, many studies have reported that lysine acetylation regulates a wide range of cellular functions in skeletal muscle (Lundby et al., 2012; Moresi et al., 2015; Tsuda et al., 2018). For example, histone acetylation in the nucleus controls MEF2- and MyoD-dependent transcription, which regulates myoblast differentiation and muscle homeostasis (Moresi et al., 2015). Tsuda found that protein acetylation

Abbreviations: Atp2a1, sarcoplasmic/endoplasmic reticulum calcium ATPase 1; Ckm, creatine kinase M-type; Ckmt2, creatine kinase S-type; DTT, dithiothreitol; FDR, false discovery rate; GO, Gene Ontology; Kac, lysine-acetylated; NAM, nicotinamide; PTM, post-translational modification; TFA, trifluoroacetic acid; TSA, trichostatin.

in the skeletal muscle mitochondria of mice was linked with intermediary metabolism (Tsuda et al., 2018). In addition, Lundby discovered a mass of lysine acetylation sites in 16 different tissues of rats, where the degree of lysine acetylation of muscle was highest (Lundby et al., 2012). Furthermore, they found that proteins involved in muscle contraction and enzymes generating ATP were all acetylated (Lundby et al., 2012), which provided a new and important clue that acetylation modification regulates the energy and metabolism of muscle.

The skeletal muscle is an organ for the maintenance of mobility, and exercise training in turn is known to positively affect the skeletal muscle system (Widegren et al., 2001; Russell et al., 2014; Nelson et al., 2020). Cellular stress triggered by exercise can alter the coordinated activity of acetyltransferases and deacetylases to regulate lysine acetylation (Marton et al., 2010; Menzies and Auwerx, 2013). Previous studies have found dynamic changes in histone acetylation and mitochondrial protein acetylation in the skeletal muscle during exercise (McGee et al., 2009; Overmyer et al., 2015). In our previous study, aerobic training or Scriptaid dramatically improved the exercise performance of mice, including endurance, grip strength, and citrate synthase activity (Huang et al., 2020). These changes were also accompanied by an increase in titin lysine acetylation in gastrocnemius tissue, which was postulated to function as a mediator to regulate muscle protein function at the molecular level (Huang et al., 2020). Given the important role of skeletal muscle in exercise or physical activities (Gan et al., 2018), we speculate that exercise-induced lysine acetylation in muscle may be an important factor mediating exercise performance.

The purpose of this study was to profile protein lysine acetylation in the skeletal muscle of exercise and control groups using different proteomic technologies and bioinformatics tools. Our preliminary data demonstrated widespread protein lysine acetylation in the skeletal muscle of mice after exercise. Subsequent proteomic studies confirmed that the different acetylation patterns of muscle proteins were closely related to their structure and function of muscle. Then, molecular docking data suggested that lysine acetylation modification could change the binding of substrates and enzymes, ultimately influencing enzyme activity and energy transformation. Taken together, exercise-induced lysine acetylation might play an important role in muscle structural and functional proteins properties, indicating the crucial role of protein acetylation in skeletal muscle physiology.

MATERIALS AND METHODS

Animals

Twenty 5-week-old male C57BL/6 mice were purchased from Beijing HFK Bioscience Co., (Beijing, China) in this study. The animal study was approved by the Tianjin Medical University Animal Care and Use Committee (approval number: SYXK-2019-0004) under the guidelines of the Chinese Academy of Sciences. The mice were housed in a temperature-controlled room (22 ± 2°C) with a 12-h light/dark cycle (light on from 08:00 to 20:00) and free access to food and water. All animals were allowed to acclimatize to the laboratory environment for 1 week.

At the beginning of the experiment, the mice were randomly divided into two groups: a sedentary control group (n = 10) and an exercise group (n = 10). Mice in the control group were kept sedentary for 6 weeks. Mice in the exercise group were familiarized with the treadmill 5 days before the experiment by exercising them for 1 h at 8 m/min; each day thereafter, the speed was increased by 2 m/min until the speed has reached 12 m/min. Then, mice in the exercise group underwent 6 weeks of treadmill exercise for 5 days per week (1 h/day) on a 0% grade at the intensity of 75% VO2max (12 m/min) as previously described (Fernando et al., 1993). During the 1-h session, the mice ran on the treadmill continuously without rest intervals throughout the whole 60-min time. By the end of the 6-week exercise, the body weight of the mice was determined with an ImpediVET analyzer (ImpediMed). Forty-eight hours after the last bout of exercise, mice were fasted for 14 h and then anesthetized with isoflurane. The gastrocnemius was dissected and weighed, frozen in liquid nitrogen, and then stored at −80°C for later analysis.

Protein Extraction, Trypsin Digestion, and TMT Labeling

Each skeletal muscle sample was ground with liquid nitrogen and transferred to a 5-mL centrifuge tube. Then, the samples were sonicated three times on ice using a high-intensity ultrasonic processor (Scientz, Ningbo, China) in lysis buffer [8 M urea, 10 mM dithiothreitol (DTT), 3 μM trichostatin (TSA), 50 mM nicotinamide (NAM), and 1% protease inhibitor cocktail], followed by centrifugation at 12,000 × g at 4°C for 10 min. After that, we discarded the supernatant and washed the remaining precipitate three times. The protein was redissolved in 8 M urea, and its concentration was determined with a BCA kit.

For trypsin digestion, 5 mM DTT was added to implement the reduction of proteins for 30 min at 56°C, and 11 mM iodoacetamide was added to perform alkylation of proteins for 15 min at room temperature in darkness. Then, the protein sample was diluted by adding 100 mM TEAB to a urea concentration of less than 2 M. In the first digestion, trypsin was added at a 1:50 trypsin-to-protein mass ratio, and this digestion was performed at 37°C overnight. For the second digestion, trypsin was added at a mass ratio of 1:100 trypsin/protein and digested for 4 h at 37°C.

After trypsin digestion, the peptide was desalted by a Strata X C18 SPE column (Phenomenex) and vacuum-dried. The peptide was reconstituted in 0.5 M TEAB and processed according to the manufacturer's protocol for the TMT kit/iTRAQ kit. In brief, one unit of TMT/iTRAQ reagent was thawed and reconstituted in acetonitrile. The peptide mixtures were then incubated for 2 h at room temperature and pooled, desalted, and dried by vacuum centrifugation.

HPLC Fractionation and Affinity Enrichment

The TMT-labeled samples were fractionated by high-pH reverse-phase HPLC using a Thermo Betasil C18 column (5 μm particles,

10 mm ID, and 250 mm length). In brief, peptides were first separated with a gradient of 8–32% acetonitrile (pH 9.0) over 60 min into 60 fractions. Finally, the peptides were combined and dried by vacuum centrifugation.

Immunoprecipitation was performed to enrich modified peptides. IP buffer solution (100 mM NaCl, 1 mM EDTA, 50 mM Tris–HCl, 0.5% NP-40, pH 8.0) was added to dissolve tryptic peptides. Then, the liquid supernatant was incubated with prewashed antibody beads (acetyl-lysine antibody beads lot number PTM1001, PTM Biolabs Inc., China) at 4°C overnight with gentle shaking. The beads were washed four times with IP buffer solution and two times with double-distilled H_2O. Then, we eluted bound peptides with 0.1% trifluoroacetic acid (TFA) and vacuum-dried them. For LC-MS/MS analysis, the obtained peptides were desalted with C18 ZipTips (Millipore) in accordance with the manufacturer's instructions.

LC-MS/MS Analysis and Data Research

Peptides were dissolved in solvent A (0.1% formic acid) and directly loaded onto a homemade reversed-phase analytical column (15 cm length, 75 μm i.d.). The gradient comprised an increase from 6 to 23% solvent B (0.1% formic acid in 98% acetonitrile) over 26 min, from 23 to 35% for 8 min, increasing to 80% in 3 min and then holding at 80% for the last 3 min, all at a constant flow rate of 400 nL/min on an EASY-nLC 1000 UPLC system. The peptides were subjected to an NSI source followed by tandem mass spectrometry (MS/MS) in a Q Exactive^{TM} Plus (Thermo) coupled online to the UPLC. The applied electrospray voltage was 2.0 kV. The m/z scan range was 350–1,800 for the full scan, and intact peptides were detected in the Orbitrap at a resolution of 70,000. The peptides were then selected for MS/MS using an NCE setting of 28. Ion fragments were detected in the Orbitrap at a resolution of 17,500 (m/z 200). A data-dependent procedure alternated between one MS scan followed by 20 MS/MS scans with 15.0 s dynamic exclusion. Automatic gain control was used to prevent overfilling of the ion trap, and 5e4 ions were accumulated for the generation of MS/MS spectra. The fixed first mass was set as 100 m/z.

Then, we processed the LC-MS/MS data with the MaxQuant search engine (v.1.5.2.8). Tandem mass spectra were searched against the UniProt database concatenated with the reverse decoy database. Trypsin/P was specified as the cleavage enzyme allowing up to four missing cleavages. In the first search and the main search, the mass tolerances for precursor ions were set as 20 and 5 ppm, respectively. Meanwhile, the mass tolerance for fragment ions was set as 0.02 Da. Carbamidomethylation on Cys was specified as a fixed modification, while acetylation modification and oxidation on Met were variable modifications. The false discovery rate (FDR) and the minimum score for modified peptides were adjusted to <1% and >40, respectively. The retrieval parameter settings and quality control of mass spectrometry are shown in **Supplementary Material**.

Bioinformatics Analyses

For subsequent bioinformatics analysis, normalization with protein quantification to remove the effect of protein expression on modification abundance was performed. Protein acetylation was identified on the basis of the following criteria: *t*-test with p-value < 0.05, fold change > 1.2 or < 0.83, which were consistent with previous studies (Ren et al., 2013; Wu et al., 2016; Huang et al., 2019; Yu et al., 2021). For hierarchical clustering based on Kac sites of proteins associated with muscle function, we collated all the categories obtained after enrichment along with their *P*-values. The Gene Ontology (GO) annotation proteome was derived from the UniProt-GOA database,[1] and the proteins were classified by GO annotation based on three categories: biological process, cellular component, and molecular function. For each category, a two-tailed Fisher's exact test was employed to test the enrichment of the identified modified protein against all proteins from the species database. The GO terms with a corrected p-value < 0.05 were considered significant. All differentially expressed modified proteins were searched against the STRING database[2] for protein–protein interactions (PPIs). Only interactions between the proteins showing acetylation variance were selected, thereby excluding external candidates. The PPI networks for the identified acetylated proteins were analyzed by Cytoscape 3.9.0 software using interaction data.

Molecular Docking

AutoDock 4.2 software, an excellent tool to recognize docking affinity between individual ligands and specific proteins (Seeliger and de Groot, 2010; Rizvi et al., 2013), was utilized in all the docking experiments. Protein receptors were taken from UniProt[3] in PDB format, and then, specific-site lysine-to-arginine (K-to-R) changes were made in PyMOL 2.5.1, mimicking deacetylated lysine residues. Ligands were obtained from PubChem[4] in SDF format and converted to PDB format by Open Babel 3.1.1. After preparing proteins and ligands, we ran Autogrid to calculate the affinity maps, and the size of the grid box was kept large enough to at least allow the ligand to rotate freely. Then, the docking of the protein and ligand was performed. Grid and docking parameter files were given as GPF files and DPF files in AutoDock. Finally, we used Chimaera 1.15 and Notepad^{++} 7.9.5 to read the results.

RNA Extraction and Quantitative Real-Time RT-PCR

Total RNA was extracted from gastrocnemius muscle and reverse-transcribed to cDNA using TransScript One-Step gDNA Removal and cDNA Synthesis SuperMix (TransGen Biotech). The synthesized cDNA was used for PCR with specific cycles. The primer sequences were as follows: MyHC I, 5′-GCCTGGGCTTACCTCTCTATCAC-3′ (forward), 5′-CTTCTCAGACTTCCGCAGGAA-3′ (reverse); MyHC IIa, 5′-CAGCTGCACCTTCTCGTTTG-3′ (forward), 5′-CCCGAAAACGGCCATCT-3′ (reverse); MyHC IIb, 5′-CAATCAGGAACCTTCGGAACAC-3′ (forward), 5′-GTCCTGGCCTCTGAGAGCAT-3′ (reverse); MyHC IIx, 5′-GGACCCACGGTCGAAGTTG-3′ (forward), 5′-CCCGAAAACGGCCATCT-3′ (reverse); and GAPDH, 5′-GCACAGTCAAGGC

[1] http://www.ebi.ac.uk/GOA
[2] https://www.string-db.org
[3] https://www.uniprot.org
[4] https://pubchem.ncbi.nlm.nih.gov

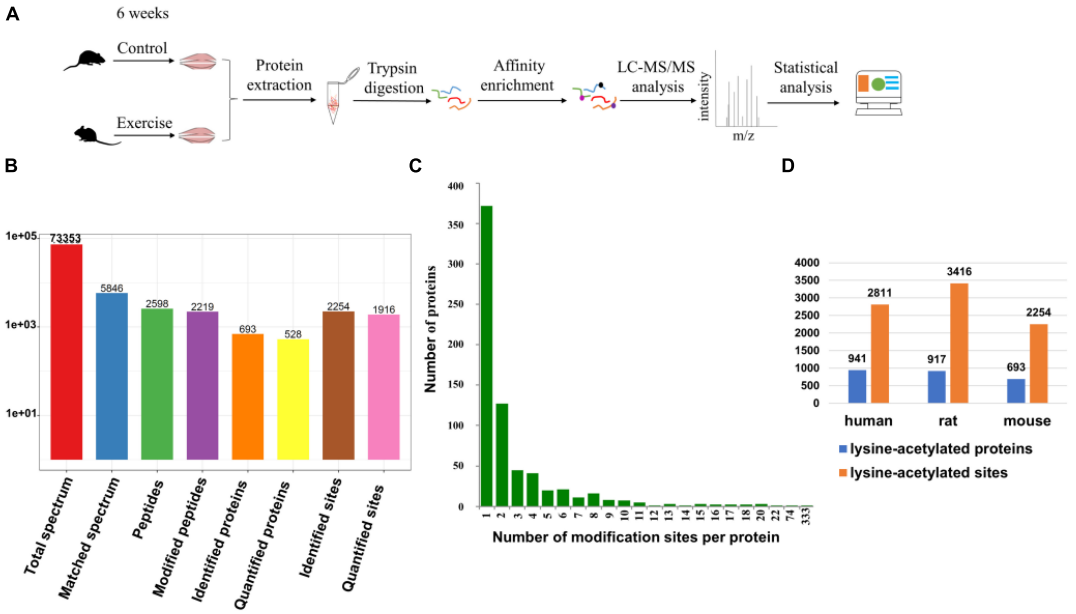
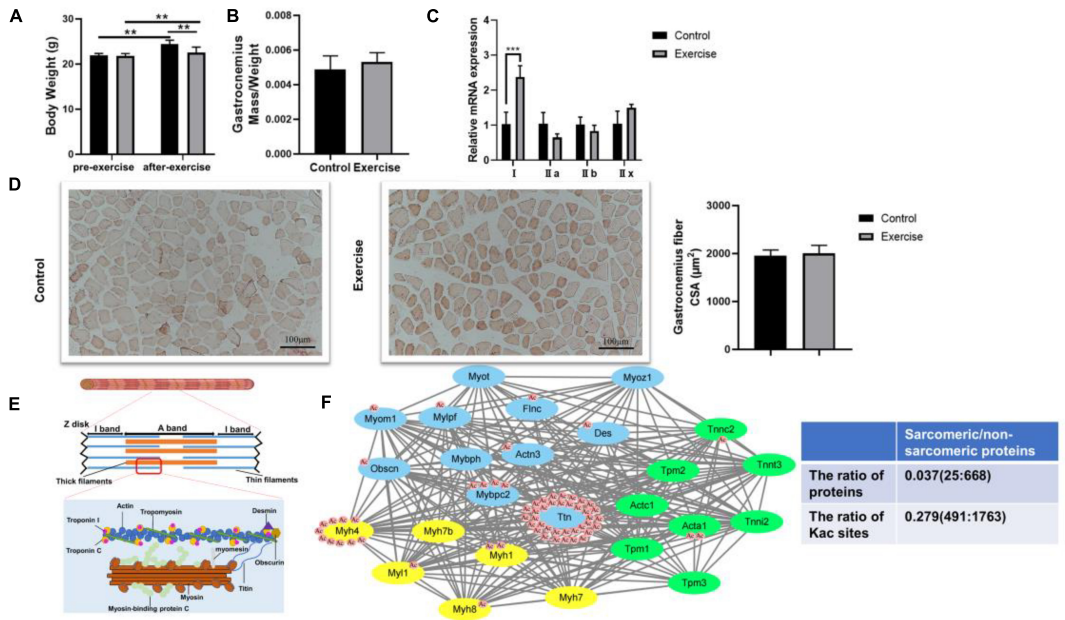


FIGURE 1 | Identification of lysine-acetylated proteins and sites in the gastrocnemius muscle. **(A)** Schematic of the LC/MS-based quantitative acetylproteomic strategy. **(B)** The basic statistical figure for MS results. **(C)** Distribution of acetylated proteins based on the number of acetylated peptides. **(D)** Comparison of our proteomic study with Lundby's (Lundby et al., 2012). The figure shows the number of lysine-acetylated proteins and sites identified in muscle from three different species.



	Sarcomeric/non-sarcomeric proteins
The ratio of proteins	0.037(25:668)
The ratio of Kac sites	0.279(491:1763)

FIGURE 2 | Effect of aerobic exercise on the muscle of mice. **(A)** Body weight of mice was examined 48 h after treadmill exercise. $^{**}P < 0.01$. **(B)** Gastrocnemius muscle mass was measured and normalized to body weight. **(C)** The gastrocnemius muscle is mainly composed of MyHC IIb and MyHC IIx fiber. Compared with the control group, MyHC I was upregulated in the gastrocnemius of trained mice. Values are means ± SEM; $n = 3$ in each group; $^{***}P < 0.001$. **(D)** Representative Oil Red O staining of muscle sections and analysis of gastrocnemius fiber CSA in the control and exercise groups. **(E)** Schematic representation of muscle sarcomeres. Only the main acetylated/deacetylated proteins in the sarcomere and the basic contractile unit of skeletal muscle are shown. **(F)** Lysine sites of sarcomeric proteins were identified in the mouse skeletal muscle, and a protein–protein interaction network was visualized with STRING. Each green node represents proteins expressed in thin filaments, each yellow node represents proteins expressed in thick filaments, and each blue node represents sarcomere-associated proteins. Some nodes are surrounded by red circles, which represent lysine acetylation induced by exercise. The table shows the comparison of sarcomeric proteins and non-sarcomeric proteins.

CGAGAAT-3′ (forward), 5′-GCCTTCTCCATGGTGGTGAA-3′ (reverse).

PCR amplification was performed using the Roche LightCycler 480 real-time PCR system (Roche Life Science, United States) and the PerfectStart Uni RT-qPCR Kit (TransGen Biotech) according to the manufacturers' instructions. The relative expression levels of the target genes were determined using the $2^{-\Delta\Delta CT}$ method.

Oil Red O Staining

Gastrocnemius samples were dissected and fixed for 24 h in 10% neutral buffered formalin. Then, we embedded tissues with paraffin and sliced them into 7-μm serial horizontal sections. The gastrocnemius muscle sections were stained with Oil Red O, and the cross-sectional area (CSA) of the muscle fiber was assessed under light microscopy (AF 6000, Leica). Five images per animal (n = 3) and at least 60 muscle cells per image were used in the statistical analysis (ImageJ software). The total average area was used to determine the CSA per square micrometer.

Statistical Analysis

The data are presented as the means ± SEM, and the differences were analyzed using Student's t-test or two-way ANOVA. All data were considered significantly different when $P < 0.05$. We used SPSS to make statistical comparisons.

RESULTS

Identification of Lysine Acetylation Proteins and Sites in the Gastrocnemius Muscle

In this study, gastrocnemius muscle samples from the two groups were mapped to identify the lysine acetylation sites of proteins, and the workflow of the experimental procedures is shown in **Figure 1A**. To verify the initial mass spectrometry data, we detected the lengths of all the obtained peptides and the quality errors. The lengths of most peptides, ranging between 7 and 20, matched the lengths of the tryptic peptides (**Supplementary Figure 1**), indicating that the sample preparation met the standard for proteomics analysis. The average mass error for all the identified peptides was nearly zero, and first-order mass errors were less than 10 ppm, meaning that the mass accuracy of the MS data met the requirement (**Supplementary Figure 2**). During the identification, a total of 73,353 secondary spectra were obtained by mass spectrometry. Then, we used mass spectrometry secondary spectra to search against protein theory data. The available efficiency was 5,846, the spectrum utilization rate was 8.0%, and the peptides were resolved into 2,598 peptides and 2,219 acetylated peptides. In addition, 2,254 acetylation sites were identified in 693 proteins, including 1,916 quantified sites in 528 quantified proteins (**Figure 1B**). Among these proteins, 372 proteins (53.70%) had one Kac site and 108 proteins (15.58%) contained five or more Kac sites (**Figure 1C**). There were 15 proteins (2.16%) that contained more than 15 Kac sites (**Figure 1C**). Interestingly, those proteins that contained more than 15 Kac sites were mainly distributed in sarcomeres, especially titin (333 sites) (Huang et al., 2020) and myosin-4 (74 sites). On average, there were 3.25 Kac modification sites per protein (**Figure 1D**) in the gastrocnemius of mice. In another independent experiment, Lundby et al. (2012) found 3,416 sites from 917 proteins in the rat muscle and 2,811 sites from 941 proteins in the human muscle, where the average numbers of acetylation sites per protein were 3.73 and 2.99, respectively (**Figure 1D**). Comparison analysis of these data of three species indicated that protein acetylation widely exists in the skeletal muscle of mice, rats, and humans.

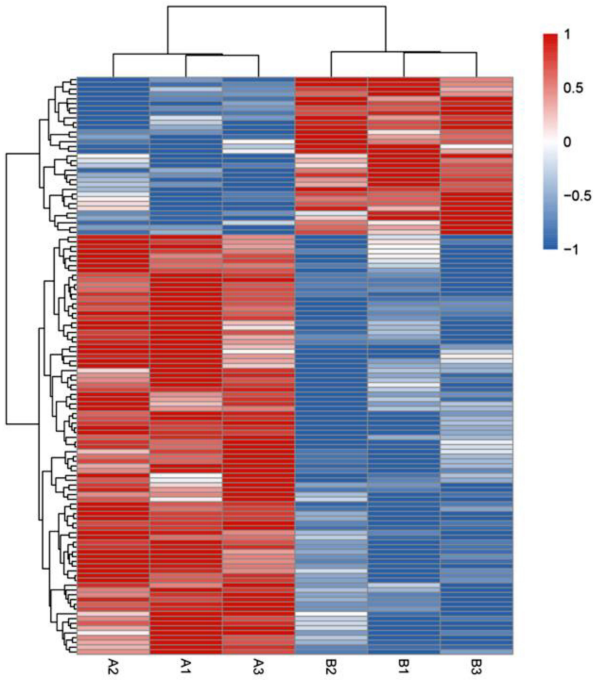


FIGURE 3 | Heatmap showing hierarchical cluster analysis of lysine-acetylated proteins in control groups (A1–A3) and exercise groups (B1–B3). The Euclidean distance was used as the distance metric, and the clustering criteria were complete. The heatmap includes an accompanying supplemental table with the list of the proteins used and their fold change (supplemental "DEP heatmap").

Effect of Aerobic Exercise on the Muscle of Mice

Previous studies have shown that physical activity significantly influences muscle features such as muscle mass, muscle force, and muscle fiber type (Kanzleiter et al., 2015; Bacurau et al., 2016; Liu et al., 2021). Different from endurance exercise, which can boost muscle strength, aerobic exercise plays a vital role in increasing the aerobic ability of the muscle. Consistent with these findings, aerobic exercise significantly restrained the body weight increase in the exercise group compared with the control group (**Figure 2A**). Although gastrocnemius mass and the CSA of gastrocnemius fiber in the exercise group did not change when compared with the control group (**Figures 2B,D**), we observed

TABLE 1 | The expression of sarcomeric proteins in gastrocnemius muscle.

Identified protein relative content	Control group (n = 3)			Exercise group (n = 3)			Ratio	P-value
Obscurin	1.011	0.999	1.009	1.003	1.011	0.986	0.994	4.85E-01
Alpha-actinin-3	1.005	0.986	1.019	1.05	1.039	1.043	1.041	1.65E-02
Myosin light chain 1/3, skeletal muscle isoform	1.105	1.077	1.119	1.017	1.035	1.035	0.938	8.88E-03
Myosin-8	1.05	1.026	1.021	1.093	1.093	1.112	1.065	3.74E-03
Myosin-7B	1.12	0.995	1.047	1.049	1.085	1.099	1.022	5.65E-01
Myosin-7	0.966	0.97	0.95	1.1	1.082	1.076	1.129	1.95E-04
Troponin C, skeletal muscle	0.98	1.008	0.988	1.093	1.084	1.024	1.076	3.06E-02
Tropomyosin alpha-1	0.925	0.949	0.972	1.016	1.045	1.024	1.084	8.22E-03
Tropomyosin alpha-3	0.98	0.943	0.942	0.98	0.956	1.032	1.036	2.50E-01
Tropomyosin beta chain	/							
Troponin I, fast skeletal muscle	0.94	0.909	0.944	0.945	0.939	0.956	1.017	2.67E-01
Troponin T, fast skeletal muscle	0.994	0.937	0.95	0.962	0.957	1.01	1.017	5.40E-01
Desmin	1.1	1.081	1.103	1.036	1.049	1.037	0.951	2.50E-03
Actin, alpha skeletal muscle	1.063	1.095	1.063	1.1	1.103	1.1	1.025	1.26E-01
Actin, alpha cardiac muscle 1	/							
Myosin regulatory light chain 2, skeletal muscle isoform	1.079	1.084	1.089	1.034	1.045	1.052	0.963	2.62E-03
Myosin-4	1.046	1.031	1.035	1.082	1.078	1.095	1.046	2.16E-03
Myosin-1	1.06	1.059	1.074	1.054	1.067	1.062	0.997	6.17E-01
Myosin-binding protein C, fast-type	1.132	1.124	1.136	1.126	1.101	1.114	0.985	1.03E-01
Myomesin-1	1.076	1.046	1.072	1.034	1.043	1.042	0.977	6.32E-02
Myozenin-1	0.85	0.913	0.897	0.923	0.979	0.974	1.081	5.22E-02
Myotilin	1.012	1.018	0.99	1.077	1.056	1.059	1.057	6.12E-03
Myosin-binding protein H	1.106	1.093	1.154	1.189	1.156	1.139	1.039	1.38E-01
Filamin-C	1.008	1.01	1.012	0.996	1	1.009	0.992	1.07E-01

Protein (peptides) relative content was measured in muscle samples of mice from the control group and exercise group, n = 3 mice/group. Student's t-test was used in SPSS; there were no significant differences between the two groups. Data about titin were shown in Huang's study (Huang et al., 2020). Although tropomyosin beta chain and actin alpha cardiac muscle 1 were identified, we did not get its quantitative information. Information about acetylated lysine sites of protein in muscle sarcomere. Modified sequence: identified peptide sequence marked with modification sites' localization probabilities and amino acid types of all sites is K (Lysine). Protein accession: the identifier of protein in UniProt. Positions: modification site localization in protein. PEP: the maximal posterior error probability for peptides. Ratio: the acetylation fold-change ratio of identified lysine sites. Score: the −10 logarithmic probability of observing the given number of matches or more by chance. Student's t-test was used in SPSS. Data about titin were shown in Huang's study (Huang et al., 2020).

that the percentage of MyHC I was increased (**Figure 2C**), suggesting a potential change of "fast" to "slow" muscle fiber. To investigate the molecular mechanism of exercise on muscle functional properties, we focused on lysine acetylation of muscle proteins. Muscle contraction relies on the correct assembly of myofibrils (Wei et al., 2018), which shows alternating light and dark bands under a microscope corresponding to I-bands and A-bands, respectively (**Figure 2E**). Myofibrils are composed of tandem arrays of basic functional contractile units called the sarcomeres (Hwang and Sykes, 2015; Wei et al., 2018), which are highly ordered structures composed of thin filaments (actin, tropomyosin, and troponin), thick filaments (myosin), and their associated proteins (such as titin, myomesin, and desmin) (**Figure 2E**). The sarcomeric function is determined by sarcomeric protein isoform expression and PTMs (Hamdani et al., 2008; Russell and Solis, 2021). In our results, sarcomeric protein levels in gastrocnemius muscle showed no change after exercise (**Table 1**), but their acetylation levels did change (**Table 2**). Sarcomeric proteins containing Kac sites were mapped to the protein network database, and the global network graph of these interactions is shown in **Figure 2F**. Exercise can induce acetylation changes at different sites in these proteins, especially in titin and myosin-4. During muscle contraction, the acetylation levels of 36 Kac sites in titin were upregulated or downregulated, including 10 Kac sites in myosin-4 (**Figure 2F**). Detailed information on these statistically significant acetylated lysine sites is shown in **Table 2** and in Huang's study (Huang et al., 2020). Although the number of sarcomeric proteins identified in the muscle was much less than that in non-sarcomeric proteins, Kac sites of sarcomeric proteins obviously are more abundant (**Figure 2F**), especially in titin, myh4, and mybpc2, 333, 74, and 17 Kac sites, respectively (**Figure 1C**). Thus, lysine acetylation is a crucial PTM of muscle sarcomeric proteins during the exercise process.

Enrichment Analysis of the Lysine Acetylation Level of Proteins

To further test the role of lysine acetylation in regulating muscle biological functions, we performed an enrichment analysis. Differential lysine acetylation levels of proteins related to muscle contraction are shown in **Figure 3**. The site-specific heatmap analysis revealed a clear boundary between the control group and the exercise group, indicating that exercise induced significant changes in the acetylation levels of these proteins,

TABLE 2 | Alterations of lysine acetylation sites in proteins of muscle sarcomere during exercise.

Protein accession	Position	Protein description	Gene name	PEP	Score	Modified sequence	Ratio	*P*-value
A2AAJ9	941	Obscurin	Obscn	3.08E-26	126.07	ADAGEYSCEAGGQK(1)LSFR	1.221	3.10E-02
O88990	411	Alpha-actinin-3	Actn3	2.77E-06	93.345	LQHLAEK(1)FQQK	0.818	3.07E-02
P05977	31	Myosin light chain 1/3, skeletal muscle isoform	Myl1	1.89E-06	111.79	EEK(1)IDLSAIK	0.7	5.92E-03
P13542	568	Myosin-8	Myh8	0.00434743	90.15	SNNFQK(1)PK	1.232	3.66E-02
P20801	85	Troponin C, skeletal muscle	Tnnc2	0.029179	51.066	QMK(1)EDAK	0.787	4.80E-03
P31001	43	Desmin	Des	0.00134246	65.467	AGFGTK(1)GSSSSMTSR	2.096	7.66E-03
P68134	330	Actin, alpha skeletal muscle	Acta1	0.00851098	66.056	IK(1)IIAPPER	0.71	1.55E-02
P68134	293	Actin, alpha skeletal muscle	Acta1	4.69E-21	88.239	K(1)DLYANNVMSGGTTMYPGIADR	1.203	7.03E-04
P97457	166	Myosin regulatory light chain 2, skeletal muscle isoform	Mylpf	8.53E-65	178.51	NICYVITHGDAK(1)DQE	0.613	2.82E-03
Q5SX39	955	Myosin-4	Myh4	3.19E-41	168.3	LEDECSELK(1)K	0.769	8.04E-03
Q5SX39	453	Myosin-4	Myh4	4.61E-06	94.547	INQQLDTK(1)QPR	0.813	4.84E-03
Q5SX39	1448	Myosin-4	Myh4	2.62E-09	111.12	SNAACAALDK(1)K	0.796	5.14E-03
Q5SX39	761	Myosin-4	Myh4	2.30E-48	149.73	LLGSIDIDHTQYK(1)FGHTK	0.82	4.18E-02
Q5SX39	914	Myosin-4	Myh4	0.00226055	100.88	CDQLIK(1)TK	1.423	2.32E-03
Q5SX39	59	Myosin-4	Myh4	0.0342729	56.404	EGGK(1)VTAK	1.548	4.31E-02
Q5SX39	1420	Myosin-4	Myh4	0.00346135	96.342	CASLEK(1)TK	1.422	1.65E-02
Q5SX39	972	Myosin-4	Myh4	0.00392593	93.096	EK(1)HATENK	1.384	2.84E-03
Q5SX39	562	Myosin-4	Myh4	6.48E-49	152.37	LYEQHLGK(1)SNNFQKPK	0.826	7.96E-03
Q5SX39	1758	Myosin-4	Myh4	0.0170478	86.136	NAEEK(1)AK	1.311	5.27E-03
Q5SX40	1451	Myosin-1	Myh1	1.01E-13	131.66	TNAACAALDK(1)K	0.75	4.97E-04
Q5SX40	1535	Myosin-1	Myh1	0.00205512	83.206	IHELEK(1)IK	1.3	7.56E-05
Q5XKE0	387	Myosin-binding protein C, fast-type	Mybpc2	0.030363	71.379	EDSYK(1)AR	0.612	7.40E-04
Q5XKE0	88	Myosin-binding protein C, fast-type	Mybpc2	0.00599854	69.864	GK(1)WQELGSK	0.698	3.18E-03
Q5XKE0	304	Myosin-binding protein C, fast-type	Mybpc2	9.19E-05	112.13	YVFENVGK(1)K	0.563	2.76E-03
Q5XKE0	1017	Myosin-binding protein C, fast-type	Mybpc2	1.21E-30	125.45	IFSENICGLSDSPGVSK(1)NTAR	1.642	2.17E-02
Q62234	237	Myomesin-1	Myom1	1.29E-14	127.02	K(1)TLEETQTYHGK	0.771	4.41E-02
Q8VHX6	735	Filamin-C	Flnc	6.84E-07	112.94	CSYVPTK(1)PIK	1.335	2.26E-03

*The annotations are the same as above (**Table 1**). There were no significant differences between the two groups. Information about acetylated lysine sites of three enzymes. The annotations are the same as above (**Table 2**).*

which could be upregulated or downregulated (**Figure 3**). GO enrichment was performed to better understand the specific role of lysine-acetylated proteins in muscle. A bubble plot of GO enrichment of proteins corresponding to lysine acetylation sites is shown in **Figures 4A–C**. GO enrichment of biological processes revealed significant protein enrichment in terms related to skeletal muscle adaptation, striated muscle contraction, regulation of muscle contraction, muscle cell development, and others ($p < 0.05$; **Figure 4A**). The results of molecular function analysis also showed that proteins related to titin binding, muscle alpha-actinin binding, and calcium ion binding were significantly enriched ($p < 0.05$; **Figure 4B**). Cellular component analysis indicated that acetylated proteins were enriched in the muscle myosin complex, I-band, sarcomere, myofibril, and others ($p < 0.05$; **Figure 4C**). In addition, a PPI network containing 26 nodes and 67 edges was constructed (**Figure 4D**). In this study, the PPI network was constructed of acetylated proteins identified as nodes and connected with each other. Many proteins in the PPI network contained numerous Kac sites. In summary, these data suggest that exercise-induced lysine acetylation is critical in muscle protein contraction and structure.

Molecular Docking Analysis of Enzymes

Extensive reversible lysine acetylation of metabolic enzymes occurs in both eukaryotes and prokaryotes (Zhao et al., 2010; Nakayasu et al., 2017), which could influence energy balance. Muscle is a high-energy-consuming tissue, so lysine acetylation will control its energy homeostasis (Menzies and Auwerx,

2013). In our study, we identified multiple Kac sites on three enzymes involved in muscle contraction, namely, creatine kinase M-type (Ckm), creatine kinase S-type (Ckmt2), and sarcoplasmic/endoplasmic reticulum calcium ATPase 1 (Atp2a1). There were 22, 8, and 20 Kac sites in Ckm, Ckmt2, and Atp2a1, respectively. There was no alteration in the protein abundance levels of the three enzymes (**Table 3**), whereas their acetylation levels did change. Interestingly, all Kac sites of the three proteins were deacetylated rather than acetylated. After exercise, the numbers of deacetylated sites of Ckm, Ckmt2, and Atp2a1 were 5, 1, and 10, respectively (**Figure 5A** and **Table 4**). Molecular docking is a well-established approach for predicting binding conformations of ligands in active or binding sites of relevant protein targets (Bafna et al., 2020). The catalytic consequences of K9, K11, K25, K247, and K365 deacetylation in Ckm, as well as Ckmt2 and Atp2a1, were evaluated using lysine-to-arginine (K-to-R) mutants *in vitro*, which mimic deacetylated lysine residues. The docking results showed that deacetylation significantly changed the substrate binding energy and binding regions (**Figures 5B,C**). For instance, the binding energy between Ckm and creatine was −5.57 kcal/mol, whereas the binding energy between Ckm^{K9R} and creatine was −5.21 kcal/mol, and the binding active site changed as well. These data suggest that deacetylation impeded two-molecule interactions and then influenced enzyme activity.

In short, a particular map of lysine acetylation sites from the skeletal muscle of mice was produced by high-resolution tandem mass spectrometry. Our results revealed that exercise-induced acetylation may play a crucial role in skeletal muscle protein binding free energy, at least to some extent.

DISCUSSION

In our study, the body weights of the mice in these two groups all increased significantly, and exercise slowed the rate of weight gain (**Figure 2A**). We did not find a significant difference in the gastrocnemius mass or the CSA of the gastrocnemius fiber between the two groups (**Figures 2B,D**), but the expression levels of MyHC genes were changed, suggesting that the aerobic training program may be able to switch the fiber from the fast- to the slow-twitch type (**Figure 2C**). While the results of Oil Red O staining revealed that there was little effect of aerobic exercise on the CSA of muscle, exercise obviously boosted lipid deposition in muscle compared with the sedentary group (**Figure 2D**), suggesting that physical training increases the energy reserves of muscle. Exercise remains beneficial for the musculoskeletal system, which is a very complex physiological process that requires an appropriate regulatory network (Egan and Zierath, 2013; Hoffman et al., 2015). Protein lysine acetylation/deacetylation in skeletal muscle could be a mediator of this network in mice during exercise. We used the acetylproteomics approach to quantify and map acetyl sites after aerobic exercise in mice. Lundby found that the muscle was the most acetylation-accessible tissue in 16 rat tissues (Lundby et al., 2012), and we also identified large numbers of

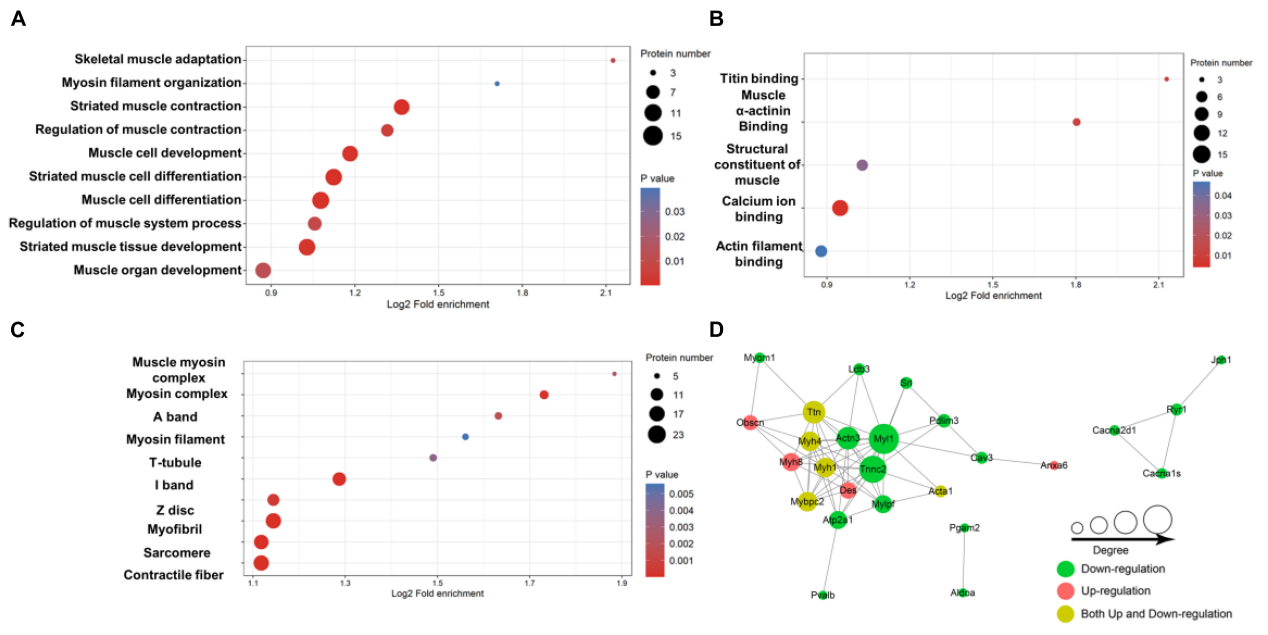
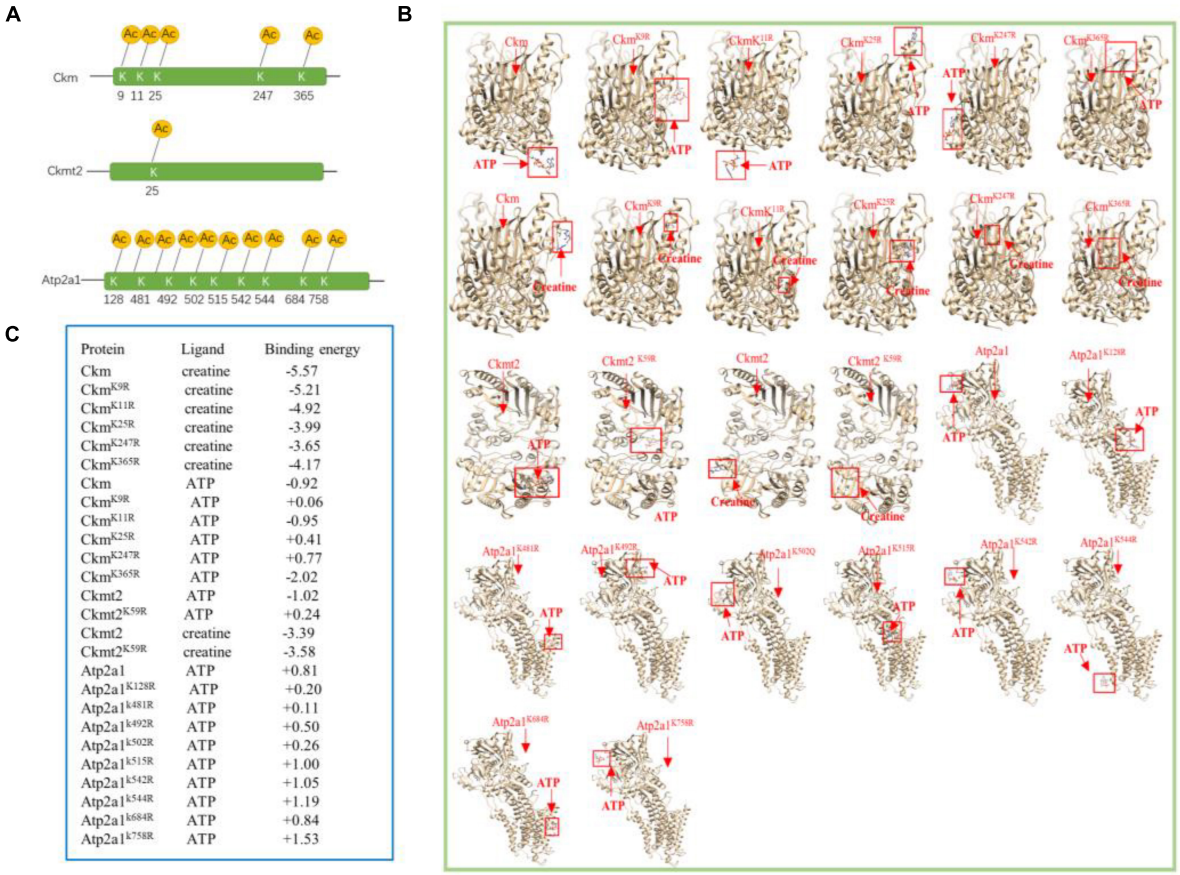


FIGURE 4 | Enrichment analysis of the lysine-acetylated proteins. Enrichment based on GO annotation in terms of biological process **(A)**, molecular function **(B)**, and cellular component **(C)**. **(D)** Protein–protein interaction network for acetylated proteins. The nodes represent proteins, and their colors represent the upregulation or downregulation of these proteins; green means downregulation (change ratio < 0.83), red means upregulation (change ratio > 1.20), and yellow means both upregulation and downregulation. The size of each node represents the number of directed edges.

TABLE 3 | The expression of three enzymes in the gastrocnemius muscle.

Identified protein relative content	Control group (n = 3)			Exercise group (n = 3)			Ratio	P-value
Creatine kinase M-type 0.976	0.973	0.976	0.976	0.977	0.982	0.991	1.009	1.19E-01
Creatine kinase S-type, mitochondrial	0.978	0.969	0.963	1.021	1.009	1.032	1.052	3.00E-03
Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	0.986	0.983	0.999	0.969	0.993	0.98	1.043	5.72E-03



Protein	Ligand	Binding energy
Ckm	creatine	-5.57
Ckm^{K9R}	creatine	-5.21
Ckm^{K11R}	creatine	-4.92
Ckm^{K25R}	creatine	-3.99
Ckm^{K247R}	creatine	-3.65
Ckm^{K365R}	creatine	-4.17
Ckm	ATP	-0.92
Ckm^{K9R}	ATP	+0.06
Ckm^{K11R}	ATP	-0.95
Ckm^{K25R}	ATP	+0.41
Ckm^{K247R}	ATP	+0.77
Ckm^{K365R}	ATP	-2.02
Ckmt2	ATP	-1.02
Ckmt2^{K59R}	ATP	+0.24
Ckmt2	creatine	-3.39
Ckmt2^{K59R}	creatine	-3.58
Atp2a1	ATP	+0.81
Atp2a1^{K128R}	ATP	+0.20
Atp2a1^{k481R}	ATP	+0.11
Atp2a1^{k492R}	ATP	+0.50
Atp2a1^{k502R}	ATP	+0.26
Atp2a1^{k515R}	ATP	+1.00
Atp2a1^{k542R}	ATP	+1.05
Atp2a1^{k544R}	ATP	+1.19
Atp2a1^{k684R}	ATP	+0.84
Atp2a1^{k758R}	ATP	+1.53

FIGURE 5 | Molecular docking analysis of enzymes. **(A)** Localizations of the multiacetylated sites in three enzymes that were identified with 5, 1, and 9 acetylated lysine residues. **(B)** AutoDock 4.2 was used to predict docking interactions of proteins and ligands. The binding positions are highlighted by red boxes. Ckm and Ckmt2 both have two ligands, and Atp2a1 has one ligand. **(C)** Docking results of the three enzymes.

Kac sites in mouse muscle proteins (**Figure 1B**). By comparing these two studies, we found that protein acetylation is widespread regardless of species, and the abundance levels of protein lysine acetylation in human, rat, and mouse muscle tissue are similar (**Figure 1D**). Interestingly, dramatic changes in the acetylation status of numerous cytoplasmic proteins were observed, but the expression levels of KATs and HDACs detected in our proteomic analysis were similar in the two groups (**Supplementary Table 1**). It is possible that other KATs and HDACs we did not identify in the mass spectrometry are involved in the progress.

In our results, more than half of the proteins (53.70%) had one Kac site and only 15 proteins (2.16%) contained >15 Kac sites (**Figure 1C**). The importance of acetylation modification is well appreciated in gene regulation, but its regulatory implications extend beyond nuclear histone modifications. We found that sarcomeric proteins accounted for a huge percentage of numerous-site proteins, especially titin (333 sites) and myosin-4 (74 sites). Protein acetylation occurs widely in sarcomeres (Gupta et al., 2008; Samant et al., 2015; Lin et al., 2016) and significantly influences sarcomere function. Gupta provided evidence that the reversible acetylation of sarcomeres plays a role in the regulation of myofilament contractile activity (Gupta et al., 2008). In our study, there were 25 sarcomeric proteins containing Kac sites, which were distributed on thin filaments, thick filaments, or *Z*-disks. After exercise, the Kac sites of 14 proteins were acetylated or deacetylated (**Figure 2F**). Thus, exercise triggered protein acetylation or deacetylation in sarcomeres, especially in titin and myosin-4. More importantly, the mean

TABLE 4 | Deacetylated sites of Ckm, Ckmt2, and Atp2a1 after exercise.

Protein accession	Position	Protein description	Gene name	PEP	Score	Modified sequence	Ratio	*P*-value
P07310	365	Creatine kinase M-type	Ckm	0.000163	113.62	LMVEMEK(1)K	0.758	4.20E-03
P07310	11	Creatine kinase M-type	Ckm	3.58E-80	189.87	FK(1)LNYKPQEEYPDLSK	0.536	6.21E-04
P07310	25	Creatine kinase M-type	Ckm	2.20E-123	205.96	LNYKPQEEYPDLSK(1)HNNHMAK	0.759	2.95E-04
P07310	9	Creatine kinase M-type	Ckm	4.46E-34	164.64	PFGNTHNK(1)FK	0.649	2.84E-03
P07310	247	Creatine kinase M-type	Ckm	0.000281	104.22	GGNMK(1)EVFRR	0.747	4.52E-03
Q6P8J7	59	Creatine kinase S-type, mitochondrial	Ckmt2	4.68E-25	123.4	K(1)HNNCMAECLTPTIYAK	0.751	6.17E-05
Q8R429	128	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	0.001152	65.179	EYEPEMGK(1)VYR	0.558	1.46E-03
Q8R429	542	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	0.000138	85.813	VPLTGPVK(1)EK	0.665	1.24E-03
Q8R429	492	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	2.71E-09	119.25	K(1)SMSVYCSPAK	0.651	2.04E-03
Q8R429	502	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	1.03E-15	117.48	SMSVYCSPAK(1)SSR	0.582	1.81E-04
Q8R429	758	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	5.39E-10	121.41	AIYNNMK(1)QFIR	0.813	1.08E-02
Q8R429	684	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	0.000925	105.98	VEPSHK(1)SK	0.671	4.82E-04
Q8R429	481	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	3.25E-05	113.61	K(1)EFTLEFSR	0.757	2.64E-03
Q8R429	544	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	0.00178	102.52	EK(1)IMSVIK	0.767	1.16E-02
Q8R429	515	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	Atp2a1	8.72E-13	106.14	MFVK(1)GAPEGVIDR	0.68	1.36E-03

lysine acetylation level of sarcomeric proteins was higher than that of their non-sarcomeric counterparts (**Figure 2F**). These findings suggested that acetylation modification plays an important role in sarcomeric proteins, which might contribute to muscle contraction. However, the effects of sarcomeric protein acetylation on myofilament contractile activity during exercise remain unclear.

To further understand the potential effect of protein acetylation on muscle structure and function, we performed a bioinformatics analysis. The site-specific heatmap showed that exercise-regulated lysine-acetylated proteins are involved in muscle contraction (**Figure 3**). According to GO enrichment analysis, the results classification for biological process, molecular function, and cellular component highlighted that these acetylated/deacetylated proteins correspond to different muscle structures or functions (**Figures 4A–C**). In addition, the protein network analysis indicated that the physiological interactions of these proteins identified in GO enrichment were likely to contribute to their cooperation in muscle (**Figure 4D**).

Since lysine residues of enzymes are always present around their active sites, protein acetylation influences the catalytic activity of enzymes involved in cellular metabolism (Hernandez-Saavedra et al., 2019; Wang et al., 2019; Min et al., 2020). Lundby reported that multiple enzymes involved in ATP generation are hyperacetylated in skeletal muscle mitochondria (Lundby et al., 2012), and protein acetylation of some enzymes was thought to be involved in impaired fatty acid oxidation and exercise intolerance (Tsuda et al., 2018). In addition, the enzymatic activity of many mitochondrial protein bacterial orthologs is regulated by lysine acetylation (Wang et al., 2010). Interestingly, we found that there were three enzymes directly linked with muscle energy regulation, namely, Ckm, Ckmt2, and Atp2a1. Then, we used AutoDock software to simulate the effects of lysine acetylation on these metabolic enzymes. Compared with wild-type enzymes, mimetic mutants appear to have different substrate-binding energies and binding positions (**Figures 5B,C**). Consistent with a previous study (Walker et al., 2021), acetylation of Ckm disrupted salt bridge formations between Ckm monomers, including K9, K11, and K25, in this study. In addition, Gorski found that acetylation at K492 played a critical role in regulating SERCA2a (sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a) activity in mice (Gorski et al., 2019). Therefore, the deacetylation of these lysine sites was likely to affect the catalytic reaction of Ckm, Ckmt2, and Atp2a1, which may be associated with the impact of acetylation on the dimer formation of Ckm and Ckmt2 (Walker et al., 2021), although site-specific contributions were indistinct.

It is widely accepted that aerobic exercise can increase exercise capacity, such as muscle oxidative capacity, muscle contraction, and muscle endurance (Overmyer et al., 2015; de Oliveira et al., 2017; Huang et al., 2020). Furthermore, muscle protein acetylation levels also significantly changed after 6 weeks of aerobic exercise. Previously, Gupta reported that reversible acetylation of sarcomeric proteins played a role in regulating myofilament contractile activity (Gupta et al., 2008). Similarly, lysine acetylation of cardiac myosin heavy chain isoforms modulates their enzymatic and motor activity (Samant et al., 2015). Some researchers have also demonstrated that altering the muscle structure and function by acetylation of existing sarcomeric proteins can optimize energy usage (Russell and Solis, 2021). With these observations, it is reasonable to speculate that lysine acetylation is associated with alterations in muscle protein binding free energy during exercise.

We showed that exercise changes muscle protein acetylation in mice, which serves as a reference for further Kac studies in human. In these future clinical and mechanistic studies, verification of the correlation between protein acetylation and skeletal muscle physiology or exercise performance should be taken into account, which will improve our understanding of the molecular response to regular exercise. Ongoing acetylproteomics studies will provide a theoretical basis for exercise prescription. In addition, novel approaches targeting the acetylation of skeletal muscle proteins, especially sarcomeric proteins, would provide important clues for the development of

an effective intervention for muscle atrophy with aging. In any case, these results from our study still need to be confirmed in clinical trials.

However, there are some limitations to this study. First, the effects of acetylation on the mechanical parameters of sarcomere proteins remain unknown. Then, we did not perform the same experiments on female mice or old mice, which may not be replicated because sex and age are also important biological variables. In addition, other exercise parameters (such as session length, frequency, and intensity) were not tested in our study. Finally, the impact of deacetylation on enzyme activity requires further experimental verification.

CONCLUSION

Our data strongly suggested that the regulatory scope of exercise-induced lysine acetylation is widespread in skeletal muscle proteins. Exploring the mechanisms of exercise-induced acetylation changes in skeletal muscle can help develop scientific exercise prescriptions. Overall, skeletal muscle exhibits extensive metabolic and energetic remodeling during exercise, and exercise-induced lysine acetylation appears to be a crucial mediator of skeletal muscle proteins.

DATA AVAILABILITY STATEMENT

The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium (http://proteomecentral.proteomexchange.org) via the iProX partner repository (Ma et al., 2019) with the dataset identifier PXD032660.

ETHICS STATEMENT

The animal study was reviewed and approved by the SYXK-2019-0004.

AUTHOR CONTRIBUTIONS

DL prepared the figures and drafted the manuscript. LF and YN edited and revised the manuscript. CC, SH, SL, LF, and YN approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Exercise for Osteoarthritis: A Literature Review of Pathology and Mechanism

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Osteoarthritis (OA) has a very high incidence worldwide and has become a very common joint disease in the elderly. Currently, the treatment methods for OA include surgery, drug therapy, and exercise therapy. In recent years, the treatment of certain diseases by exercise has received increasing research and attention. Proper exercise can improve the physiological function of various organs of the body. At present, the treatment of OA is usually symptomatic. Limited methods are available for the treatment of OA according to its pathogenesis, and effective intervention has not been developed to slow down the progress of OA from the molecular level. Only by clarifying the mechanism of exercise treatment of OA and the influence of different exercise intensities on OA patients can we choose the appropriate exercise prescription to prevent and treat OA. This review mainly expounds the mechanism that exercise alleviates the pathological changes of OA by affecting the degradation of the ECM, apoptosis, inflammatory response, autophagy, and changes of ncRNA, and summarizes the effects of different exercise types on OA patients. Finally, it is found that different exercise types, exercise intensity, exercise time and exercise frequency have different effects on OA patients. At the same time, suitable exercise prescriptions are recommended for OA patients.

Keywords: osteoarthritis, exercise, pathology, mechanism, therapy

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INTRODUCTION

Osteoarthritis (OA) has a very high incidence worldwide, and it is strongly associated with age (van Saase et al., 1989). Most of the patients with OA are aged over 60. With the aging of the population, the disease has become a common joint disease today. Heredity, hormones, diet, obesity, smoking, and drinking can lead to OA (Felson et al., 1997). Its early symptoms mainly include pain and joint stiffness, and later secondary changes such as muscle atrophy and joint contracture occur (Bennell et al., 2012). Therefore, we advocate early intervention for patients with OA to prevent further deterioration of the disease. However, the disease treatment still encounters many shortcomings, and further research and exploration are needed. Currently, the treatment methods for OA include surgery, drug therapy, and exercise therapy (Spahn et al., 2013). In recent years, the treatment of certain diseases by exercise has received increasing research and attention. Exercise is an economical and effective treatment (Ettinger et al., 1997). Proper exercise can improve the physiological function of various organs of the body and improve the overall morphology of the body (Benedetti et al., 2018). In addition, exercise can also relieve pain

(Belavy et al., 2021; Zheng et al., 2021; Peng et al., 2022; Wu et al., 2022). For OA patients, ladder treatment is generally adopted, starting with basic treatment. If it is ineffective, drug therapy or surgery can be used, and exercise therapy is one of the basic treatment methods. The effects of different exercise types on OA have been widely studied.

At present, the treatment of OA is usually symptomatic. Limited methods are available for the treatment of OA according to its pathogenesis. Exercise can alleviate OA at a molecular level. Only by clarifying the mechanism of exercise treatment of OA and the influence of different exercise intensities on normal joints and OA patients can we choose the appropriate exercise prescription to prevent and treat OA. This review mainly expounds the mechanism that exercise alleviates the pathological changes of OA by affecting the degradation of the ECM, apoptosis, inflammatory response, autophagy, and changes of ncRNA, and summarizes the effects of different exercise types on OA patients. Finally, it is found that different exercise types, exercise intensity, exercise time and exercise frequency have different effects on OA patients. At the same time, suitable exercise prescriptions are recommended for OA patients.

PATHOLOGICAL CHANGE MECHANISM OF OSTEOARTHRITIS

For OA patients, the integrity of the entire joint tissue is damaged, including articular cartilage, subchondral bone, and synovial membrane (Loeser et al., 2012). Articular cartilage is mainly composed of the extracellular matrix (ECM), consisting of water, collagen, proteoglycans, mucopolysaccharides, type II collagen, and chondrocytes (Luo et al., 2017). With the presence of prolonged, excessive mechanical stimulation of the body, articular cartilage will suffer. In the early stage of articular cartilage injury, the concentration of growth factors in the ECM increases as chondrocytes gather in the damaged area, resulting in transient cell proliferation and ECM synthesis (Suri and Walsh, 2012). As the damage worsens, the blood supply to the articular cartilage worsens to the point that the cartilage does not have adequate access to nutrients. This condition results in cartilage cell apoptosis, ECM synthesis, and the disappearance of the articular cartilage degeneration (Eyre, 2004). The two bones constantly rub, resulting in joint pain, swelling, and function limitation. Its continuous development causes OA (Rim et al., 2020). Subchondral bone includes subchondral cancellous bone and cortical plates. X-ray and Magnetic Resonance Imaging (MRI) diagnosis can reveal the abnormal remodeling of subchondral bone and a series of changes in bonemorphology, such as bone spurs, osteophytes, and wear in OA patients (Braun and Gold, 2012). This sequence of changes may be caused by an imbalance in the production and destruction of osteoblasts and osteoclasts (Burr and Gallant, 2012). This morphological change of subchondral bone may also cause damage to the articular cartilage overlying it. Patients with OA have an exceptionally high probability of suffering from synovitis, and this condition is related to the pain and function of the knee joint during OA development (Sowers et al., 2011). The synovial membrane is the connective tissue membrane covered on the inner surface of the joint capsule, which can produce synovial fluid to reduce joint friction and the loss of cartilage and ensure the metabolism and nutrition supply of joint cartilage (Pap et al., 2020). Synovial cells mainly include synovial macrophages, fibroblast-like synovial cells, and mesenchymal stem cells. The macrophages can engulf the damaged tissue. When synovitis occurs in the body, the macrophages decompose to produce inflammatory factors, and the generation and degradation of cartilage matrix are in dynamic balance under normal conditions. Inflammatory mediators can destroy this balance, decompose chondrocytes, and aggravate synovitis (Da et al., 2007). Fibroblast-like synovial cells can produce hyaluronic acid, which is an essential component of joint synovial fluid. During OA progression, the content of hyaluronic acid is remarkably reduced, resulting in the reduction of joint function and damage to the integrity of the joint surface (Scanzello and Goldring, 2012).

Above all, articular cartilage, synovium, and subchondral bone abnormalities are the main pathological changes of OA (Valdes and Spector, 2010). Considering that articular cartilage receives nutrients through synovial fluid, articular cartilage in patients with synovitis may undergo pathological changes. Moreover, the increase of macrophages in patients with synovitis may cause subchondral bones in OA to form osteophytes. Ayral et al. (2005) evaluated the correlation between synovitis and the severity of cartilage structure damage in OA patients through a one-year multicenter longitudinal study involving 422 patients. After arthroscopic and pain scoring, they found that compared with patients with normal synovial membrane, patients with synovitis had more severe articular cartilage lesions. The degree of deterioration after 1 year was statistically different. Yusup et al. (2015) studied 40 patients with knee OA and scored the structures such as joint cartilage, subchondral bone, and synovial membrane by using 3.0-T MRI and found that synovitis mainly occurred in the early and late stage of OA patients. The destruction of joint cartilage and a series of changes in subchondral bone could induce synovitis, and a strong correlation was observed among the three parameters. Some studies (Norrdin et al., 1998) use horse as a model to study the pathological changes of OA, in which the morphological changes of subchondral bone occur before articular cartilage injury. In other studies (Brandt et al., 1991), dog is used as the model to investigate the pathological changes of OA, in which the morphological changes of early subchondral bone coincided with an articular cartilage injury. Generally, the pathological mechanisms of articular cartilage, synovium, and subchondral bone in OA mainly include the degradation of ECM, cell proliferation, cell apoptosis, inflammatory reaction, changes of non-coding RNA, and methylation (Mobasheri et al., 2017) (**Figure 1**).

Degradation of Extracellular Matrix

The ECM is a complex network of large molecules such as polysaccharides and proteins around cells. This structure and special cells make up the cartilage (Theocharis et al., 2019). Many diseases are associated with changes in the composition and properties of ECM, such as OA. In healthy articular cartilage, the synthesis and metabolism of ECM should always maintain

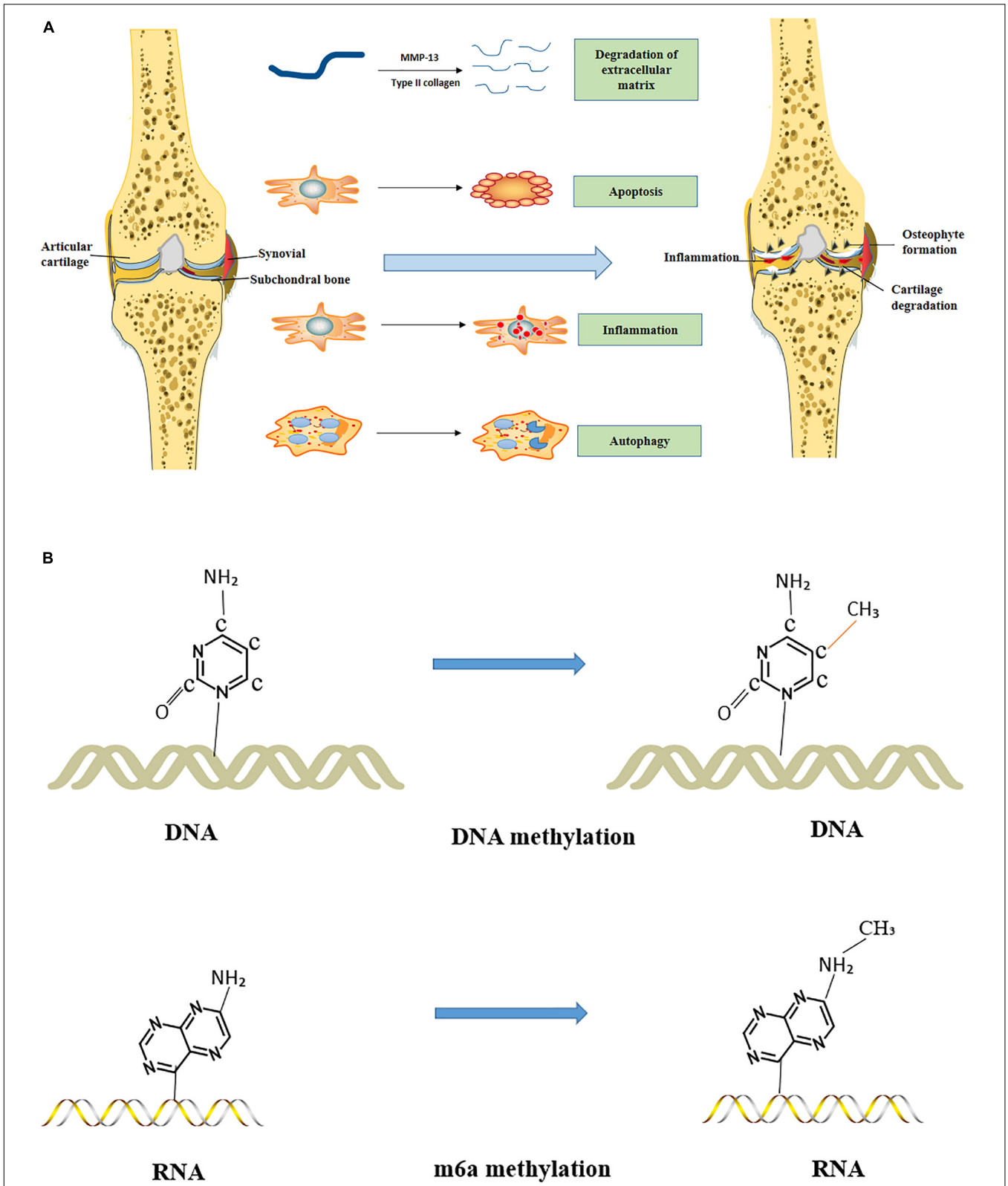


FIGURE 1 | Pathogenesis of Osteoarthritis (OA). **(A)** The degradation of ECM, apoptosis, inflammatory response, and autophagy mechanisms in OA. **(B)** Methylation in OA.

a dynamic balance to maintain homeostasis. The secretion and operation of some components of ECM are completed by articular cartilage (Rahmati et al., 2017). When the activities of synthesis and catabolism of articular cartilage are imbalanced, the details and homeostasis of ECM are also affected (Guo et al., 2002). Considering that the degradation of ECM leads to the loss of cartilage tissue, ECM also plays a role in maintaining the function of chondrocytes. The continuous degradation of ECM will induce OA.

Based on the summarizing of articles related to the pathogenesis of OA and the function of chondrocytes, Goldring and Goldring (2007) found that the degradation of ECM and decomposition of collagen could lead to the gradual loss of the shape and position of articular cartilage to induce OA. Setayeshmehr et al. (2019) summarized the functions and effects of various ECM scaffolds through summarizing and analyzing the related articles on hybrid and composite scaffolds derived from chondrocyte ECM. They concluded that the degradation of chondrocyte ECM could lead to cartilage degeneration. Malemud (2017) analyzed the role of matrix metalloproteinases in OA. They found that in the ECM of the cartilage, some essential proteins would degrade. Matrix metalloproteinases can promote or inhibit the degradation of these proteins, change the biomechanical properties of tissues, and destroy articular cartilage. In addition, based on the analysis of the action mechanism of ECM and its degrading enzymes in OA, the ECM of cartilage in OA patients can release certain fibronectin, thereby inducing the expression of related proteases and degrading the components of the ECM (Pérez-García et al., 2019).

Kapoor et al. (2011) and Theocharis et al. (2019) also found that the tissue protein would be hydrolyzed gradually during the development of OA. Then, some catabolic mediators will be produced, which will induce the expression of some related cytokines and proteases, and finally lead to ECM degradation. This situation will lead to prolonged OA. Based on the analysis of the changes of some macromolecules in the ECM of early OA patients, the content of proteins related to ECM was changed, such as collagen and cartilage protein. Hence, the degradation of ECM and even the deterioration of OA disease occurred (Lorenzo et al., 2004).

Apoptosis

Apoptosis is an active gene-determined process that automatically ends life, and it is often called programmed cell death, a basic biological phenomenon of cells (Musumeci et al., 2011). Apoptosis involves endogenous and exogenous pathways, which play an essential role in maintaining the function of various tissues in the body (Elmore, 2007). A correlation has been observed between the degree of cartilage injury and apoptosis, which is a vital mechanism of cartilage injury (Hwang and Kim, 2015). Moreover, the apoptosis of OA chondrocytes is related to cartilage degradation (Kim et al., 2003). When OA occurs, it will produce matrix-degrading enzymes, leading to the degradation of the ECM and the destruction of cell homeostasis. Cell stress induces an oxidation reaction, leading to the apoptosis of chondrocytes and regulating the pathological changes of cartilage tissues (Bauer et al., 2006).

Histologically, Musumeci et al. (2011) studied the articular cartilage of normal individuals and OA patients by staining apoptotic cells. They found that the articular cartilage of OA patients changed in structure. The pro-apoptotic receptor on the cell surface could induce apoptosis through an exogenous pathway in the damaged articular cartilage. Aigner et al. (2004) summarized the incidence, induction mechanism, and morphology of apoptosis in OA patients and found that apoptosis occurred in patients with OA, but the incidence was not high. The body induced apoptosis through specific proteoglycans, signaling molecules, and other pathways to regulate the pathological changes of articular cartilage and accelerate or delay the progression of OA. Based on the synthesis of related articles on OA and apoptosis, some articles indicate that apoptosis induces OA, while other articles indicate that OA induces apoptosis. These two views are disputed, and more reports believe that these conditions affect and promote each other and have a correlation (Zamli and Sharif, 2011). Chondrocytes in the knee joints of patients with OA and the apoptosis of chondrocytes and its relationship with cartilage degradation have been studied. Notably, the findings indicate that first, in some populations, the morphology and function of cartilage are normal (Hashimoto et al., 1998). Still, many apoptotic cells appear, indicating that apoptosis may lead to degenerative changes in articular cartilage, thus inducing OA. Furthermore, the number of apoptotic articular cartilage cells in the OA population increased, and the number of apoptotic cells was related to cartilage degradation. Finally, when all subjects, including the average population and OA patients, were analyzed, a correlation was found between age and apoptosis of chondrocytes. Similarly, rabbit chondrocytes have been studied and compared with mature rabbits. Results show that the cell density of each layer of articular cartilage in rabbits decreased, and the expression level of pro-apoptotic genes increased. These studies further proved the correlation between age and chondrocyte apoptosis at the animal level and the phenomenon of apoptosis that existed in the early stage of OA (Todd Allen et al., 2004). In another study involving horses, a positive correlation was found between the severity of chondrocyte injury and apoptosis. The expression level of pro-apoptotic factors is higher in horses that often suffer from OA. Apoptosis participates in the pathogenesis of OA. Apoptosis has been observed on human femoral head cartilage (Thomas et al., 2011). In comparison with the average population, the expression of receptors and the degree of apoptosis in OA patients' articular cartilage was much higher. In the late stages of OA, the degree of apoptosis become even worse (Héraud et al., 2000).

Inflammatory Reaction

The inflammatory reaction is a basic pathological process mainly involving a defensive response when the body is stimulated. Inflammation is involved in the pathological process of many diseases, such as cancer (Gianni et al., 2016), tendon or ligament injury (Gracey et al., 2020). As early as the middle of the 19th century, studies pointed out that inflammation was closely related to OA. Articular chondrocytes and synovial cells all expressed inflammatory mediators (Liu-Bryan, 2013). Inflammatory factors

such as IL-1β and TNFα participate in the inflammatory response in articular chondrocytes and synovial cells (Malfait, 2016). The cells mainly involved in the inflammatory response are macrophages and monocytes. The degree of inflammation is related to the degree of joint dysfunction and inflammatory factors (Scanzello et al., 2011). In the early stage of OA, the expression of monocytes and inflammatory mediators increased, whereas with the continuous development of OA, the expression of monocytes and inflammatory mediators was gradually decreased (Benito et al., 2005).

Rosshirt et al. (2019) used the knee joints of 55 OA patients as the research object, described the activation state of T cells, and found that a large proportion of T cells were activated to participate in OA inflammation, which mainly affected the joint itself the most. Inflammation can promote catabolism and participate in the pathogenesis of the disease. van den Bosch (2019) found a large number of inflammatory mediators in the tissues of patients with OA. These inflammatory mediators can induce the generation of degrading enzymes in articular cartilage, leading to the degradation of the ECM and the destruction of cartilage tissue. Lieberthal et al. (2015) established a post-traumatic OA model and observed the relationship between inflammation and OA progression. They found that an inflammatory reaction occurred in the early stage of OA. In patients with, multiple inflammatory pathways were activated and produced multiple inflammatory mediators such as cytokines and chemokines, which played an essential role in the pathogenesis of OA (Scanzello, 2017a). The genomic expression profiles of OA patients have been collected and subjected to meta-analysis, and the results show that MAP kinase, NF-κB activation, and oxidative phosphorylation can induce inflammatory signals and participate in the pathological change mechanism of OA (Li et al., 2014). Macrophages are immune cells that play an essential role in the inflammatory response (Bondeson et al., 2010). Woodell-May and Sommerfeld (2020) explored the role of immune cells such as macrophages in the synovial membrane of patients with OA. They found that in OA, macrophages could release oxygen free radicals, proteases, and inflammatory factors, thus affecting the microenvironment of inflammation. In the wound healing stage, macrophages also release IL-1, IL-6, and other inflammatory factors to regulate the inflammatory response. By stimulating protease, inflammation can cause cartilage degeneration and eventually induce OA. Based on the relationship between mechanical injury and OA, mechanical damage can lead to mechanical inflammation, which activates NF-kB and inflammatory mitogen-activated protein kinase, thereby causing a series of functional problems of the join (Vincent, 2019). If the rash persists for a long time, it will affect the repair of cartilage tissue. Based on the summary of articles related to inflammation in OA (Goldring and Otero, 2011), when some risk factors inducing OA appear, the expression of pro-inflammatory factors and various related enzymes are upregulated in articular cartilage and synovial tissue through specific signaling pathways. Inflammatory elements, which are essential for cartilage damage and repair, can change adjacent joint tissues and form a vicious circle (Houard et al., 2013). The knee joint is damaged under severe mechanical stimulation, causing catabolism and stress response of chondrocytes, and finally inducing inflammation, leading to joint pain. Inflammation is one of the important mechanisms that lead to the pathological changes of joint cartilage and synovial membrane (Scanzello, 2017b).

Autophagy

During autophagy, cells degrade their damaged organelles and macromolecular substances by using lysosomes to regulate autophagy-related genes, which can achieve the renewal of organelles and is essential for cell metabolism (Guo et al., 2021). Autophagy is involved in the occurrence of OA. Through cellular autophagy, the function of damaged articular cartilage can be restored, thereby alleviating the pathological process of OA. Excess ROS will lead to cartilage degradation and inhibit the synthesis of ECM. Kongara and Karantza (2012) showed that autophagy could maintain the typical morphology of cartilage and the dynamic balance of ECM synthesis and metabolism by regulating the body's ROS.

Barranco (2015) found that the inhibition of the Akt-mTOR signaling pathway in chondrocytes can promote the autophagy of articular chondrocytes and regulate oxidative stress (Xue et al., 2017), thus participating in the development process of OA. If autophagy is activated, the damaged mitochondria and peroxidase bodies are removed, thus inhibiting the production of reactive oxygen species in the body and protecting the articular cartilage from pathological changes. Based on the summary of the roles of autophagy in OA, in the early stage of OA, moderate autophagy contributes to the survival of chondrocytes and is essential for preventing and delaying OA (Duan et al., 2020). Li et al. (2016) found that autophagy was mainly committed in the chondrocytes of patients with OA. By regulating oxidative stress response and apoptosis, the pathological changes of the knee joint can be alleviated, and chondrocytes can be protected from various stimulations. With the growth of age, the incidence of OA increases gradually, and this phenomenon is related to autophagy. Autophagy gradually weakens with age. Therefore, the structure and function of articular cartilage decreases with age, leading to pathological changes in the knee joint (Mathew et al., 2009). Caramés et al. (2010) that in OA animal models, the expression of autophagy regulatory factors is downregulated, and the steady-state of cartilage is damaged, indicating that autophagy can protect articular cartilage and play an essential role in maintaining cartilage steady state. The decrease of autophagy will induce OA. Taking articular cartilage of OA and non-OA patients as the research object, we can find that autophagy regulates the expression of OA-related genes. In comparison with patients without OA, autophagy is expressed in the chondrocytes of OA patients at a higher level, and the manifestation of autophagy markers is also upregulated (Sasaki et al., 2012). Similarly, Chang et al. (2013) took human chondrocytes as the research object and found that many autophagy-related proteins are expressed in the articular cartilage of patients with OA. In the pathogenesis of OA, autophagy plays a role in protecting chondrocytes and promoting metabolism. However, excessive autophagy causes a large number of chondrocyte deaths.

Changes in Non-coding RNA

Non-coding RNA (ncRNA) is an RNA that does not code for protein, mainly including miRNA, lncRNA, and circRNA. These RNAs can exert biological functions at the RNA level without being translated into proteins. ncRNA plays an essential role in the pathological process of many diseases, such as cardiovascular disease (Jusic and Devaux, 2020), cancer (Karreth and Pandolfi, 2013), diabetes (Beltrami et al., 2015). ncRNA also plays a vital role in the process of OA. It can promote or inhibit cartilage formation by regulating the degradation of cell-matrix, cell proliferation, apoptosis, and inflammatory response, thereby inducing or treating OA (Hong and Reddi, 2012).

Changes in the expression levels of many miRNAs can induce pathological changes in OA. MiR-204/-211 and miR-29b-3p are common miRNAs, which are differentially expressed in patients with OA. Huang et al. (2019) established an OA mouse model and found that miR-204/-211 was missing, and Runx2 was increased. Mesenchymal progenitor cells proliferated abnormally at the same time by Micro-CT and histological determination. Akt signal North is activated, thus inducing the dysfunction of various components in the joint and finally leading to OA. Therefore, miR-204/-211 can maintain intra-articular homeostasis and ensure that articular chondrocytes and synovial cells function usually. Chen et al. (2017) used rat chondrocytes as the research object. Through luciferase reporter gene detection, they found that miR-29b-3p in patients with OA was upregulated, and miR-29b-3p ultimately led to the degeneration of articular cartilage tissue by targeting and inhibiting the expression of rat GRN mRNA. In addition, microarray technology was used to detect the expression of miRNA in chondrocytes. They found that miRNA-140, miRNA-455, miR-146a, miR-155, and miR125b differed in OA patients and the average population, thus inducing pathological changes of articular cartilage, synovial membrane, and subchondral bone (Swingler et al., 2012). lncRNA also plays a vital role in OA. Throughout the cartilage development, different lncRNA is regulated, and the regular expression of lncRNA can prevent cartilage differentiation disorders. During cartilage degeneration, other lncRNA plays various roles (Zhu et al., 2019). Ye et al. (2018) studied the articular cartilage of patients with OA. They found that the expression of ZFAS1 in OA chondrocytes was downregulated, and ZFAS1 might reduce the activity of chondrocytes and induce pathological changes of articular cartilage tissues by targeting the Wnt3a signaling pathway. Similarly, the role of circa in OA has been widely studied. Cyclic RNA plays a multi-faceted regulatory role in the progression of OA (Zhang W. et al., 2021). Chen et al. (2020) found that in OA tissues, the expression levels of circRNA-UBE2G1 and HIF-1a were significantly increased, while the expression of miR-373 was downregulated. Functional testing showed that circRNA-UBE2G1 could bind to miR-373, thereby inhibiting the interaction of miR-373 and HIF-1a, damaging the chondrocytes, and leading to a series of pathological changes. In conclusion, ncRNA is closely related to OA. The differential expression of miRNA, lncRNA and circRNA in healthy people and OA patients can lead to pathological changes in articular cartilage, synovial membrane, and subchondral bone and affect the pathological process of OA.

Methylation

Methylation is the catalyzed transfer of methyl groups from an active compound to another compound. This process can form various methyl compounds or result in chemical modification of particular proteins or nucleic acids to start methylation products (Urnov, 2002). Methylation mainly includes DNA methylation and m6a methylation (Dai et al., 2021).

DNA methylation is a chemical modification of DNA that alters genetic behavior without altering the DNA sequence. Its primary process is under the action of DNA methyltransferase. DNA methylation can cause changes in chromatin structure, DNA conformation, DNA stability, and the way DNA interacts with the protein, thereby controlling gene expression (Reynard, 2017). When CtBP1 and CtBP2 are overexpressed, the pro-inflammatory factors are increased, while the NLRP3 signaling pathway is activated to induce OA. DNA methylation in the CtBPs promoter reduces the expression level of CtBPs in OA tissues and regulate CtBP-mediated signal transduction, finally participating in the pathogenesis of OA (Sun et al., 2020). In addition, DNA methylation can participate in the pathogenesis of OA by affecting the expression of genes such as matrix metalloproteinase-3, matrix metalloproteinase-9, and type II collagen (Cui and Xu, 2018).

N6- methyladenine (m6a) is one of the most abundant chemical modifications of eukaryotic messenger RNA. m6a modifications mainly include m6a methyltransferase catalysis, m6a demethylase removal, and m6a binding protein recognition (Ma and Ji, 2020). This process is widely involved in regulating various life cycle stages such as mRNA splicing, processing, translation, and degradation. It is related to osteosarcoma, rheumatoid arthritis, osteoporosis, OA, and abnormal physiological functions (Zhang W. et al., 2020). The strange expression of m6a-related gene and protein in OA can trigger the imbalance of m6a methylation, regulate the expression of OA-related genes to participate in the occurrence and development of OA, and is closely related to the poor prognosis of patients (Yang et al., 2021). METTL3 is a methylated gene of m6a. He et al. (2021) studied mice *in vivo* and *in vitro* and induced the OA model with inflammatory stimuli such as TNF-α. The results showed that the expression of METTL3 was decreased in the OA model. Bcl2 is a downstream target gene of METTL3, and the presentation of METTL3 can promote m6A methylation of Bcl2 mRNA, thereby inhibiting chondrocyte apoptosis and autophagy. The detection of synovial tissue in patients with OA revealed that METTL3 could also induce autophagy by inhibiting ATG7 (Chen X. et al., 2021). In addition, METTL3 may participate in OA by regulating the inflammatory response (Sang et al., 2021). In summary, methylation is also an essential mechanism for pathological changes in OA. Furthermore, the epigenetic mechanism plays an essential role in the pathogenesis of OA.

MECHANISM OF EXERCISE IMPROVING OSTEOARTHRITIS

Exercise is good medicine. An increasing number of studies supports that exercise can enhance physical fitness, build

TABLE 1 | Mechanism of exercise in the treatment of Osteoarthritis (OA).

Researchers	Model	Exercise types	Related gene/cytokines/protein	Involved in pathways	Improved organization	Functions	Change
He et al., 2020	OA mice model	Cell stretch	Irisin	Erk	Articular cartilage	Apoptosis	↓
Griffin et al., 2020	OA mice model	Wheel-running exercise	—	—	Subchondral bone	Inflammation	↓
Lu et al., 2021	OA rat model	Treadmill exercise	Maresin-1, MMP-13	PI3K/AKT, NF-κB	Synovial	Inflammation	↓
Griffin et al., 2012	OA mice model	Wheel-running exercise	KC, leptin, IL-1Ra	—	Subchondral bone, Articular cartilage	Inflammation	↓
Cormier et al., 2017	OA rat model	Prior wheel running	—	—	Subchondral bone, Articular cartilage	Inflammation	↓
Chen et al., 2020	OA rat model	Treadmill and wheel exercise	IL-1b, IL-6, TNF-a	JNK/NF-kB	Articular cartilage, synovial	Inflammation	↓
Rios et al., 2019	OA rat model	Aerobic exercise	IL-6, TNF-α	—	Subchondral bone	Inflammation	↓
Li K. et al., 2021	OA mice model	Wheel-running exercise	TLR4, MMP-13	—	Articular cartilage	Degradation of ECM	↓
Yang et al., 2020	OA rat model	Treadmill exercise	TRAIL	TRAIL/NF-κB/NLRP3	Articular cartilage	Apoptosis, Inflammation	↓
Allen et al., 2017	OA rat model	Treadmill exercise	—	—	Subchondral bone	Inflammation	↓
Zhang X. et al., 2019	OA rat model	Treadmill exercise	Lc3B, SQSTM1	—	Articular cartilage	Autophagy	↑
Zhang H. et al., 2019	OA rat model	Treadmill exercise	HDAC3	HDAC3/NF-KappaB	Articular cartilage	Inflammation	↓
Galois et al., 2004	OA rat model	Running training	Hsp70	—	Articular cartilage	Apoptosis	↓
Oka et al., 2019	OA mice model	Treadmill exercise	IL-1β, MMP-13	—	Articular cartilage	Inflammation, Degradation of ECM	↓
Blazek et al., 2016	OA rat model	Treadmill exercise	MMP-13,Type II collagen	—	Articular cartilage	Degradation of ECM	↓
Yang et al., 2019	OA rat model	Treadmill exercise	IL - 1β	AMPK/NF – κB	Articular cartilage	Inflammation	↓
Assis et al., 2016	OA rat model	Aerobic exercise	IL-1β, caspase-3, MMP-13	—	Articular cartilage	Inflammation	↓
Baur et al., 2011	OA mice model	Running exercise	ROS, SOD2	—	Articular cartilage	Autophagy	↓
Assis et al., 2015	OA rat model	Treadmill exercise	muscle-specific ring-finger protein 1, atrogin-1	—	Articular cartilage	Degradation of ECM	↓
Yamaguchi et al., 2013	OA rat model	Running	C2C, CPII	—	Articular cartilage	Degradation of ECM	↓
Assis et al., 2018	OA rat model	An aerobic and an aquatic exercise	IL-10, TGF-β, collagen I and II	—	Articular cartilage	Degradation of ECM	↓
Milares et al., 2016	OA rat model	An aquatic exercise	IL1-β, caspase-3	—	Articular cartilage	Inflammation	↓
Szychlinska et al., 2019	OA rat model	Physical activity	IL-6	—	Articular cartilage	Inflammation	↓
Qian et al., 2014	OA rat model	Passive motion	Proteoglycans, type II collagen fibers	—	Articular cartilage	Apoptosis	↓
Yang et al., 2017	OA rat model	Treadmill exercise	LXA4	NF-κB	Articular cartilage	Inflammation	↓
Castrogiovanni et al., 2019	OA rat model	Physical Activity	IL-1β, IL-6, TNF-α, MMP-13	—	synovial	Inflammation	↓
Iijima et al., 2016	OA rat model	Treadmill walking	BMP-2, BMP-6	—	Subchondral bone	Cartilage matrix synthesis	↑
Boudenot et al., 2014	OA rat model	Interval training exercise			Subchondral bone	Apoptosis	↓
Iijima et al., 2017	OA rat model	Treadmill exercise	BMP-2, BMP-4, BMP-6, BMP receptor 2, pSmad-5	BMP	Articular cartilage, Subchondral bone	Inflammation, Apoptosis	↓
Oka et al., 2021	OA mice model	Treadmill exercise	Gremlin-1, MMP-13	—	Articular cartilage	Inflammation	↓
Vasilceac et al., 2021	OA rat model	Resistance training	MMP-2	—	Articular cartilage	Degradation of ECM	↓
Hong et al., 2014	OA rat model	Treadmill exercise	IL-6, EPAS-1, MMP-13	—	Articular cartilage	Degradation of ECM, Apoptosis	↓
Na et al., 2014	OA rat model	Treadmill exercise	C9	—	serum	Inflammation	↓
Cifuentes et al., 2010	OA rat model	Impact exercise	ACAN, COL2a1, TIMP3, MMP	—	Articular cartilage	Autophagy	↑
Yang et al., 2018	OA rat model	Treadmill exercise	LXA4	NF-κB	Synovial	Inflammation	↓
Hsieh and Yang, 2018	OA rat model	Swimming exercises	collagen II, MMP13	—	Articular cartilage, Synovial	Degradation of ECM, Apoptosis	↓
Hao et al., 2021	OA rat model	Body weight-supported treadmill training	collagen II, MMP13	—	Articular cartilage, Subchondral bone	Degradation of ECM, Apoptosis	↓

(Continued)

TABLE 1 | (Continued)

Researchers	Model	Exercise types	Related gene/cytokines/protein	Involved in pathways	Improved organization	Functions	Change
Iijima et al., 2015	OA rat model	Short-term gentle treadmill walking	—	—	subchondral bone	Apoptosis	↓
Al-Hashem et al., 2017	OA rat model	Swim exercise	TBARS, TNFa, SOD	—	Articular cartilage	Inflammation	↓
Martins et al., 2019	OA rat model	Aerobic training	MIA, IL1β, TNF	—	Articular cartilage	Inflammation	↓
Musumeci et al., 2015	OA rat model	Treadmill exercise	lubricin	—	Articular cartilage, Synovial	Cartilage matrix synthesis	↑
Musumeci et al., 2013	OA rat model	Treadmill exercise	caspase-3	—	Articular cartilage	Apoptosis	↓
Tian et al., 2021	OA rat model	Treadmill exercise	15-HETE	PI3k-Akt	Synovial	Inflammation	↓
Fallah Mohammadi et al., 2013	OA rat model	Treadmill exercise	IL – 1β, TNF – α	—	Articular cartilage	Inflammation	↓
Zhang J. et al., 2021	OA rat model	Swimming exercise	caspase-3	—	Articular cartilage	Apoptosis	↓
Li Z. et al., 2021	OA rat model	Treadmill exercise	P2 × 7	IRE1-mTOR-PERK	Articular cartilage	Autophagy	↑
Guan et al., 2011	OA chicken model	mechanical stimulation	HDAC4	—	Articular cartilage	miR-365	↑
Zhou et al., 2021	OA mice model	Treadmill running	—	—	Articular cartilage	lncRNA H19	↑
Liu Q. et al., 2016	OA cell model	mechanical stimulation	TMSB4	—	Articular cartilage	lncRNA-MSR	↑
Liu et al., 2017	OA cell model	mechanical stimulation	TNF-α	—	Articular cartilage	circRNA-MSR	↓
Fang et al., 2021	OA rabbit model	running experiment	PCNA, SOX9, Col II, Aggrecan	—	Articular cartilage	circUNK	↑

up the body, and prevent and treat certain diseases, playing an increasingly important role in people's lives (Ruegsegger and Booth, 2018). Studies (Pedersen and Saltin, 2015) have summarized the mechanism of exercise in treating 26 different conditions, providing a theoretical basis for treating diseases by exercise. The treatment of OA by exercise has attracted increasing attention and has gradually become an OA research hotspot. In the present paper, the pathological mechanism of exercise in OA treatment was summarized through the induction of relevant literature, as shown in **Table 1**. Exercise relieves the pathological changes of OA by affecting the degradation of the ECM, apoptosis, inflammatory response, autophagy, and changes of ncRNA. And training is used to treat OA (**Figure 2**).

The Role of Exercise in the Degradation of Extracellular Matrix

Exercise can delay the pathological process of OA by inhibiting the degradation of the ECM. Articular cartilage degradation is an essential pathological change of OA. Blazek et al. (2016) used OA rats as the research object. Exercise and non-exercise were used as intervention means to compare the whole gene expression of the transcriptome of articular cartilage in rats. Microarray analysis showed 644 differentially expressed genes in the articular cartilage of exercise rats. Therefore, exercise can prevent OA by changing genes related to OA's pathogenesis and regulating the degradation and synthesis of ECM by changing metabolic pathways to alleviate the pathological changes of articular cartilage with sound prevention effects on OA. An OA rat model has been established to evaluate the expression of IL-10, TGF-β, and collagen type I and II in articular cartilage. The presentation of the above biochemical indicators increased in the articular cartilage of mice after exercise, indicating that exercise is very beneficial to articular cartilage. Moreover, considering that collagen type II is an essential component of ECM, exercise may delay the progression of OA by inhibiting the degradation of ECM and promoting cartilage synthesis (Assis et al., 2018). Vasilceac et al. (2021) conducted resistance training for eight weeks for OA rats. They analyzed whether ELISA changed the activity of MMP-2 in the tendons around the knee joint and finally found that exercise could reduce the activity of MMP-2 in the quadriceps tendon of OA rats and greatly relieve the adverse effects of OA on the knee joint. Results show that exercise may reduce the degradation of the ECM by inhibiting the activity of MMP-2 from achieving the purpose of treating OA. Exercise in different stages of the course of OA produces other effects. Type II collagen (CoII) and matrix metalloproteinase-13 (MMP-13) are essential components related to the degradation of the ECM. Hsieh and Yang (2018) established an OA rat model, in which the samples were allowed to swim in different stages of the course of OA. They found that swimming training in the early stage of OA could increase CoII. The level of MMP-13 can be reduced to maintain a balance between the degradation and anabolism of ECM and prevent cartilage damage through exercise training in the early stage of OA rather than that in the late stage.

Overall, the degradation of the ECM is the pathological change mechanism of OA. Exercise can protect articular cartilage and delay the progression of OA by inhibiting this mechanism, and it is a crucial intervention to prevent and treat OA.

The Role of Exercise in Apoptosis

Apoptosis is one of the mechanisms for the pathological changes of OA. Exercise delays the pathological process of OA by inhibiting apoptosis. Taking articular cartilage of OA rats as a research sample, Yang et al. (2020) detected the expression

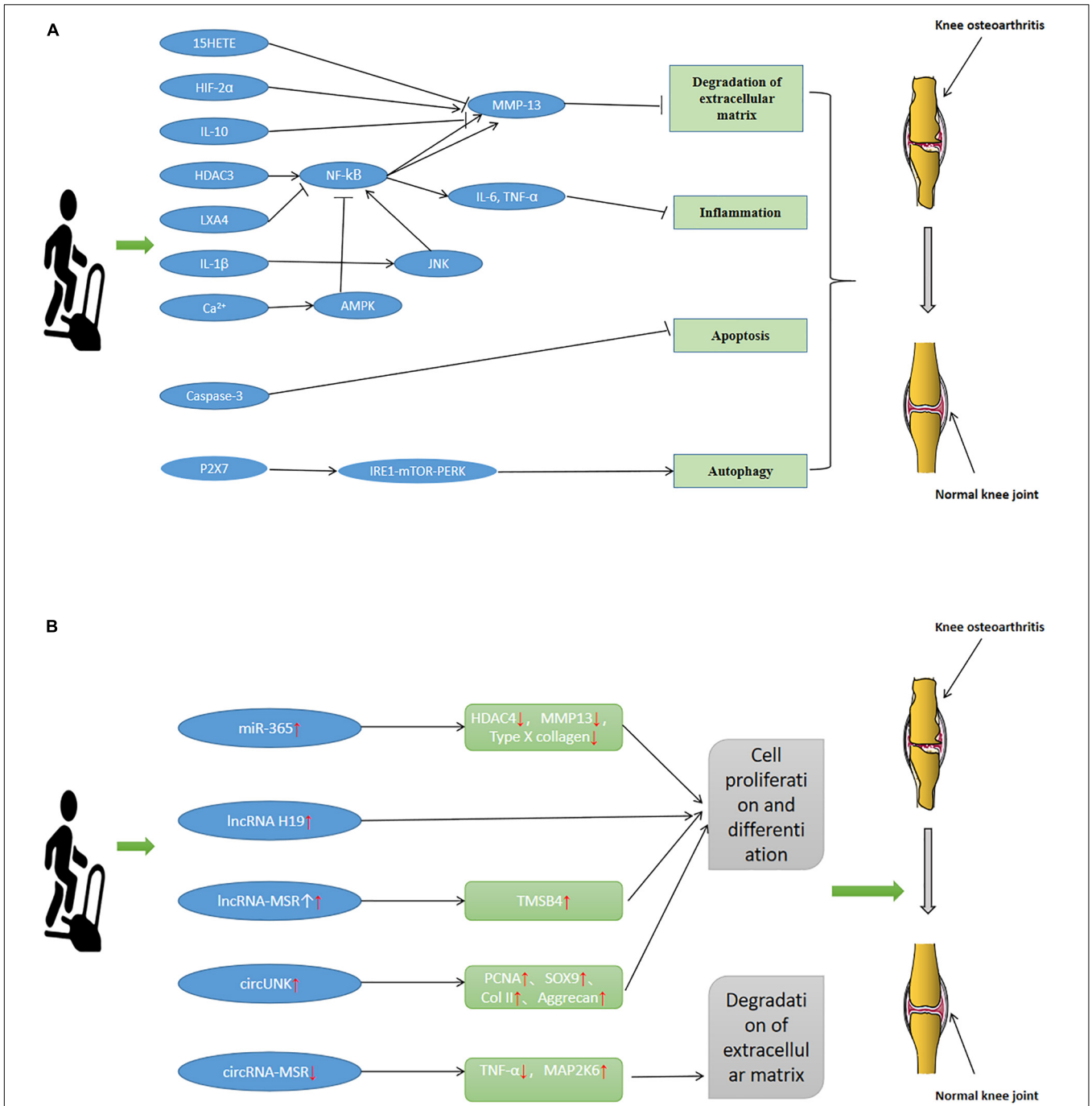


FIGURE 2 | Pathological change mechanism of Osteoarthritis (OA). Exercise relieves the pathological changes of OA by affecting the degradation of the ECM, apoptosis, inflammatory response, autophagy and changes of ncRNA. **(A)** Mechanism of pathological changes of OA through degradation of ECM, apoptosis, inflammatory response, and autophagy. **(B)** Mechanism of pathological changes of OA through ncRNA.

of relevant genes in articular cartilage after exercise through bioinformatics analysis. Results show that the levels of TRAIL, NF-κB p65, and NLRP3 in cartilage after activity were decreased. Exercise could inhibit apoptosis and prevent OA by regulating the TRAIL/NF-κB/NLRP3 signaling pathway of OA. By comparing OA rats with mild, moderate, and high-intensity training and comparing the expression of caspase three and Hsp70, we found that mild and moderate exercise could inhibit apoptosis and protect the articular cartilage (Galois et al., 2004). Qian et al. (2014) established an OA rat model, and the experimental group was subjected to passive motion. Based on the measurements of the proteoglycan content of the cartilage matrix, the number

of type II collagen fibers, and apoptotic chondrocytes in the experimental and control group, the changes in biochemical signals caused by passive exercise in the early and middle stages of OA differed. In comparison with the control group, the cartilage matrix proteoglycan content and type II collagen fiber level remarkably increased three weeks after passive motion in the early stage of OA. The number of apoptotic cells was significantly reduced. However, three weeks after passive exercise in the middle stage of OA, the number of apoptotic cells was not significantly changed. Therefore, passive exercise at the early stage of OA may delay articular cartilage degeneration by inhibiting apoptosis, preventing, and treating OA. After intermittent training for OA rats, the pathological changes of their subchondral bones were assessed by immunolabeling with cleaved caspase-3 in the cortical subchondral bone. Intermittent aerobic training may prevent the OA-induced reduction in bone mineral density by reducing apoptosis (Boudenot et al., 2014). Studies (Iijima et al., 2015) have established the OA rat model and analyzed the pathological conditions of rat articular cartilage and subchondral bone before and after four weeks of exercise. They found that exercise might inhibit apoptosis and protect cartilage tissue, thus delaying OA progression. Musumeci et al. (2013) established the OA rat model to study the effect of exercise on articular cartilage. First, drugs were used to induce pathological changes in the articular cartilage. Then, exercise intervention was performed on rats to observe the morphological changes of articular cartilage. The results show that exercise might induce the expression of lubricating oil and inhibit the activity of caspase-3, thereby reducing apoptosis and delaying or even reversing pathological changes of articular cartilage. In some studies (Zhang J. et al., 2021) concerning establishing the OA rat model, the experimental group was intervened by swimming for four weeks. The morphological changes of cartilage were analyzed by hematoxylin-eosin (H&E) staining. The expression of caspase-3 was analyzed by Western blot and qPCR. The results showed that after four weeks of swimming, the abnormal morphology of articular cartilage was improved, and the level of caspase-3 protein decreased, indicating that exercise might reduce apoptosis by inhibiting the level of caspase-3 protein, thereby protecting articular cartilage and preventing and treating OA.

The Role of Exercise in Inflammatory Response

Exercise can inhibit the inflammatory response by reducing pro-inflammatory factors, thereby delaying the pathological changes of OA, which is the most common mechanism of activity in OA treatment. The inflammatory response mechanism of exercise therapy for OA has been widely studied, and many related pathways regulate the inflammatory response of OA, such as PI3k/Akt, NF-κB p65, JNK/NF-kB, HDAC3/NF-kappaB, and AMPK/NF-κB signaling pathways. Lu et al. (2021) established the OA rat model and allowed them to exercise on the treadmill. They found that after running exercise, the mice produced maresin-1, and the increased level of maresin-1 activated the PI3k/Akt pathway and inhibited the NF-κB p65 pathway, thus playing an anti-inflammatory role and delaying the pathological changes of OA. Griffin et al. (2012) established the OA mouse model by inducing a high-fat diet and then letting the mice run to observe the expression of inflammation-related factors. Finally, they found that exercise could regulate the expression of pro-inflammatory factors, promote joint health, and reduce the severity of pathological changes in joints of OA mice. To study the signal transduction of JNK/NF-kB in KOA patients, we established the 0A rat model and conducted a controlled intervention experiment. Finally, the knee joint diameter in the exercise group is lower than that in the OA group, indicating that exercise is conducive to KOA recovery. The IL-1b, IL-6, and TNF-a levels decreased, indicating that exercise can reduce the inflammatory response by regulating the JNK/NF-kB signaling pathway, which ultimately can delay the pathological changes of OA (Chen et al., 2020). Osteoarthritis rats were subjected to moderate-intensity exercise on the treadmill. The H&E staining and toluidine blue O staining were used to detect cartilage injury. The expression levels of some biochemical signals in the articular cartilage were examined via immunohistochemistry and other methods. The results showed that moderate-intensity treadmill exercise could reduce the inflammatory response and protect the articular cartilage by inhibiting the HDAC3/NF-kappaB pathway (Zhang H. et al., 2019). Similarly, Yang et al. (2019) intervened OA rats with treadmill exercise and used the articular cartilage as the research object. Observation and analysis results show that moderate-intensity exercise can reduce the sensitivity of articular cartilage and chondrocytes to inflammatory response through the AMPK/NF-κB signaling pathway, and it is an essential mechanism for reversing the pathological changes of articular cartilage. The analysis of biochemical indicators of OA rats after aerobic exercise show that the expression levels of IL-1β, caspase-3, and MMP-13 in OA rats decreased after exercise, and aerobic exercise could inhibit the inflammatory response of OA and prevent and treat the pathological changes of cartilage (Assis et al., 2016). After water sports, OA rats' articular cartilage and inflammatory mediators were changed. After eight weeks of the experiment, the cell damage degree of the rat was relieved, and the expression levels of IL-1β and caspase-3 were reduced. Therefore, sports can regulate OA inflammatory factors and inhibit inflammatory reactions to treat OA (Milares et al., 2016).

The Role of Exercise in Autophagy

In OA, autophagy is a cellular protective response. Exercise can protect the knee joints of KOA patients by inducing autophagy, which is mainly regulated by oxidative stress. Relatively few studies have demonstrated the specific mechanism pathways through which exercise protects the knee joint through autophagy. Zhang X. et al. (2019) used sodium iodoacetate to induce OA rat model, and the experimental group was subjected to treadmill exercise for four weeks. The study found that serum IL-1β was decreased, IL-4 was increased, and the expression of type II collagen in articular cartilage was increased in rats undergoing treadmill exercise compared with those in OA rats that did not experience any activity. Therefore, treadmill exercise may protect the knee joints of OA patients by promoting the autophagy of articular cartilage. Baur et al. (2011)

TABLE 2 | Different exercise types on human Osteoarthritis (OA).

Researchers	Number of studies/subjects	Intervention studied	Exercise effect
Vincent et al., 2019	*N* = 90	Eccentric and Concentric Resistance Exercise	Modify function and pain symptoms
DeVita et al., 2018	*N* = 30	Quadriceps strength training	Increase muscle strength and improve symptomatic and functional outcomes
Abbott et al., 2013	*N* = 206	Manual therapy and exercise therapy	Improve knee joint function of patients
Lund et al., 2008	*N* = 79	A land-based exercise	Improve pain and muscle strength
Chen S.-M. et al., 2019	*N* = 70	Resistance Exercise	Improve muscle strength, dynamic balance and body function
Kabiri et al., 2018	*N* = 78	Aerobic exercise combined with resistance training	Relieve pain and improve function
Allen et al., 2021	*N* = 345	Stepped exercise	Improve the symptoms of the patient
Bennell et al., 2014b	*N* = 100	Neuromuscular versus quadriceps strengthening exercise	Relieve pain and improve function
Ettinger et al., 1997	*N* = 439	An aerobic or a resistance exercise	Relieve pain and improve function
Suzuki et al., 2019	*N* = 52	Multiple exercise	Improve muscle strength and joint flexibility
Krauß et al., 2014	*N* = 209	Exercise Therapy	Relieve pain and improve function
León-Ballesteros et al., 2020	*N* = 32	Quadriceps strengthening exercise	Relieve pain
Rewald et al., 2020	*N* = 55	Aquatic Cycling	Relieve pain and improve function
Chen H. et al., 2019	*N* = 171	A home-based exercise	Relieve symptoms, increase the physical functioning, and improve quality of life
Alkatan et al., 2016	*N* = 48	Swimming and Cycling Training	Reduce joint pain and stiffness and improve muscle strength and functional capacity
Silva et al., 2008	*N* = 64	Water-based and land-based exercises	Relieve pain and improve function
Kuntz et al., 2018	*N* = 31	Yoga	Relieve pain and improve function
Huang et al., 2018	*N* = 250	Quadriceps functional exercise	Relieve pain and improve function
Taglietti et al., 2018	*N* = 31	Aquatic exercises	Relieve pain and improve function
Vincent and Vincent, 2020	*N* = 88	Resistance exercise	Relieve pain
Holm et al., 2021	*N* = 90	Strength training	Relieve pain
Waller et al., 2017	*N* = 87	High intensity aquatic resistance training	Decrease fat mass and improve walking speed
Fernandes et al., 2017	*N* = 165	Neuromuscular exercise	Improve the quality of life of patients
Ferraz et al., 2018	*N* = 48	Resistance Training	Relieve pain and increase muscle strength
Hsu et al., 2021	*N* = 66	Resistance Training	The body composition, blood biochemistry and lower limb function of patients were improved.
Devrimsel et al., 2019	*N* = 60	Neuromuscular electrical stimulation	Relieve pain and improve function
Hinman et al., 2007	*N* = 71	Aquatic physical therapy	Relieve pain and improve physical function, strength, and quality of life
Xiao et al., 2021	*N* = 68	A Wuqinxi exercise	Relieve pain and improve function
Yuenyongviwat et al., 2020	*N* = 86	Hip abductor strengthening exercises	Expedite improvement of less pain, symptoms, activity in daily living and quality of life
Rabe et al., 2018	*N* = 42	The Combined Application of Neuromuscular Electrical Stimulation and Volitional Contractions	Alleviate pain and improve physical performance
Lai et al., 2018	*N* = 40	Strength exercise	Improve the knee flexion proprioception
Steinhilber et al., 2017	*N* = 210	Tübingen exercise therapy	Increase muscle strength
Kuptniratsaikul et al., 2019	*N* = 80	Underwater treadmill exercise	Relieve pain and improve function
Oliveira et al., 2012	*N* = 100	Quadriceps strengthening exercises	Improve pain, function, and stiffness
Wang et al., 2007	*N* = 38	Aquatic exercise	Improve knee and hip flexibility, strength and aerobic fitness
Nery et al., 2021	*N* = 60	A progressive resistance exercise	Relieve pain and improve function
Wang et al., 2016	*N* = 39	Whole-body vibration training with quadriceps strengthening exercise	Improve symptoms, physical function and spatiotemporal parameters
Pisters et al., 2010	*N* = 200	Behavioral graded activity	Increase the patient' s exercise compliance and physical activity
An et al., 2013	*N* = 28	Baduanjin	Relieve pain and improve function
Trans et al., 2009	*N* = 52	Whole body vibration	Increase muscle strength and proprioception
Sevick et al., 2000	*N* = 439	Resistance training	Improve physical function
Ojoawo et al., 2016	*N* = 45	Proprioceptive exercises	Relieve pain and joint stiffness
Villadsen et al., 2014	*N* = 165	Neuromuscular exercise	Relieve pain and improve activity of daily living
Wang et al., 2021	*N* = 128	Quadriceps strengthening exercises	Relieve pain, increase physical function, improve self-efficacy and improve quality of life.

(Continued)

TABLE 2 | (Continued)

Researchers	Number of studies/subjects	Intervention studied	Exercise effect
Jorge et al., 2015	*N* = 29	Progressive resistance exercise	Relieve pain, improve function and improve quality of life.
Penninx et al., 2002	*N* = 439	Aerobic and resistance exercise	Relieve pain and improve walking speed.
Simão et al., 2012	*N* = 32	Whole-body vibration training	Improve patients' self-perception of pain, balance, gait quality and inflammatory markers.
Lun et al., 2015	*N* = 72	Hip and leg strengthening exercise	Improve pain, function, and quality of life
Maurer et al., 1999	*N* = 113	Isokinetic quadriceps exercise	Relieve pain and improve function
Bruce-Brand et al., 2012	*N* = 41	Resistance training and neuromuscular electrical stimulation	Improve function, disability and pain
Hiyama et al., 2012	*N* = 40	Walking exercise	Improve executive function and dual-task performance
Foley et al., 2003	*N* = 105	A hydrotherapy resistance exercise with a gym based resistance exercise	Improve muscle strength and function.
Tsauo et al., 2008	*N* = 60	Sensorimotor training	Improve the patients' proprioception in the knee joints and their self-reported function
Topp et al., 2002	*N* = 102	Dynamic or isometric resistance training	Improve functional ability and reduce knee joint pain
Munukka et al., 2016	*N* = 87	Aquatic resistance training	Improve cardiorespiratory fitness
Samut et al., 2015	*N* = 42	Isokinetic and aerobic exercise training	Enhance muscle strength and functional ability
Wang et al., 2011	*N* = 84	Aquatic exercises and land-based exercises	Relieve pain, improve knee joint range of motion and quality of life
Chen P.-Y. et al., 2021	*N* = 68	Tai chi exercise	Enhance physical function
Song et al., 2003	*N* = 72	Tai chi exercise	Improve symptoms, balance, and physical functioning.

established an OA mouse model to study the effect of running on articular cartilage and bone of OA patients and observed the changes of biochemical signals and articular cartilage of running mice after eight weeks. They found that the content of reactive oxygen species in mice increased after exercise. Exercise can promote autophagy and protect the articular cartilage and bone of OA patients by regulating oxidative stress. Another study (Cifuentes et al., 2010) has established an OA rat model. The experimental group was exposed to treadmill exercise for 8 weeks to observe the pathological changes of articular cartilage. In comparison with OA rats that did not undergo exercise, the protein and polysaccharide contents on the surface of the articular cartilage of rats after eight weeks of the exercise was relatively high. This experiment confirmed that training can enhance the oxidative stress mechanism and protect articular cartilage. Moderate-intensity exercise plays different roles in different stages of OA progression. In the early stage of OA, the average power of movement can delay the progression of OA by promoting autophagy. In the late stage of OA, moderate-intensity exercise can over-activate purinergic receptor P2X ligand-gated ion channel 7 and increase the number of apoptotic cells, thus aggravating the progression of OA. Throughout the OA progression, the body may promote autophagy or apoptosis through the IRE1-mTOR-PERK signal axis to delay or accelerate the pathological process of OA (Li Z. et al., 2021).

The Role of Exercise in Non-coding RNA

Exercise can alleviate the pathological changes of OA by regulating the expression of ncRNA. The practice affect the face of miRNA, lncRNA, and circRNA in articular cartilage, synovial membrane, and subchondral bone of OA patients.

miRNA is related to maintaining the typical morphology of articular cartilage. The detection of miRNA expression in OA rats revealed that compared with the non-exercise rats, 394 differentially expressed miRNAs were detected in the exercise rats (Yang et al., 2020). The analysis of articular cartilage from different animals revealed that exercise could change the miRNA expression and improve the pathological changes of articular cartilage through a series of mechanisms. Dunn et al. (2009) analyzed the expression of miRNA in bovine articular cartilage. They found that the expression patterns of miR-221 and miR-222 in weight-bearing medial anterior condylar articular cartilage was higher than those in non-weight-bearing medial posterior condylar articular cartilage. When the articular cartilage was loaded with weight, miR-221 downregulated type II collagen and Sox9, and miR-222 downregulated HDAC4 and MMP-13, maintaining the typical morphology of articular cartilage. Guan et al. (2011) subjected chicken chondrocyte samples to mechanical stimulation to analyze the roles of relevant miRNA in the mechanical stimulation using microarray technology. Results show that mechanical stimulation could upregulate the miR-365 expression in chondrocytes. miR-365 stimulated the differentiation of chondrocytes by targeting histone deacetylase 4 (HDAC4) and finally alleviated the pathological process of cartilage tissue. In addition, the expression levels of many lncRNA changed during exercise. Zhou et al. (2021) established an OA mouse model. Mice with moderate-intensity exercise intervention had an upregulated lncRNA H19 expression, thickened articular cartilage, and resolved OA compared with mice without exercise intervention. Under the stimulation of mechanical stress, lncRNA-MSR was activated and then competitively bound to miR-152, thereby promoting the expression of TMSB4 and leading to the degradation of the

ECM (Liu Q. et al., 2016). The regulatory role of circRNA during exercise is also crucial. A total of 104 circRNA were differentially expressed (44 upregulated and 60 downregulated), with increased circRNA-MSR expression, in damaged articular cartilage compared with intact articular cartilage. circRNA-MSR expression was downregulated after mechanical stress was applied to the cartilage. The downregulation of circRNA-MSR can inhibit the expression of TNF-α and promote the degradation of the extracellular chondrocyte matrix, thus enhancing the structure and function of cartilage (Liu et al., 2017). In addition, circRNA-MSR can directly target miR-643 to u-regulate MAP2K6. The downregulation of circRNA-MSR expression can promote cell proliferation and reduce cartilage damage (Jia and Wei, 2021). qRT-PCR and Western blot have been used to analyze the genes related to cartilage differentiation in cartilage tissues. The results show that the expression of circUNK was upregulated, which improved the cartilage injury in OA rabbit and promoted the expression of molecules related to cartilage differentiation, such as PCNA, SOX9, Col II, Aggrecan, and protein-polysaccharide. These molecules had sound effects on the proliferation and differentiation of articular cartilage. In conclusion, exercise or mechanical stimulation can lead to changes in the expression of ncRNA, which prevents and improves the pathological changes of articular cartilage, synovial membrane, and subchondral bone through a series of mechanisms, thereby delaying the progression of OA (Fang et al., 2021).

EFFECTS OF DIFFERENT EXERCISE TYPES ON HUMAN OSTEOARTHRITIS

Many types of training can relieve pain, enhance muscle strength and improve joint stiffness (Daenen et al., 2015). For healthy people, exercise can promote good health, while for OA patients, dysfunction can be improved and diseases can be treated (Skou et al., 2018). At present, there are many types of sports for the treatment of OA, such as aerobic exercise, anti-resistance exercise, neuromuscular training, etc (Jansen et al., 2011). In addition, Chinese traditional sports such as Baduanjin, Wuqinxi, and yoga are also applied to the prevention and treatment of OA (Li et al., 2020). This paper summarizes the research on training types of OA patients by summarizing related literature, as shown in **Table 2**.

CONCLUSION AND OUTLOOK

At present, the incidence of OA is very high, and its pathogenesis remains unclear. The treatment of OA by exercise has received increasing research attention. Not all types of sports used can alleviate OA. The result of different types, intensity, and time of sports on OA differs.

Some studies believe that exercise does not affect OA. For example, Rios et al. (2020) intervened in KOA rats with aerobic exercise for 12 weeks and measured bone mineral density and knee joint injury. The results showed that training did not affect the common knee injury, accelerate the progression of OA, and alleviate the pathological changes of OA. Other studies believe that exercise accelerates the progression of OA. For example, Liu S.-S. et al. (2016) established a rat model of exercise-induced OA. They analyzed and compared the expression levels of various related mRNA, protein, and pathways in the standard and injury group of exercise-induced OA by using RT-qPCR, Western blot analysis, and immunohistochemical staining. The results showed that excessive pressure would lead to abnormal expression of many biochemical signals and abnormal activation of the Wnt/β-catenin pathway, leading to induced OA. Exercise has different effects on healthy and damaged articular cartilage (Rojas-Ortega et al., 2015). Notably, for articular cartilage injury, if high-intensity practice is continued, the activity of catabolic proteins is more vital than that of anabolic proteins. The body's metabolism is imbalanced, thus efficiently inducing OA. Twelve weeks of high-intensity treadmill training in rats will increase the levels of some apoptosis-related proteins and inflammation-related factors, such as caspase-3, IL-1α, and TNF-α, which is the precursor of OA (Franciozi et al., 2013). The results indicate that high-intensity exercise may lead to the occurrence and development of OA. In addition, moderate exercise can delay the pathological process of OA. For example, a daily external force has been used to compress OA mice under low or medium intensity, and the pathological changes of articular cartilage were observed in the second and sixth weeks. Moreover, low- and medium-intensity compression can reduce the degeneration of articular cartilage and osteophytes of subchondral bone in mice and is very beneficial to the damaged joints, making it an effective method for the treatment of OA (Holyoak et al., 2019).

At present, many exercises have therapeutic effects on OA, such as aerobic exercise, strength training, swimming, neuromuscular exercise, proprioceptive training, and balance training. Different types of motion produce other effects. Aerobic exercise is the most widely used in OA patients, and it can reduce the expression of IL-1β, caspase-3 and MMP-13 and prevent cartilage degradation in KOA rats (Assis et al., 2016). Aerobic exercise may be the best training method to reduce pain and improve body function (Goh et al., 2019). However, aerobic exercise with different intensities has different effects on OA patients with varying degrees of injury. Low-intensity aerobic exercise had a better therapeutic effect in patients with severe OA (Messier et al., 2021), while high-intensity aerobic exercise had a better therapeutic effect in patients with mild OA (Multanen et al., 2017). In addition, strength training could reduce the activity of MMP-2 in the quadriceps tendon of the OA rat model (Vasilceac et al., 2021), which was the most effective in improving muscle strength, and neuromuscular training was the best training method to relieve OA pain (Ageberg and Roos, 2015). Swimming intervention in the early stage of OA can alleviate the stiffness of the knee joint and is better than land exercise (Lund et al., 2008; Hsieh and Yang, 2018; Munukka et al., 2020). Land exercise can be performed after the patients' joints have a certain degree of flexibility. Land exercise is better than water exercise in improving pain and enhancing function (Escalante et al., 2011). Many traditional techniques are being applied more and more in OA, such as

Baduanjin (An et al., 2008), tai chi chuan (Zhang Z. et al., 2020), Wuqinxi (Xiao and Li, 2021), and yoga (Kuntz et al., 2018). They can improve the physical function of OA patients and have a significant impact on the psychological status of OA patients. In addition, new intervention methods such as virtual reality and sports games have been gradually used to improve people's physical and psychological conditions (Sadeghi and Jehu, 2022). These sports have excellent development prospects in the treatment of OA.

Although many types of exercise can be used to prevent or treat OA, our most recommended method is to formulate a unique exercise prescription for each patient with OA based on the FITT (Frequency, Intensity, Time, and Type) principle. According to the exercise prescription, a study (de Rooij et al., 2017) formulated a personalized rehabilitation program for 126 OA patients for 20 weeks. It was finally found that personalized exercise therapy could effectively improve the OA of the knee joint and the body function of the patients. Exercise prescription recommendations for patients with OA are as follows (Bennell et al., 2014a): (1) Exercise frequency: It is recommended that in the initial stage, the patient had better exercise at least 12 times within three months to master the skills and ensure compliance, and then the frequency was gradually increased and maintained to two to three times a week, and a week of moderate-intensity exercise lasting 150 to 300 min was accumulated; (2) Exercise intensity: Moderate intensity exercise is recommended. Namely, the heart rate is 120–150 beats/min, and the oxygen consumption during exercise is 50–70% of the maximum oxygen consumption; (3) Exercise time: The recommended exercise time is 30–60 min per day. The exercise time was gradually increased from a short time to 30–60 min/d; (4) Exercise type: generally, aerobic exercise and strength training are recommended. Aerobic exercise such as swimming, Tai Ji Chuan, unfavorable for mountaineering, climbing stairs and other excessive weight-bearing movements, strength training have equal length, such as Zhang or isokinetic resistance movement, etc., recommend the weight-bearing exercise is given priority to; (5) Precautions: Pain relief can be obtained only after 8–11 weeks of exercise therapy. Continuous exercise for more than 12 weeks is generally recommended to relieve decreased muscle strength and muscle atrophy associated with OA. Patients should also receive regular education during training to improve their self-management awareness, compliance and exercise efficacy. It is normal to feel some discomfort or pain during exercise. Ice application is required at the joints for 15–20 min after training. If severe pain occurs during exercise or swelling aggravates the next day, you should timely adjust the amount of activity. Different types of patients may have other exercise prescriptions. Patients with higher obesity are more suitable for aquatic exercise. For patients with upper limb OA, emphasis should be placed on improving the affected joints' range of motion and flexibility. For patients with lower limb OA, emphasis should be placed on improving patients' muscle strength and body stability. Therefore, we should formulate individualized exercise prescriptions according to the degree of lesion and needs of OA patients.

This review describes the pathological change mechanism of OA and the molecular mechanism of exercise in the treatment of OA. By using RT-qPCR, Western blot analysis, and immunohistochemical staining, we have found that the expression levels of related mRNA, protein, and pathways were changed in OA patients after exercise. This review also summarized animal experiments related to exercise and OA and the role of different exercise types in human OA, described the research progress of exercise in the prevention and treatment of OA, and provided a basis for exercise intervention to treat OA in the future. Exercise, as an intervention means, has a great development prospect in the treatment of OA.

AUTHOR CONTRIBUTIONS

X-AZ and X-QW: conceptualization, project administration, and funding acquisition. HK, X-AZ, and X-QW: writing – review and editing. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Traditional Chinese Medicine and Sarcopenia: A Systematic Review

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Sarcopenia has become a key challenge for healthy aging in older adults. However, it remains unclear whether traditional Chinese medicine can effectively treat sarcopenia. This systematic review analyzes the current evidence for the effect of traditional Chinese medicine (TCM) on sarcopenia. We searched for articles regarding sarcopenia treated by TCM in Cochrane library, PubMed, SinoMed, Web of Science, Embase, and the China National Knowledge Infrastructure (from inception until 10 December 2021). Two researchers independently screened the literature in accordance with the inclusion and exclusion criteria designed by PICOS principles. The risk of bias was assessed by the Cochrane Risk of Bias (ROB) tool. The quality of evidence was assessed by the grading of recommendations, assessment, development, and evaluation (GRADE). Participants' characteristics, interventions, and the relevant results of the included studies were extracted and synthesized in a narrative way. The total number of participants in the 21 included studies was 1,330. Most of the studies evaluated physical function (n = 20) and muscle strength (n = 18), and a small number of studies (n = 6) assessed muscle mass. Overall, it was found that TCM had a positive impact on muscle strength (grip strength, chair stand test) and physical function (6-m walking speed, timed up and go test, sit and reach) in patients with sarcopenia, inconsistent evidence of effects on muscle mass. However, the small sample size of the included studies led to imprecision in the results, and the presence of blinding of the studies, allocation concealment, and unreasonable problems with the control group design made the results low grade. Among these results, the quality of evidence for grip strength (n = 10) was of medium grade, and the quality of evidence related to the remaining indicators was of low grade. This systematic review showed that traditional Chinese Qigong exercises and Chinese herbal medicine have a positive and important effect on physical performance and muscle strength in older adults with sarcopenia. Future high-quality multicenter randomized controlled trials (RCTs) with large samples are needed to determinate whether acupuncture and other therapies are effective in treating sarcopenia.

Keywords: sarcopenia, traditional Chinese medicine, Chinese herb, Qigong exercise, acupuncture, systematic review

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INTRODUCTION

Sarcopenia is a progressive and pervasive age-related primary skeletal muscle disorder involving the accelerated loss of muscle strength and mass, which is associated with increased adverse outcomes, including fall fracture, disability, and mortality (Cruz-Jentoft and Sayer, 2019; Chen et al., 2020). Sarcopenia is recognized as an independent condition and was given an International Classification of Diseases-10 code in 2016. The 2019 European Working Group on Sarcopenia in Older People (EWGSOP) updated definition suggests that physical performance should be considered a measure of the severity of sarcopenia (Cruz-Jentoft et al., 2019). More than 50 million people worldwide currently have sarcopenia, and it is expected that more than 200 million people will have sarcopenia by 2050 (Sousa et al., 2016). Physical dysfunction is the primary problem caused by sarcopenia. In Western society, as many as 42% of individuals under 60 years of age have difficulties performing the activities of daily life (e.g., walking speed or standing up from a chair), 15–30% report being unable to lift or carry 10 pounds or more, and more than 30% are confronted with physical disabilities (Louie and Ward, 2010). Sarcopenia has become a key challenge for healthy aging in older adults because the early symptoms are not obvious and are difficult to prevent and manage effectively. The main international treatments for sarcopenia are currently exercise, high-protein nutritional supplementation, and medication (Cruz-Jentoft and Sayer, 2019). However, medications (such as sex hormones, growth hormone, vitamin D, testosterone, and angiotensin-converting enzyme inhibitors) and nutritional supplementation are ineffective (Li et al., 2022). Relevant evidence-based clinical practice guidelines were published in 2018 with strong recommendations for exercise as the primary treatment for sarcopenia (Dent et al., 2018). Exercise has a positive impact on the health of older adults, but aging is usually accompanied by a significant decline in the body's motor organs and functions, thus emphasizing the importance of appropriate exercise intensity and exercise forms for older adults. Traditional Chinese medicine (TCM), the oldest existing medical model for maintaining health and curing diseases, includes intervention methods such as herbal medicine, acupuncture, moxibustion, Tuina, and Qigong (Chan, 2005). Qigong is a low-load aerobic exercise that is effective in preventing skeletal muscle atrophy with long-term practice (Penn et al., 2019). Chinese herbs, which are pure in nature, have few toxic side effects, and are effective in treating chronic diseases, may become an important treatment to sarcopenia. TCM has gradually been recognized by the public as a supplement to Western medical treatment (Yu et al., 2006). However, no previous study has evaluated the quality of the evidence for TCM for the treatment of sarcopenia.

Moreover, the mechanism by which TCM affects sarcopenia is not yet clear, and it may be related to enhancing neural recruitment, maintaining protein homeostasis, and reducing autophagy and inflammation. Therefore, we performed a systematic review to investigate the clinical evidence of current TCM therapies to treat sarcopenia and analyze their effects.

METHODS

Search Strategy

Six electronic databases—Cochrane library, PubMed, SinoMed, Embase, Web of Science, and the China National Knowledge Infrastructure—(were screened from inception until 10 December 2021. The following Medical Subject Headings (MeSH) terms and their synonyms were used either singularly or in combination: ("Traditional Chinese exercise" OR "Qigong" OR "Tai Chi" OR "Gongfu" OR "Yi Jin Jing" OR "Ba Duan Jin") AND ("Sarcopenia" OR "Sarcopenias"); ("acupuncture" OR "electric acupuncture") AND ("Sarcopenia" OR "Sarcopenias"); ("Chinese herbal medicine" OR "herbal medicine" OR "herbs") AND ("Sarcopenia" OR "Sarcopenias"). Reference lists of related reviews were searched for additional studies.

Inclusion and Exclusion Criteria

The PICOS strategy was defined as follows: "P" (patient)—patients with sarcopenia of any age, gender, or race; "I" (intervention)—TCM; "C" (comparison)—comparison with a blank group or a different intervention group; "O" (outcome)—relevant indicators to evaluate muscle and body function; and "S" (study design)—randomized controlled studies, cohort studies, observational studies, or case–control studies.

Articles were included if they met all of the following criteria: 1. participants were diagnosed with sarcopenia based on any established definition (by a working group, a certain article, or clinical experience); 2. patients' age $\geq$ 60 years; 3. the study included at least one traditional Chinese medicine treatment method, which could be herbal medicine, traditional Chinese exercise, acupuncture, and their combination. 4. Outcomes included muscle mass, muscle strength, physical function, or related biochemical indicators.

The exclusion criteria were as follows: 1. no original data were included (e.g., review, protocol, and abstract); 2. the participants had other accompanying diseases (e.g., cancer, liver cirrhosis, diabetes, stroke, depressive disorder, and metabolic syndrome).

Data Extraction

Two researchers screened the literature independently in accordance with the inclusion and exclusion criteria and used the data extraction table to extract information, such as 1. basic information (e.g., author, year of publication, number of participants and age range); 2. group design measures and measured time points; 3. main outcome results. Any disagreement between the two authors was resolved by a consensus procedure. A third author was further consulted if the disagreement persisted.

Risk of Bias and Quality Assessment of the Individual Studies

Two authors independently assessed the methodological quality of these studies using the Cochrane Risk of Bias (ROB) tool. The tool assessed the following seven characteristics: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment;

incomplete outcome data; selective reporting; and other bias. Based on the results of the risk of bias assessment of the included studies, the two authors independently assessed the quality level of the study results using GRADE software. According to the GRADE working group instructions, five factors, namely bias, inconsistency, indirectness, imprecision, and publication bias, lead to lower quality of evidence; and for each study, the quality of evidence was categorized into four levels: high, medium, low, and very low (Guyatt et al., 2008).

Data Analysis

There was considerable heterogeneity in the included studies in terms of diagnosis of disease, sample size, outcome indicators, and interventions. We concluded that based on these heterogeneities and differences in study design, meta-analyses would not provide valid results and the risk of meta-analysis providing incorrect results was considerable. Participants' characteristics, interventions, and the relevant results of the included studies were extracted and synthesized in a narrative way.

RESULTS

Literature Search and Study Selection

The selection process for this systematic review is shown in **Figure 1**. We used a 2-week period to identify 860 studies from the electronic database by the search strategy described above. After removing duplicate literature, 562 studies remained. After reading the titles and abstracts, 528 studies were excluded. The remaining 34 papers were read in full text. Full-text review removed 13 of these documents, leaving 21 studies that met all of the inclusion and exclusion criteria.

Characteristics and Quality of Studies

The results of data extraction are shown in **Tables 1**, **2**. A total of 19 trials were from China, one trial was from Brazil, and one trial was from Poland. A total of 21 studies involved a total of 1,330 participants, ranging from 15 to 214 per study. The age range of the included population was between 60 and 101 years. These studies included samples with different diagnostic criteria. Namely, nine studies referred to the Asia working group for sarcopenia (Ren et al., 2016; Zhao et al., 2016; Zhu et al., 2016, 2018; Wen et al., 2018; Liang et al., 2019; Chen, 2020; Zhou et al., 2020; Chen et al., 2021); three studies used European working group for sarcopenia diagnostic criteria (Soares Mendes Damasceno et al., 2019; Fang et al., 2020; Morawin et al., 2021); six studies (Yan et al., 2007; Gong et al., 2011; Jing et al., 2011; Liu et al., 2016; Wang et al., 2016; Zhu et al., 2017) complied with Roubenoff's view of sarcopenia (Rosenberg, 2011); two studies did not provide diagnostic criteria, but only described subjects as having been diagnosed with sarcopenia in the hospital (Yang and Chen, 2016; Liang et al., 2019); and one study used the 2011 ISCCWG (International Sarcopenia Consensus Conference Working Group) diagnostic criteria (Liu et al., 2020). There was a large difference in outcome indicators in the included studies, and there were many scales and no specific content and scoring criteria. Twenty-one studies were divided into three broad categories by intervention methods: six herbal medicine studies, two acupuncture studies, and 13 Traditional Chinese exercise studies, with interventions ranging in duration from 10 days to 10 months.

A total of 20 trials were randomized controlled trials, and one study was a before–after study in the same patient. There were 20 randomized controlled studies mentioned randomization, but four of these studies (Ren et al., 2016; Wang et al., 2016; Zhao et al., 2016; Chen, 2020) did not provide detailed information. Only one study (Fang et al., 2020) provided a specific method of allocation concealment, this was not reported in most of the studies. All of the studies analyzed baseline information, and comparability of the baseline characteristics between the groups was an indicator of whether randomization was actually achieved. Imperfect diagnostic criteria led to uncertain additional risks in seven studies. Only one study (Soares Mendes Damasceno et al., 2019) specifically mentioned that the trial was single-blinded, but the lack of blinding was considered a relatively low risk factor for reducing the quality of the evidence. Overall, the low risk level accounted for about 53% of all risk levels assessed, and the uncertainty was about 46%, as shown in **Table 3**. All of the studies had small sample sizes, with the largest sample size being 214 and the smallest sample size being 15, and the smaller sample sizes reduced statistical efficacy and limited the reliability of the results. A total of 11 studies used multiple methods of combined treatment; the main confounding factors were not clearly described; and the results were not adjusted for confounding factors. Most of the included studies were conducted in China, so the effect of ethnicity may have added to the limitations of the results. A total of nine studies reported ethical approval (Gong et al., 2011; Zhu et al., 2016; Wen et al., 2018; Liang et al., 2019; Soares Mendes Damasceno et al., 2019; Fang et al., 2020; Liu et al., 2020; Chen et al., 2021; Morawin et al., 2021). According to the GRADE working group guidelines, the favorable factors of a larger sample size, clear and direct data, and high consistency of results improve the quality grade of grip strength results. The evidence for grip strength was of moderate quality among the results generated from these studies, while the evidence for the remaining results was of low quality, as shown in **Tables 4**–**6**.

Outcome Characteristics and Major Findings

There were six studies (Ren et al., 2016; Wen et al., 2018; Liang et al., 2019; Chen, 2020; Li, 2020; Chen et al., 2021) regarding Chinese herbal medicine for treating sarcopenia conducted on the basis of routine rehabilitation (exercise and nutrition), and three studies each used Ba Zhen decoction and Bu Zhong Yi Qi decoction. To investigate the effect of herbs on muscle strength and muscle mass, four studies (Ren et al., 2016; Wen et al., 2018; Liang et al., 2019; Chen, 2020) measured grip strength and the appendicular skeletal muscle mass index (ASMI kg/m^2). Physical function was assessed in a variety of ways, with four studies (Ren et al., 2016; Liang et al., 2019; Chen, 2020; Li, 2020) using walking speed, three studies (Wen et al., 2018; Liang et al., 2019;

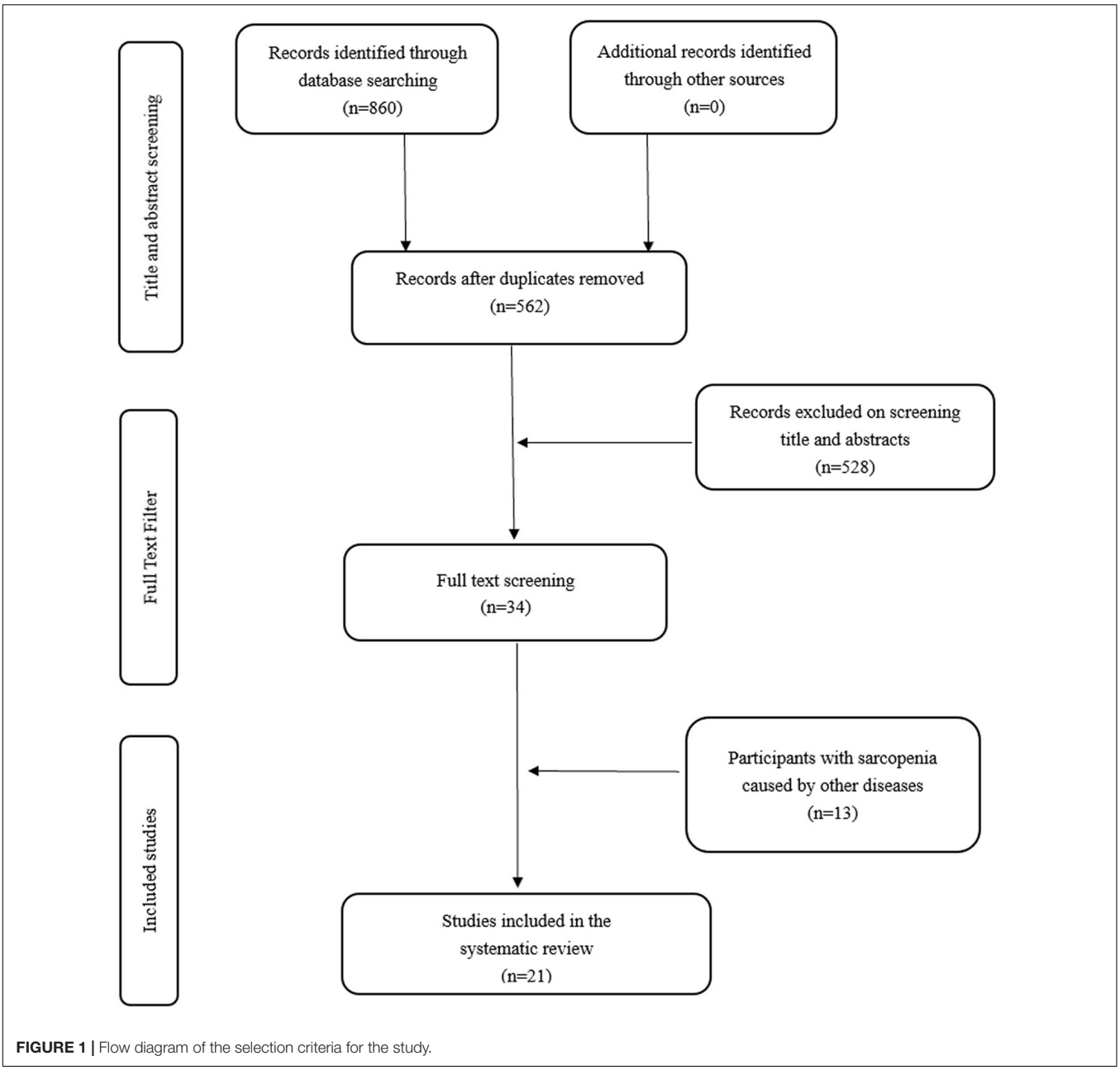


FIGURE 1 | Flow diagram of the selection criteria for the study.

Li, 2020) using activities of daily living (ADL), and one study (Wen et al., 2018) also using the short physical performance battery (SPPB). The results of five studies (Ren et al., 2016; Wen et al., 2018; Liang et al., 2019; Chen, 2020; Li, 2020) showed a significant increase in muscle strength and physical function in the herbal group compared with the control group ($p < 0.05$). Meanwhile, the results of three studies (Ren et al., 2016; Wen et al., 2018; Chen, 2020) showed a significant increase in muscle mass in the herbal group compared to the control group, while one study showed (Liang et al., 2019) no significant change in muscle mass with herbal medicine. The remaining study (Chen et al., 2021) investigated the effect of Bu Zhong Yi Qi decoction on inflammatory factors in patients with sarcopenia, and after taking it, the patients had lower serum IL-6 and TNF-α levels than the control group ($p < 0.05$).

There were 13 studies focused on Chinese traditional exercise (TCE). Among them, ten studies (Yan et al., 2007; Gong et al., 2011; Jing et al., 2011; Liu et al., 2016; Wang et al., 2016; Yang and Chen, 2016; Zhao et al., 2016; Zhu et al., 2017, 2018; Fang et al., 2020) involved Yi Jin Jing; two studies (Zhu et al., 2016; Morawin et al., 2021) involved Tai Chi; and one study (Zhou et al., 2020) involved Ba Duan Jing (BDJ). Among the 10 studies on the use of Yi Jin Jing for sarcopenia, eight studies used Yi Jin Jing only; one study (Zhao et al., 2016) involved a combination of Tuina, Yi Jin Jing, and resistance exercise; and another study (Yan et al., 2007) used Yi Jin Jing combined with Tuina. In

TABLE 1 | Characteristics of the included studies of Traditional Chinese Qigong exercises.

Study	Age	Number		Diagnostic criteria	Intervention		Outcome measures
		A	B		A	B	
Wang et al., 2016	66.79 ± 4.76	38	37	Roubenoff's view	Yi Jing Jin, three times a week for 1 h each time for 12 weeks	No training	In-chair sitting-to-standing and squats, shoulder flexibility, sit and reach
Zhu et al., 2017	65.6 ± 11.4	32	31	Roubenoff's view	Yi Jing Jin, once per day for 40 min for 12 weeks	Health education	Grip strength, in-chair sitting-to-standing and squats
Jing et al., 2011	68.22 ± 4.09	15	16	Roubenoff's view	Yi Jing Jin, three times a week for 1 h each time for 8 weeks	No training	6-m gait speed, in-chair sitting-to-standing and squats, shoulder flexibility, sit and reach
Zhao et al., 2016	67.8 ± 3.8	6	6	AWGS	Yi Jing Jin combined with Tuina, three times a week for 40 min each time for 8 weeks	No training	Grip strength, 6-m gait speed
Liu et al., 2016	67.86 ± 6.86	31	30	Roubenoff's view	Yi Jing Jin, three times a week for 8 weeks	No training	PT, AP, TW
Yang and Chen, 2016	77.5 ± 4.3	30	30	Unspecified	Yi Jing Jin, three times a week for 16 weeks	Tuina, three times a week for 16 weeks	Walking steps, lower extremity muscle strength score, skeletal muscle mass index
Fang et al., 2020	82.8 ± 8.5	15	14	EWGSOP	Yi Jing Jin, three times a week for 6 months	Health education	TUGT, MFES
Yan et al., 2007	>60	12	0	Roubenoff's view	Yi Jing Jin combined with Tuina for 8 weeks	–	In-chair sitting-to-standing and squats
Zhu et al., 2018	67.17 ± 10.72	20	20	AWGS	Yi Jing Jin, once daily for 12 weeks	Tuina, three times a week for 12 weeks	FGA
Gong et al., 2011	66.4 ± 5.47	30	30	Roubenoff's view	Yi Jing Jin, three times a week for 8 weeks	No training	PT, AP, TW
Zhu et al., 2018	88.8 ± 3.7	24	27	AWGS	Tai-Chi, five times a week for 40 min each time for 8 weeks	No training	Grip strength, 6-m gait speed, TUGT, FTSST
Morawin et al., 2021	73.6 ± 7.9	40	40	EWGSOP	Tai-Chi, for 10 months	Health education	6-m gait speed, Grip strength, CRP, TNFα
Zhou et al., 2020	72.67 ± 9.56	20	20	AWGS	BDJ, five times a week for 8 weeks	No training	TUGT, in-chair sitting-to-standing and squats, Berg scale

A: Intervention Group; B: Control Group.
TUGT, group timed-up-and-go test; FTSST, five-times-sit-to-stand test; RMS, root mean square; AEMG, average electromyographic activity; IEMG, integrated electromyogram; CRP, C-reactive protein; TNFα, tumor necrosis factor; MFES, Modified Falls Efficacy Scale; PT, peak torque; AP, average power; TW, total work.

two of the studies (Yang and Chen, 2016; Zhu et al., 2018), the control group underwent Tuina intervention. To evaluate physical function, four studies (Jing et al., 2011; Zhao et al., 2016; Zhu et al., 2016; Morawin et al., 2021) used a 6-m walking speed test; three studies (Zhu et al., 2016; Fang et al., 2020; Zhou et al., 2020) used the Time Up and Go Test (TUGT); and three studies (Jing et al., 2011; Wang et al., 2016; Li, 2020) used sit and reach. The scales used in these studies included the Berg Balance Scale, Modified Falls Efficacy Scale (MFES), Functional Gait Assessment (FGA), Barthel Index, Five Times Sit-to-Stand Test (FTSST), Tetrax index, and EPESE Physical Assessment Scale. Ten studies showed significant improvements in physical performance after the intervention compared with their respective control groups ($p < 0.05$). Yang and Chen (Yang and Chen, 2016) used walking steps to assess physical performance, but no time frame was given; lower extremity muscle strength scores were used to assess muscle strength, but no specific measurements or scoring methods were given. To evaluate muscle strength, six studies (Wang et al., 2016; Zhao et al., 2016; Zhu et al., 2016, 2017; Zhou et al., 2020; Morawin et al., 2021) used grip strength; four studies (Yan et al., 2007; Jing et al., 2011; Wang et al., 2016; Zhu et al., 2017) used the number of in-chair sitting-to-standing and squats in 15 s; and two studies (Gong et al., 2011; Liu et al., 2016) used the Biodex isometric muscle strength testing system. There were 10 studies showed that after exercise, patients' muscle strength increased significantly compared with their respective control groups ($p < 0.05$). To evaluate muscle mass, two studies

TABLE 2 | Characteristics of the included studies of Chinese herbal medicine and acupuncture.

Study	Age	Diagnostic criteria	Intervention		Outcome measures	Components/points
			Intervention group	Control group		
Chen, 2020	78 ± 5.21	AWGS	Bu-Zhong-Yi-Qi decoction combined with conventional treatment for 90 days	Conventional treatment: nutritional support and exercise for 90 days	Grip strength, 6-m gait speed	*Atractylodes macrocephala*, Astragalus, Radix pseudostellariae, *Ficus hirta*, Tortoise plastron, Degelatined deer-horn, Placenta Hominis, Angelica, Fructus Aurantii, Cimicifuga, Radix Bupleuri, Liquorice, Radix Moghaniae
Wen et al., 2018	73.11 ± 4.80	AWGS	Bu-Zhong-Yi-Qi decoction combined with conventional treatment for 12 weeks	Conventional treatment: nutritional support and exercise for 12 weeks	Grip strength, SPPB, Barthel	*Atractylodes macrocephala*, Astragalus, Radix pseudostellariae, *Ficus hirta*, Tortoise plastron, Degelatined deer-horn, Placenta Hominis, Angelica, Fructus Aurantii, Cimicifuga, Radix Bupleuri, Liquorice, Radix Moghaniae
Chen et al., 2021	66 ± 7.27	AWGS	Bu-Zhong-Yi-Qi decoction combined with conventional treatment for 90 days	Conventional treatment: nutritional support and exercise for 90 days	IL-6, TNF-α	*Atractylodes macrocephala*, Astragalus, Radix pseudostellariae, *Ficus hirta*, Tortoise plastron, Degelatined deer-horn, Placenta Hominis, Angelica, Fructus Aurantii, Cimicifuga, Radix Bupleuri, Liquorice, Radix Moghaniae
Ren et al., 2016	73.45 ± 3.46	AWGS	Bazhen decoction combined with conventional treatment for 12 weeks	Conventional treatment: nutritional support and exercise for 12 weeks	Grip strength, 6-m gait speed	*Atractylodes macrocephala*, Renshen, Liquorice, Poria cocos, Chuanxiong, Radix Rehmanniae Praeparata, Angelica, Radix Paeoniae Alba
Li, 2020	71.87 ± 5.26	Unspecified	Bazhen decoction combined with conventional treatment for 8 weeks	Conventional treatment: walk and Yi Jin Jing for 8 weeks	6-min walking distance, ADL, sit and reach	*Atractylodes macrocephala*, Renshen, Liquorice, Poria cocos, Chuanxiong, Radix Rehmanniae Praeparata, Angelica, Radix Paeoniae Alba
Liang et al., 2019	72.24 ± 3.20	AWGS	Bazhen decoction combined with conventional treatment for 12 weeks	Conventional treatment: nutritional support and exercise for 12 weeks	Grip strength, 6-m gait speed, ADL	*Atractylodes macrocephala*, Renshen, Liquorice, Poria cocos, Chuanxiong, Radix Rehmanniae Praeparata, Angelica, Radix Paeoniae Alba
Soares Mendes Damasceno et al., 2019	72 ± 7.90	EWGSOP	Acupuncture	No training	TUGT, Grip strength, IL6, IL10, and TNF-α	R3, BP3, BP6, VB34, F8, E36, TA6
Liu et al., 2020	68.12 ± 5.84	ISCCWG	Acupuncture combined with exercise (aerobic exercise, resistance exercise and balance training)	acupuncture combined with exercise (aerobic exercise, resistance exercise, and balance training)	Fugl-Meyer, Berg Scale, 4-m gait speed	Group A: ST36, K13, SP6 Group B: ST31, ST32, GB34

(Zhao et al., 2016; Morawin et al., 2021) used the ASMI (kg/m^2), but their findings showed no significant change in muscle mass after the intervention compared to the control group. In the Tai Chi study, one of the studies showed no improvement in grip strength in the Tai Chi group compared with the control group after 8 weeks of exercise, but there was a significant improvement in iliopsoas muscle strength ($p < 0.0001$).

TABLE 3 | Risk of bias evaluation for the included randomized controlled trials (RCTs).

Projects	High risk	Low risk	Unclear risk
Random sequence generation	1	19	0
Allocation concealment	0	1	19
Blinding of participants and personnel	0	1	19
Blinding of outcome assessment	0	0	20
Incomplete outcome data	0	20	0
Selective reporting	0	20	0
Other bias	0	13	7
Total	1 (0.007%)	74 (53%)	65 (46%)

Among the included studies, two studies were on acupuncture. In one study, acupuncture combined with exercise (aerobic exercise, resistance exercise, and balance training) and two groups of acupuncture points were compared. The results showed that patients who received acupuncture at the ST36 showed better 4-m gait speed than those in the other group (Liu et al., 2020). Another clinical study, which did not choose acupuncture at ST36 for treating sarcopenia, showed that acupuncture did not increase muscle strength and physical function (Soares Mendes Damasceno et al., 2019).

DISCUSSION

TCM may be used to delay sarcopenia by regulating the synthesis and degradation of muscle-related proteins, replenishing

TABLE 4 | Muscle strength for sarcopenia.

Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk (TCM)		
Grip strength	The mean grip strength in the intervention groups was 2.00 higher (0.44–3.55 higher)	641 (10 studies)	⊕⊕⊕⊖moderate[a]
Squats	The mean squats in the intervention groups were 2.25 higher (1.12–3.39 higher)	209 (3 studies)	⊕⊕⊖⊖low[a,b]
In-chair sitting-to-standing	The mean in-chair sitting-to-standing in the intervention groups was 2.45 higher (1.51–3.39 higher)	209 (3 studies)	⊕⊕⊖⊖low[a,b]
Peak torque of knee extensor muscle group (60°/s)	The mean 60°/speak torque of knee extensor muscle group in the intervention groups was 10.12 higher (0.90–19.35 higher)	121 (2 studies)	⊕⊕⊖⊖low[a,b]

**The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
CI, Confidence interval.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[a] *The included studies did not mention the allocation covert method or blind method, which made the bias risk of the study uncertain.*
[b] *Small sample size.*

TABLE 5 | Physical performance for sarcopenia.

Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk (TCM)		
6-m walking speed	The mean 6-m walking speed in the intervention groups was 0.21 higher (0.2–0.22 higher)	416 (2 studies)	⊕⊕⊖⊖Low[a,b]
TUGT	The mean TUGT in the intervention groups was 2.81 lower (4.08–1.55 lower)	69 (2 studies)	⊕⊕⊖⊖Low[a,b]
Sit and reach	The mean sit and reach in the intervention groups was 1.39 higher (0.9–1.88 higher)	228 (3 studies)	⊕⊕⊖⊖Low[a,b]

**The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
CI, Confidence interval.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[a] *The included studies did not mention the allocation covert method or blind method, which made the bias risk of the study uncertain.*
[b] *Small sample size.*

nutrients, promoting blood circulation, and eliminating inflammation, as shown in **Figure 2**.

Traditional Chinese exercises have originated from traditional Chinese medicine, and include Wu Qin Xi, Yi Jin Jing, Ba Duan Jin, and Tai Chi. These are gymnastic exercise consisting of various components such as endurance, resistance, balance, flexibility, breathing, and meditation (Nascimento et al., 2019). Exercise has a positive impact on the health of older adults, but the body's motor organs and functions decline significantly with aging; as a result, it is important to emphasize the appropriate form and intensity of exercise for older adults (Colleluori and Villareal, 2021). Yi Jin Jing is a kind of static exercise. After high-intensity interval static exercise in aging rats, the PGC-1α/FNDC5/UCP1 signaling pathway was activated, PGC-1α was upregulated, mitochondria increased, muscle fiber thickening was observed, and the skeletal muscle atrophy state was improved (Liu et al., 2021). The results of the included studies consistently show that Yi Jin Jing is an effective way to build muscle strength to prevent muscle atrophy, but there are limitations to the findings. Yi Jin Jing may be more helpful in improving lower limb strength and less effective in improving upper limb strength, considering that after practicing Yi Jin Jing, grip strength did not improve significantly, but the number of squats and in-chair sitting-to-standing within 15-s period increased significantly (Jing et al., 2011). Zhao et al. (2016) used a complex intervention that combined Tuina with Yi Jin Jing as one

TABLE 6 | Muscle mass for sarcopenia.

Outcomes	Illustrative comparative risks* (95%CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk (TCM)		
Muscle mass	The mean muscle mass in the intervention groups was 0.52 higher (0.1 lower to 1.14 higher)	472 (6 studies)	⊕⊕⊖⊖low[a,b]

**The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
CI, Confidence interval.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[a] *The included studies did not mention the allocation covert method and blind method, which made the bias risk of the study uncertain.*
[b] *Three studies, Ren et al. (2016), Wen et al. (2018), and Chen (2020), showed an increase in muscle mass, while the fourth study Liang et al. (2019) showed no significant change in muscle mass.*

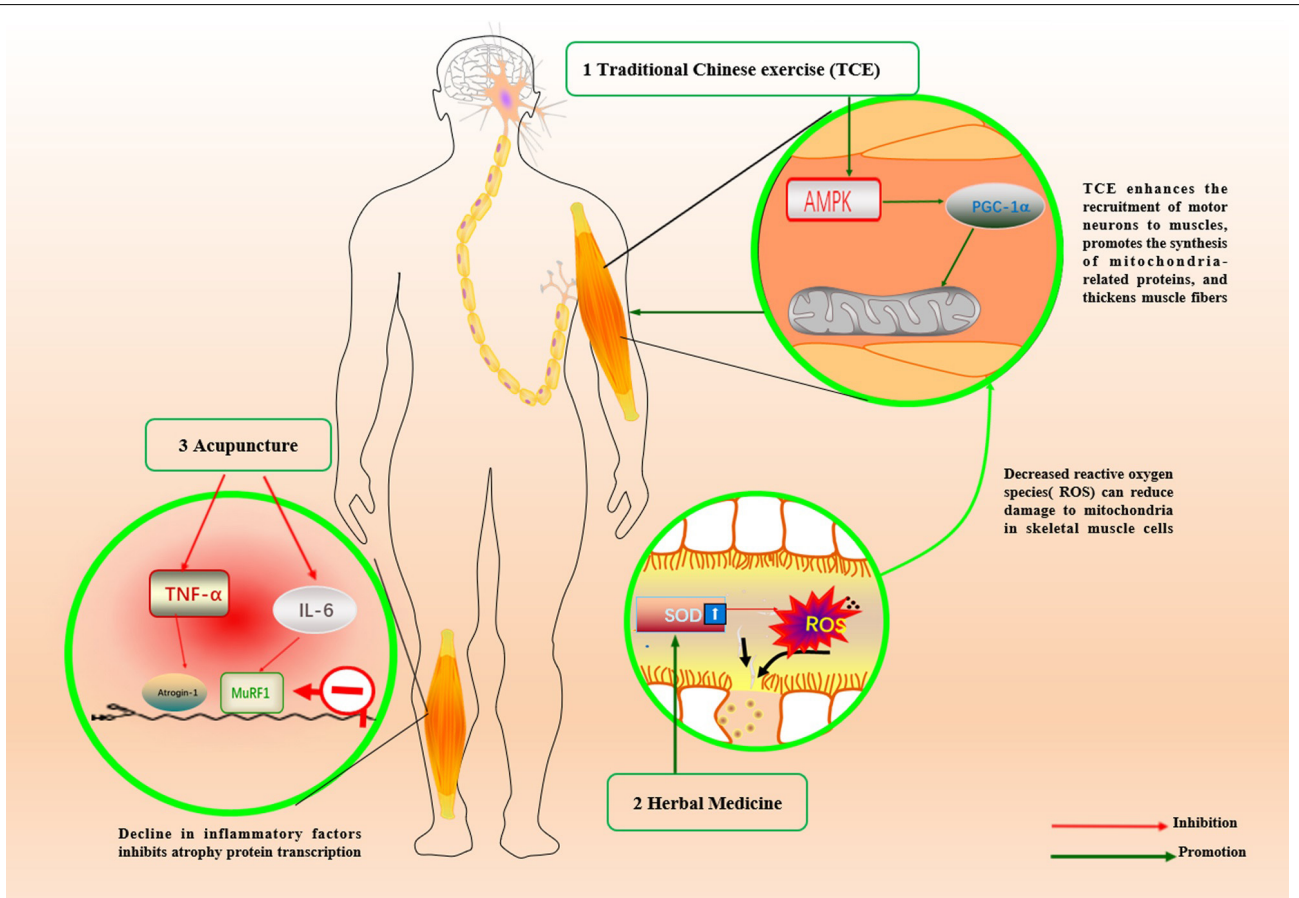


FIGURE 2 | Mechanism of traditional Chinese medicine in the treatment of sarcopenia.

intervention and then combined it with another intervention, resistance exercise. The results showed that the three treatment measures group was more effective than Tuina combined with Yi Jin Jing or resistance exercise in improving muscle strength and physical function ($p < 0.05$). Whether the beneficial effects of the combination of two or more exercises on the body are caused by the own advantages of the different exercises or simply by the increase in the total amount of exercise cannot be determined. Moreover, the use of multiple treatments simultaneously can easily lead to poor patient compliance and reduce the credibility of the study results. In this study, only walking speed increased, and was statistically significant in the Tuina combined with Yi Jin Jing group compared to the no intervention group; however, there was a significant difference in grip strength compared

to pre-intervention. There was an increase in muscle strength after using Tuina combined with Yi Jin Jing intervention, as evidenced by an increase in the number of chair stand tests performed over a 15-s period compared with the pre-treatment period (Yan et al., 2007). However, this evidence does not allow for precise conclusions that Yi Jin Jing combined with Tuina can improve muscle strength, despite significant differences in indicators before and after the intervention. Besides the lack of favorable evidence from the control group, there were other confounding factors such as the difference in the severity of the disease before and after. Yi Jin Jing was more effective than Tuina in FGA scores and total scores (Zhu et al., 2018). However, the degrees of increase in walking times and mean lower limb strength score in the massage group were significantly higher than that in the Yinjjing group ($p < 0.05$) in another study (Yang and Chen, 2016). Therefore, additional evidence is needed to determine whether Yi Jin Jing or Tuina is more effective.

In studies of Tai Chi for balance problems in the elderly, the diversity of its style may lead to uncertainties in its therapeutic effects. Morawin et al. (2021) used Yang-style 24-form Tai Chi after which patients had increased walking speed and decreased fat mass. Another study (Zhu et al., 2016) used a simple 8-style Taijiquan and showed significant improvements in lower extremity muscle strength and physical performance in the TC group compared to the control group, but the gender of their included population was all male making the results limited. Yang-style 24-form Tai Chi is the form most commonly used to improve balance in the elderly (Liu and Frank, 2010; Sherrington et al., 2019). However, many studies currently use simplified Tai Chi for treatment. A meta-analysis showed that traditional Tai Chi was more effective than simplified Tai Chi in preventing falls in the elderly (Li et al., 2021). However, some studies have also concluded that customized therapeutic Tai Chi is more effective than traditional Tai Chi in reducing the incidence of falls in older adults who are at a higher risk of falling (Li et al., 2018; Penn et al., 2019). During Tai Chi practice, the stability of individual gait is lower than that of normal gait (Yang and Liu, 2020). Although the low stability of gait in Tai Chi increases the risk of falls, it stimulates the body's postural control system (Jahnke et al., 2010). To maintain balance, the body must autonomously adapt to make postural adjustments and enhance neuromuscular control so as to improve the ability to control body balance. A plantar pressure test system of the elderly after practicing Tai Chi showed that their heel impulse was greater than that of the no-intervention group, suggesting that it promoted better neuromuscular control (Li et al., 2016). This also reflects the yin and yang theory of Tai Chi, which seeks balance in the body between stability and instability. A different study demonstrated that 48 weeks of Taijiquan stability training significantly improved the stability limits of older adults, with 32, 68, and 19% increases in endpoint excursion, movement velocity, and directional control, respectively, compared with the baseline (Li, 2014).

We found only one study (Zhou et al., 2020) on the use of BDJ for sarcopenia. It may be due to the fact that BDJ does not have the same strong influence and wide dissemination as Taijiquan and Yi Jin Jing. The results from a 12-week clinical trial of sitting BDJ showed that it improved balance but not lower limb strength, possibly because sitting BDJ focused more on coordination than on muscle strengthening (Bao et al., 2020). Elderly individuals who have difficulty moving are advised to practice sitting BDJ.

According to Chinese medicine theory, Ba Zhen decoction and Bu Zhong Yi Qi decoction are commonly used Chinese herbal formulas to benefit Qi energy and strengthen the function of spleen and stomach to reduce weakness. The results of the included studies can only indicate that herbal medicine has a beneficial effect on improving muscle strength and physical function in patients based on exercise and nutritional supplementation. Bu Zhong Yi Qi decoction was able to reduce inflammatory factors in patients (Chen et al., 2021), but due to the small sample size, there was a risk of deviation. Animal studies have shown that Astragalus, which is contained in Bu Zhong Yi Qi decoction, has antioxidant and anti-aging effects. Astragalus polysaccharides, the main component of Astragalus, have been shown to significantly increase the activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), as well as anti-hydroxyl radicals in D-gal-induced aging mice (Li et al., 2012). Both Ba Zhen decoction and Bu Zhong Yi Qi decoction contain *Atractylodes macrocephala* and Chuanxiong. *Atractylodes macrocephala* can increase SOD activity, scavenge reactive oxygen radicals, and reduce malondialdehyde content in the erythrocytes of mice over 12 months of age (Li et al., 1996). In aging rats, the SOD content in the serum and rectus femoris muscle was increased by gavage of an herbal cuisine containing *Atractylodes macrocephala* and Astragalus, thus reducing oxidative damage and delaying the aging of skeletal muscles (Li and Liu, 2018). Chuangxiong contains tetramethylpyrazine (TMP), which can improve age-related musculoskeletal disorders in humans and prolong the lifespan (Liu et al., 2019).

The inability of acupuncture to relieve symptoms in patients with sarcopenia may be due to the selection of acupuncture points, but acupuncture may help regulate inflammatory cytokines IL-6 and TNF-α in their bodies (Soares Mendes Damasceno et al., 2019). This is because each point has a clear therapeutic effect, but it is important to combine multiple related points together for systematic acupuncture treatment depending on the condition of the disease. Liu et al. (2020) compared two different groups of acupuncture points and showed that the group with acupuncture containing the Zusanli Point (ST36) outperformed the other group in terms of walking speed. ST36 is the most frequently used acupoint in skeletal muscle-related diseases and is often used to increase muscle function and strength (Ahmedov, 2010). This may be because ST36 is located on the lateral side of the lower leg, the superficial layer is distributed with the lateral sural cutaneous nerve, and the deep layer has branches of the anterior tibial artery and vein. Acupuncture at this point can stimulate the nerve to activate the motor cortex, stimulate muscle contraction, and increase the blood flow of skeletal muscles to improve muscle strength and muscle mass of the lower limb (Noguchi et al., 1999; Ohkubo et al., 2009; Sun et al., 2019). There is a lack of clinical cases of acupuncture for sarcopenia, but there is evidence from relevant animal experiments. These studies are mostly animal models of skeletal muscle atrophy caused by other diseases, which is still different from natural aging-induced

skeletal muscle atrophy. Although there are some limitations, the mechanism of sarcopenia treatment by acupuncture can be elucidated to some extent. Muscle-specific E3 ubiquitin ligases, such as atrogin-1 and MuRF1, play a key role in muscle atrophy (Egerman and Glass, 2014). Electroacupuncture in the ST36 and SP9 of rats with diabetes-induced muscular atrophy has been shown to reduce the expression of MURF-1, prevent the degradation of the myosin heavy chain, and delay the process of muscular atrophy (Chen et al., 2019). Autophagy can remove damaged proteins and provide materials for protein self-renewal to inhibit apoptosis of skeletal muscle cells. It has also been reported that electroacupuncture at ST36 and GB30 points can promote autophagy to improve gastrocnemius atrophy in rats with dystrophic muscular atrophy (Zhao et al., 2015).

Limitations and Directions for Future Research

This is the first systematic review of TCM for the treatment of sarcopenia. This review included clinical and preclinical studies of three major types of TCM approaches for sarcopenia—traditional Chinese Qigong exercises, acupuncture, and Chinese herbal medicine—using a reproducible search method in the available databases. Here, we highlighted the role and problems of TCM in the field of sarcopenia by summarizing and analyzing the current literature. In addition, we used the current evidence to explain the potential mechanisms. However, the available preclinical study models are not fully consistent with the pathogenesis of sarcopenia and there are mechanistic differences. The inclusion criteria for our study were strict, and we excluded studies on TCM for the treatment of secondary sarcopenia (such as metabolic disorders and cancer), thus neglecting the use of TCM for sarcopenia in these diseases. Although global diagnostic criteria for sarcopenia are now available, some earlier studies relied on expert scholarly views of sarcopenia at the time, which has led to an increased risk of uncertain bias. The limited number of eligible studies, the small amount of data, the intervention methods, and the high heterogeneity of the measurement methods prevented a meta-analysis of the existing literature. To improve the quality of evidence for future studies, there is a need for consensus on inclusion criteria for patients with sarcopenia and standardization of muscle strength, muscle function, and muscle mass testing. In the future, a large number of high-quality studies will make it possible to conduct meta-analyses of different methods such as traditional Chinese Qigong exercises, herbal medicine, and acupuncture separately, providing a higher level of evidence to determine whether TCM is effective in treating sarcopenia. Further comparative studies between several methods could be added for superiority analysis.

CONCLUSION

Traditional Chinese Qigong exercises and Chinese herbal medicine have a positive effect on physical performance and muscle strength in older adults with sarcopenia. Future high-quality multicenter RCTs with large samples are needed to determinate whether acupuncture and other therapies are effective in treating sarcopenia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LF conceived the review. SL, ZL, YM, and RZ searched the literature. CG was responsible for data analysis and writing of the first draft. XX, CG, and YM performed the data management and figure modification. LF and YM modified the manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Immediate Effects of Functional Electrical Stimulation-Assisted Cycling on the Paretic Muscles of Patients With Hemiparesis After Stroke: Evidence From Electrical Impedance Myography

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Background: Electrical impedance myography (EIM) has been applied to assess muscle health conditions in neuromuscular disorders. This study aimed to detect immediate muscle electrical impedance property alterations in lower extremity of chronic stroke survivors immediately after functional electrical stimulation (FES)-assisted cycling training.

Methods: Fourteen chronic stroke survivors were recruited for the current study. EIM measurements were conducted before and immediately after 40-min FES-assisted cycling training for each subject. Four interested muscle groups [rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and the medial head of gastrocnemius (MG)] were selected. Correlation analysis was performed to reveal a significant correlation between changes in EIM parameters and clinical scales [Fugl–Meyer Assessment of the lower extremity (FMA-LE); 6-min walking test (6MWT)].

Results: Immediately after training, reactance (X) and phase angle (θ) values significantly increased on the TA and MG muscles. Significant correlation was observed between X value and FMA-LE scores ($r = 0.649$, $p = 0.012$) at MG as well as X and FMA scores of the ankle joint ($r = 0.612$, $p = 0.02$). Resistance (R) and θ were significantly correlated with 6MWT score (R-6MWT: $r = 0.651$, $p = 0.012$; θ-6MWT: $r = 0.621$, $p = 0.018$).

Conclusion: This brief report demonstrated that EIM can reveal the intrinsic property alteration in the paretic muscle of chronic stroke survivors immediately after FES-assisted cycling training. These alterations might be related to muscle hypertrophy (i.e., increases in muscle fiber size). This brief report might aid the understanding of the mechanism of electrical stimulation-assisted exercise in improving muscle function of stroke survivors.

Keywords: cycling, electrical impedance myography (EIM), muscle, stroke, functional electrical simulation (FES)

INTRODUCTION

Stroke is reported to be the second-largest cause of death worldwide (GBD 2016 Stroke Collaborators, 2019), in addition to causing substantial sensorimotor dysfunction and restricting the performance of daily life activities in survivors (Scherbakov et al., 2013). The locomotion-related abilities needed for daily activities are affected by neurological deficits, poor motor control, and uneven muscle stiffness post-stroke (Chen et al., 2003; Peri et al., 2016). Muscle weakness and uncoordinated contraction are among the main targets of the rehabilitation process for the lower extremities in stroke survivors.

Functional electrical stimulation (FES) and cycling training are common rehabilitation interventions used to improve locomotion function in chronic stroke survivors. These interventions help reduce muscle spasticity and improve muscle function (Raasch and Zajac, 1999; Howlett et al., 2015). FES is a common rehabilitation intervention used to improve motor function in stroke survivors. It involves applying short bursts of electrical pulses on the intact peripheral motor nerves to elicit action potentials that propagate along the axons toward the target muscle. The electrical pulses can facilitate the voluntary contraction of paretic muscles to generate functional movement. Moon revealed that muscle tone and stiffness of the ankle dorsiflexor muscle were reduced after an FES intervention (Moon et al., 2017). A study that combined FES with locomotion-like movement revealed a positive effect on gait speed and muscle spasticity immediately after 20 min of training (Yamaguchi et al., 2012). However, the alteration of muscle properties that underpins functional improvement remains underexplored. For example, it was reported that FES had a critical limitation in that it rapidly induces muscle fatigue due to its highly synchronized activation of muscle fibers (Bickel et al., 2011). Therefore, a quantitative evaluation of the muscle changes induced by stimulation and exercise is warranted.

Electrical impedance myography (EIM) is a non-invasive tool used for the assessment of muscle conditions in neuromuscular disorders. During EIM measurements, a series of weak multifrequency currents is passed through the muscle of interest *via* electrodes. The resultant voltage within the local area is then measured. Reactance (X), resistance (R), and the phase angle (θ) are calculated to determine the intrinsic muscle properties, including the amount of extra- and intracellular fluids in the muscle, the location of tissue interfaces, and cell membrane integrity (Shiffman et al., 1999; Mulasi et al., 2015). In our previous study, EIM was applied to determine the effects of muscle fatigue during and immediately after sustained muscle contractions. It was found that the change in resistance was related to the accumulation of metabolites in the muscle tissue after contraction (Li L. et al., 2016). A study conducted in mice utilized EIM as a tool to assess muscle changes after electrical stimulation. The results revealed significant changes in the X, R, and θ values when compared to the baseline assessment (Li J. et al., 2016). However, there is limited knowledge on the immediate effects of electrical stimulation training on spastic muscles in stroke survivors. Therefore, determining the electrical property changes in muscle induced by FES using EIM is a relevant area of study. The findings might be helpful for investigating internal morphologic alterations in muscle (Shiffman et al., 2003), changes in the intramuscular environment (body cell mass and intracellular water) (Huang et al., 2014), and physiological metabolite accumulation (Li L. et al., 2016) due to stimulation or muscle contraction.

This study aims to use EIM to detect immediate changes in muscle impedance properties after FES-assisted cycling training in people with chronic stroke. Our hypothesis is that EIM can reveal transitory changes in exercised muscle after one training session. The alterations present immediately after an intervention might provide insights for the design of clinical interventions involving FES for stroke survivors (including time window and intensity) and may help to reveal the mechanism behind FES-assisted cycling training in stroke.

METHODS

Study Design

This was a self-controlled pilot study that comprised part of an ongoing randomized clinical trial. The inherent muscle properties of the rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and medial head of gastrocnemius (MG) were recorded by EIM. The study was reviewed and approved by the Joint CUHK-NTEC Clinical Research Ethics Committee (Ref. no: 2016.093-T). The study was conducted in accordance with the Declaration of Helsinki. All recruited subjects provided written consent before the experimental procedures began.

Participated Subjects

A convenient sample of fourteen persons with stroke (9 women and 5 men, mean age of 57.19 years old) was recruited in this study. The time since stroke ranged from 3 to 29 years (**Table 1**). None of the participated subjects had a known history of any other neuromuscular diseases or neurological disorders. The inclusion criteria were as follows: (1) first-ever stroke with unilateral hemiparesis; (2) hemiparesis over 6 months after a stroke; (3) available range of motion at the bilateral ankle joints from 10° dorsiflexion to 30° plantar flexion, at the bilateral knee joints from 0 to 150° flexion, and at the hip joints from 0 to 100° flexion; (4) sufficient cognitive function to understand and perform corresponding tasks; and (5) no history of traumatic injury or surgery of the lower limbs. The exclusion criteria were as follows: (1) high spasticity of the muscles of the ankle, knee, and hip joints; (2) inability to exercise on a cycle ergometer; and (3) antispastic medication use within half a year prior to the study.

Procedures

This study utilized EIM to assess inherent property alterations in the RF, TA, BF, and MG immediately after FES-assisted cycling training. The EIM assessment was performed on the bilateral RF, TA, BF, and MG before and after a 40-min FES-assisted cycling training session.

TABLE 1 | Clinical information of subjects.

ID	Gender	MAS		Stroke type	Paretic side	Age (y)	Duration (y)	FMA-LE	FMAac	6MWT
		Knee (F/E)	Ankle (PF/DF)							
1	Female	1/0	2/1	Ischemic	Left	60–65	8	25	17	280
2	Female	1/1	1/1	Ischemic	Right	55–60	3	30	11	260
3	Female	1/1	2/1	Hemorrhagic	Left	65–70	10	25	13	224
4	Male	2/2	1/2	Ischemic	Left	65–70	11	19	11	308
5	Female	2/1	2/2	Ischemic	Left	55–60	7	24	8	304
6	Female	2/1	2/2	Hemorrhagic	Right	65–70	8	20	10	185.5
7	Male	2/1	2/1	Ischemic	Right	35–40	5	25	10	295.3
8	Male	2/2	3/3	Hemorrhagic	Right	55–60	7	16	10	244.5
9	Female	1/1	1/1	Ischemic	Left	70–75	5	21	5	172.9
10	Male	1/1	2/2	Ischemic	Left	60–65	3	25	9	170
11	Male	1/1	1/1	Ischemic	Left	55–60	3	28	9	366
12	Male	2/1	1/1	Ischemic	Right	60–65	5	21	14	315
13	Female	0/1	0/1	Hemorrhagic	Right	35–40	3	17	9	188.8
14	Female	1/1	1/0	Ischemic	Right	60–65	4	20	6	264
Mean						58.9	5.9	22.6	10.1	255.6

FMA-LE, fugl–meyer assessment of the lower extremity; FMAac, FMA score of ankle joint and coordination; MAS, modified Ashworth scale; F, flexion; E, extension; PF, plantar flexion; DF, dorsiflexion.

Clinical Assessments

Clinical assessments, including the 6-min walk test (6MWT), Fugl–Meyer assessment of the lower extremity (FML-LE), modified Ashworth scale (MAS), and Berg balance scale (BBS), were performed to evaluate participants' gait, lower limb function, and balance. The clinical assessments were performed by the same licensed physical therapist. The order of the clinical tests was conducted randomly before training.

Electrical Impedance Myography Assessment

The composition of the four muscle groups was assessed by EIM (Imp SFB7 Impedimed, Inc., Sydney, NSW, Australia). The muscle groups of paretic side were assessed before and after training, and the muscles of the non-paretic side were assessed before training only. The muscle belly of each muscle group was the target area for the evaluation (**Figure 1**).

Before each test, an alcohol pad was applied to clean the skin. Four electrodes (an inner pair of voltage electrodes and one pair of current electrodes on the outer regions) were attached linearly along with the muscle. The distance of the inner pair of current electrodes was 30 mm and that of the outer two current electrodes was 80 mm. The dimensions of the electrodes were 2.5 cm × 1 cm (**Figure 1A**). Each target muscle was measured three times. The acquired values were averaged for statistical analysis.

Functional Electrical Stimulation-Assisted Cycling

The cycling device consisted of an interactive cycling system with a motor (UIRobot UIM241Co4P-IE/57-76, Shanghai, China) and a pair of pedal meters (Power Tap P1 Pedal Meter, CycleOps, Madison, WI, United States). Every recruited subject participated in a 40-min FES-assisted cycling training session (two 15-min sessions with 10 min of rest). Subjects were asked to abstain from any high-intensity exercise on the day before the experiment. During the training sessions, subjects were seated on the chair of the system and pedaled with FES assistance. A goniometer was applied to measure the angles of both knees while adjusting the distance between the chair and the cycling system to ensure a maximum knee extension angle of approximately 140–150° when pedaling (Hu et al., 2021).

A programmable FES device (P-9632FineCure Easy Walker, Guangzhou, China) with four portable channels, including electrodes (AXLEGAARD PALS electrodes, Axelgaard Manufacturing Company, CA, United States, Neurostimulation Electrodes, United States), was employed to provide muscle stimulation. Four pairs of electrodes were attached to the skin surface over the muscle belly of the four paretic lower limb muscles. For RF, MG, and BF, 5 cm × 8 cm surface electrodes were used, and 5 cm × 5 cm surface electrodes were used for TA due to the smaller area on the skin surface. The FES pulse bandwidth was set between 100 and 420 μs, and the stimulation frequency was 20 Hz. The stimulation intensity could be modulated between 0 and 100 mA. The intensity of the stimulation of these 4 muscles was determined by taking the FES amplitude that induced a visible twitch on the corresponding muscles without causing any pain or discomfort to the subjects (**Figure 1B**). Detailed information about FES-assisted cycling training can be found in our previous study (Hu et al., 2021).

Data and Statistical Analysis

The EIM parameters X, R, and θ were obtained at frequencies of 5–1,000 kHz and exported for analysis. Only EIM parameters collected at a high frequency (100 kHz) were analyzed to avoid interference from the high impedance of the electrode–skin

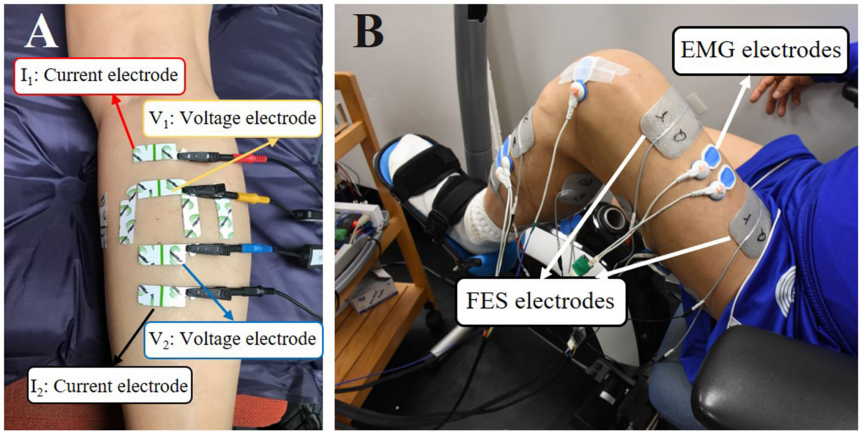


FIGURE 1 | (A) Demonstration of EIM assessment on the MG muscle. The outer two electrodes (the red and black ones) were current electrodes, and the inner two electrodes (the yellow and blue ones) were voltage electrodes. The longitudinally and transversely arranged electrodes were used, and only results from longitudinal measurement were used for statistical analysis. **(B)** A male subject was performing FES-assisted cycling training. The FES was triggered by muscle activation signals captured by surface electromyography (sEMG) electrodes.

contact surface (Li L. et al., 2017). The clinical assessment scale scores were recorded for correlation analysis.

The parameters R, X, and θ (mean ± SE) were analyzed and reported. Paired t-test analysis was conducted to compare the R, X, and θ values between the pre- and post-training sessions, as well as between the paretic and non-paretic sides for normally distributed data. The Wilcoxon matched-pairs signed rank sum test was used for non-normally distributed data. The Shapiro–Wilk test was applied to verify the normality of the data. Correlation analysis was conducted between the clinical scale scores (i.e., FMA-LE, BBS, 6MWT, and MAS) and the pre–post training differences in the R, X, and θ values of the four muscle groups (difference value = post-training value - pre-training value on the paretic side). Pearson's correlation analysis was employed for normally distributed data, while Spearman's correlation analysis was employed for non-normally distributed data. Statistical significance was defined as $p \leq 0.05$ (two-tailed). Statistical analysis was conducted using SPSS 23 software (IBM Inc., WA, United States).

RESULTS

Comparison Between the Paretic and Non-paretic Muscles Before Training

The R, X, and θ of the four tested muscle groups were compared between the paretic and non-paretic sides. θ was significantly smaller in all of the measured muscles on the paretic side compared to the non-paretic side (RF, paretic: 8.57 ± 1.1, non-paretic: 9.35 ± 1.0, p = 0.004; TA, paretic: 16.42 ± 1.0, non-paretic: 17.40 ± 0.8, p = 0.046; BF, paretic: 10.08 ± 1.4, non-paretic: 11.07 ± 1.3, p = 0.001; MG, paretic: 11.92 ± 1.4, non-paretic: 13.94 ± 1.4, p = 0.003). X was significantly lower in the paretic RF (paretic: 8.33 ± 0.4, non-paretic: 9.10 ± 0.4, p = 0.019), TA (paretic: 10.21 ± 0.5, non-paretic: 11.58 ± 0.4, p = 0.023), and MG (paretic: 8.02 ± 0.5, non-paretic: 9.93 ± 0.4, $p < 0.001$). No significant difference in R was present between the paretic and non-paretic muscles (**Figure 2**).

Comparison Between the pre- and Post-training Sessions at the Paretic Side

Statistical analysis revealed that immediately after the training session at the paretic muscles, the R-values for the RF (pre-training: 65.09 ± 6.8, post-training: 70.21 ± 7.2, p = 0.029), BF (pre-training: 53.04 ± 6.4, post-training: 55.60 ± 6.7, p = 0.047), and MG (pre-training: 43.37 ± 4.2, post-training: 46.19 ± 4.4, p = 0.006) were significantly increased. The X values were significantly increased for the TA (pre-training: 10.21 ± 0.5, post-training: 10.99 ± 0.4, p = 0.023) and MG (pre-training: 8.02 ± 0.5, post-training: 8.98 ± 0.5, $p < 0.001$). The θ values were significantly increased for the TA (pre-training: 16.42 ± 1.0, post-training: 17.26 ± 1.0, p = 0.002) and MG (pre-training: 11.92 ± 1.4, post-training: 12.40 ± 1.4, p = 0.021) (**Figure 2**). No significant change in other impedance variables was found in the RF or BF (**Figure 2**).

Analysis of the Correlation Between the Clinical Scale Scores and Impedance Parameters

The correlations between the clinical scale scores and the changes in impedance parameters (ΔR, ΔX, and $\Delta\theta$) were analyzed (**Figure 3**). For the MG, the ΔX value was significantly correlated with the FMA-LE scores (r = 0.649, p = 0.012), and the ΔX value was significantly correlated with the FMA score of the ankle joint and coordination (r = 0.612, p = 0.02). The ΔR and $\Delta\theta$ values were significantly correlated with the 6MWT scores (X-6MWT: r = 0.651, p = 0.012, θ-6MWT: r = 0.621, p = 0.018).

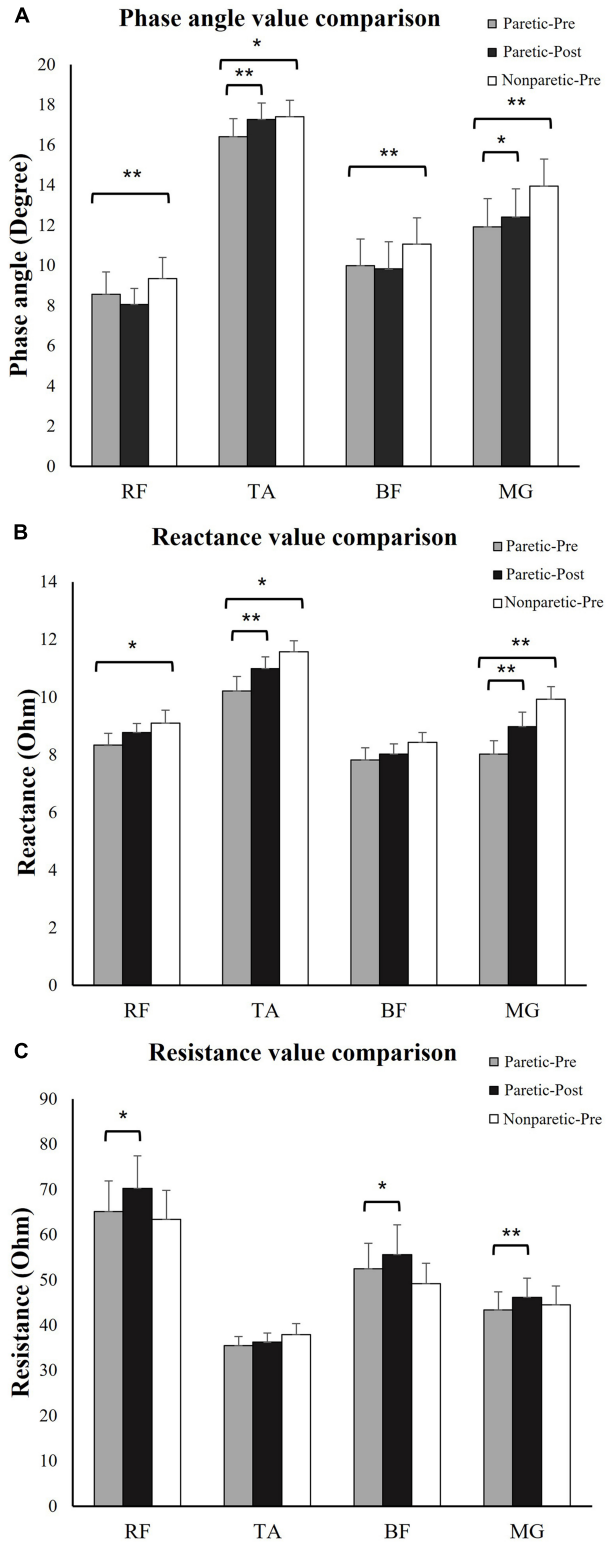


FIGURE 2 | Electrical impedance myography (EIM) parameters comparison. **(A)** Phase angle (θ) comparison: θ was significantly lower in paretic BF, TA, BF, and MG compared to non-paretic side. Immediately after training, θ significantly increased in TA and MG. **(B)** Reactance (*X*) value comparison: *X* was significantly lower in paretic BF, TA, and MG compared to non-paretic side. Immediately after training, *X* significantly increased in TA and MG. **(C)** Resistance (*R*) value comparison: *R* significantly increased in RF, BF, and MG after training. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$. RF, rectus femoris; TA, tibias anterior; BF, biceps femoris; MG, medial head of gastrocnemius; paretic-pre, paretic muscle pre-training; paretic-post, paretic muscle post-training; non-paretic-pre, non-paretic muscle pre-training.

DISCUSSION

The present study found significant electrical impedance changes in muscles immediately after FES-assisted cycling training. The study also explored the correlation between changes in impedance and clinical scores.

Immediate Effects of Functional Electrical Stimulation-Assisted Cycling

The present results indicated significant elevation of the *R*, *X*, and θ values of different muscle groups (**Figure 2**). Hwang investigated the training effects of electrical stimulation combined with exercise on muscle structure changes in chronic stroke survivors. The authors reported a significant increase in muscle pennation angle and muscle thickness (Hwang et al., 2015). Nevertheless, the quantity of myofibers might not be altered immediately after a single training session. The observed changes in the myofiber structure may be due to repetitive muscle contraction. An increase in muscle fiber size would lead to elevations in the *X* and θ values (Rutkove et al., 2002). During voluntary muscle contractions and FES-assisted muscle contractions, temporary hypertrophy and swelling of individual muscle fibers and muscle cross-sectional area (CSA) increased (Konopka and Harber, 2014). The swelling in individual muscle fibers did not fade immediately after a long duration of repeated contractions (Yasuda et al., 2015). The muscle membrane area enlarged within the tissue, which increased the momentary charge storage capability of the tissue and created a greater time shift when an alternating current passed through the muscle (Shiffman and Rutkove, 2013). In addition, muscle fibers were arranged more regularly and compactly during the period of temporary hypertrophy because the swollen muscle fibers occupied more space and squeezed the intramuscular tissue aside. As a result, when performing EIM, the electrical current flowed more through the cytomembrane area of the muscle when passing between the two voltage electrodes than it did before the cycling training. As indicated in previous studies, *X* and θ value alterations are related to muscle CSA and muscle fiber size (Li et al., 2013, 2014; Li X. et al., 2017). Hu and coworkers also applied ultrasound and EIM simultaneously and found that muscle thickness and fascicle length positively correlated with the *R* and θ values (Hu et al., 2019). The observed results suggested that the increased *X* and θ values indicated muscle hypertrophy and CSA increased immediately after FES cycling training. However, the present study explored only the immediate effects of FES-assisted training and did not assess the cumulative training effects of prolonged muscle contraction. In future EIM studies, multiple sessions of training need to be conducted to assess

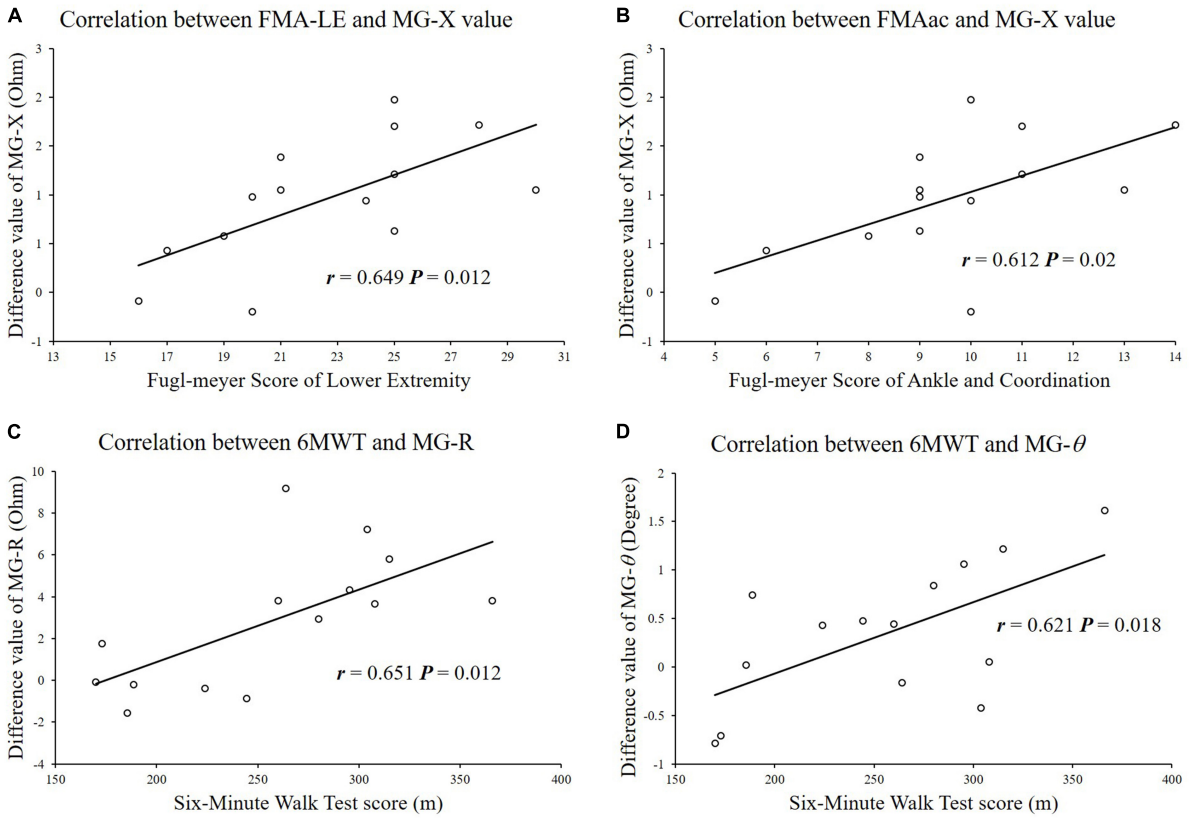


FIGURE 3 | Correlation analysis between impedance parameters and functional clinical scale scores. **(A)** FMA-LE scores were significantly correlated with difference of reactance values in MG. **(B)** FMAac scores were significantly correlated with difference of reactance values in MG. **(C)** 6MWT scores were significantly correlated with difference of resistance values in MG. **(D)** 6MWT scores were significantly correlated with difference of reactance values in MG.

whether FES-assisted cycling training contributes to muscle CSA and myofiber increases as well as functional improvement.

Muscle fatigue after a long duration of training might also play a role in muscle property alterations. Muscle fatigue is a complicated psychophysiological state that involves muscle weakness, pain, and a reduction in force production (Romani, 2008). It was reported that persistent force generation and repeated contraction influence the intramuscular environment and may also be associated with hypertrophy by causing hypoxic conditions and the accumulation of metabolic subproducts (Takarada et al., 2000). Li revealed that due to a significant accumulation of metabolites and intracellular fluids during muscle contraction, the conductivity improved and *R* decreased (Li L. et al., 2016). Todd applied EIM to biceps tissue and demonstrated a significant decrease in *R* and *X* values during a fatiguing exercise protocol (Freeborn and Fu, 2019). The alteration of impedance parameters observed in the present study might be related to the accumulation of metabolites and intracellular fluids associated with muscle fatigue. However, the impedance parameters in the present study increased immediately after the training, which contradicts the findings reported in the study by Li and Todd. The reason might be the difference in the study setup since muscle contractions during cycling induced many more muscle length changes than the isometric contractions in Li's study. The continuous dynamic muscle contractions generated by FES in the present study influenced the internal muscle tissues substantially, and the insulating boundaries (connective tissues) were relatively shifted and twisted (Shiffman et al., 2003). Repetitive muscle contractions led to more significant morphological alterations than the accumulation of metabolites, which might be the reason for the increase in *R* and *X* values. Further investigations of metabolism with a combination of different measuring techniques might be required to substantiate the findings, as multiple types of pathological changes could contribute to the results. Nonetheless, this is an inference based on the results of the present study and requires further investigation.

Clinical Relevance

The alteration of muscle impedance properties after training was positively correlated with clinical scores, which suggested that residual motor function might play a role in muscle intrinsic property alterations after FES-assisted cycling training. Stroke survivors with higher motor function might perform cycling with more voluntary muscle contraction than those with lower motor function levels (**Figure 3**). Detection of the immediate training effects using EIM also suggested the feasibility of evaluating the cumulative training effect delivered by FES-assisted cycling

training. Therefore, in our future study, we would aim to design a study to clarify the effects of long-term cumulative training and explore the underlying mechanism of the intrinsic muscle property alterations induced by physical training.

Limitations

There are a number of limitations in the present study. First, the sample size of this study was limited, which might result in bias. Second, in the present study, only the muscle alterations immediately after a single session of training were examined, and we could not clarify the contribution of voluntary exercise vs. FES to the changes based on the observed results. It would be interesting to explore the effect of voluntary contraction and FES, which would provide more guidance for clinical treatment. Thus, additional randomized controlled studies with large sample sizes and multiple training sessions are required to elucidate the effect of FES and cycling training. In addition, there were differences in the parameter changes for different muscle groups. Thus, to explore muscle performance changes, in future studies, we will record the stimulation intensity for each muscle group and conduct additional quantitative assessments of muscle function, such as by using handheld dynamometers to measure muscle strength, ultrasound to measure muscle architecture, and electromyography techniques to measure muscle activation.

CONCLUSION

This brief report illustrated the immediate effect of FES-assisted cycling training on muscle intrinsic properties, as well as the correlation between clinical scores and intrinsic muscle property alterations in chronic stroke survivors. There were measurable changes in muscle impedance in four muscle groups of interest after chronic stroke, and these changes were related to motor function. The results showed that EIM is a sensitive technique that can be used to detect intrinsic muscle property alterations immediately after 40 min of FES-assisted cycling training. Therefore, EIM could provide a novel understanding of the mechanism of muscle function improvements from the perspective of intrinsic muscle properties after FES and cycling training. This could assist clinicians in diagnosing and evaluating muscle changes after FES training in chronic stroke survivors and provide alternative options for therapists providing rehabilitation therapy.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Joint Chinese University of Hong Kong-New Territories East Cluster (CUHK-NTEC) Clinical Research Ethics Committee (Ref. no: 2016.093-T). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL and RT conceived and designed the study, made contributions to experiments, and reviewed and edited the manuscript. CH and KL performed the experiments. CH and LL wrote the manuscript. All authors read and approved the final manuscript.

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The Effect of Modified Tai Chi Exercises on the Physical Function and Quality of Life in Elderly Women With Knee Osteoarthritis

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Background: Knee osteoarthritis (KOA) is the leading cause of pain and stiffness, affecting older adults' physical function and quality of life. As a form of mind-body exercise, Tai Chi has been recommended as an exercise prescription for KOA patients. This study examined the effects and continuation of modified Tai Chi exercises on physical function and quality of life in elderly women with KOA.

Methods: We conducted a single-blind, randomized controlled trial (RCT) on 40 older women with KOA. The participants were randomized to a 12 weeks Tai Chi or control group. The Tai Chi group attended a kind of modified Tai Chi training sessions three times per week; the control group attended wellness education sessions once a week. The primary outcome was the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Secondary outcomes were the Berg Balance Scale (BBS), Timed Up and Go (TUG), Short-Form 36 (SF-36), Pittsburgh Sleep Quality of Index (PSQI), Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SDS).

Results: After the 12-weeks the Tai Chi group showed significan improvement in the WOMAC pain (mean difference, −5.09 points, p = 0.001), WOMAC stiffness (mean difference, −3.60 points, p = 0.002), WOMAC physical function (mean difference, −11.21 points, p = 0.001) compared to the control group. In addition, the Tai Chi group had also significant improvement in the BBS (mean difference, 1.70 points, p = 0.008), TUG (mean difference, −0.52s, p = 0.001), SF-36PCS (mean difference, 7.60 points, p = 0.001), MCS (mean difference, 7.30 points, p = 0.001), PSQI (mean difference, −3.71 points, p = 0.001), SDS (mean difference, −5.37 points, p = 0.025) and SAS (mean difference, −5.06 points, p = 0.002).

Conclusion: The modified Tai Chi exercises are an effective treatment for improved physical function and quality of life in elderly women with KOA.

Clinical Trial Registration: The trial was registered in Chinese Clinical Trial Registry (ChiCTR2000040721), http://www.chictr.org.cn/edit.aspx?pid=65419&htm=4.

Keywords: modified Tai Chi, elderly women, knee osteoarthritis, physical function, quality of life

INTRODUCTION

Knee osteoarthritis (KOA) is one of the common chronic joint diseases in the elderly population (Sharma, 2021), resulting in pain, physical functional limitations, and low quality of life (Lee et al., 2018; Hawker, 2019). Epidemiological studies show that 8.1% of the elderly (age ≥60) in China suffer from symptomatic KOA. The prevalence of KOA in women is 10.3%, higher than that of 5.7% in men (Tang et al., 2016; Vinaa and Kwoha, 2018); KOA affects women more frequently than men and has a greater impact on women's physical health (Yue et al., 2020). Patients with KOA commonly suffer from decreased physical function and quality of life due to joint pain and limited physical activity (Rosemann et al., 2007). In addition, increased pain and loss of physical function in KOA patients also progressively worsen their quality of life (Dominick et al., 2004). A cross-sectional study showed that KOA patients had lower scores in physical activity, mental health, and sleep disturbances than healthy people (Cook et al., 2007).

At present, conventional treatment methods for KOA include pharmacological interventions, physical therapy, and surgical treatment (Hochberg et al., 1995; Hermann et al., 2018; Sari et al., 2019). Exercise therapy is an essential part of KOA management; it is beneficial in reducing joint pain, improving functional impairment, and preventing joint mobility limitations (Juhl et al., 2014). Indeed, several studies have shown that exercise can relieve the symptoms of KOA by increasing muscle strength, improving neuromotor control, and optimizing joint range of motion (Woo et al., 2007; Zhu et al., 2016). A systematic review indicated that exercise could significantly reduce pain and improve physical function in KOA (Fransen et al., 2015). Currently, there is not enough evidence to recommend that one kind of exercise is better than the other, but patients can choose according to their preferences and circumstances, both of which determine the enthusiasm of patients to participate in the exercise (Kolasinski et al., 2020).

Tai Chi is a traditional Chinese mind-body exercise that combines meditation, breathing, and movement and effectively relieves pain, prevents falls, and improves anxiety and depression (Li et al., 2001; Lan et al., 2002). A systematic review found short-term improvement in pain, physical function, and stiffness in patients with KOA practicing Tai Chi (Lauche et al., 2013). In a previous randomized, single-blind trial comparing Tai Chi and physical therapy, Tai Chi exerted an effect similar to physical therapy in treating KOA; it gave rise to a more significant improvement in depression and quality of life (Wang et al., 2016). In 2019, the American College of Rheumatology recommended Tai Chi intervention as an exercise prescription for KOA (Kolasinski et al., 2020).

Although the evidence shows that Tai Chi is safe (Shengelia et al., 2013), some difficult movements in traditional Tai Chi exercises may exert excessive loads on the lower limb joints in KOA patients with physical dysfunction. However, previous studies have paid little attention to this issue. Therefore, our research was designed for this characteristic of KOA patients. Firstly, we assessed each participant's balance; secondly, each participant's range of motion and pain were assessed using a joint range of motion and pain assessments. Finally, we personalize it based on participants' characteristics and expert opinions. This study aimed to examine the effect of a 12-week modified Tai Chi exercise on the physical function and quality of life with knee OA and the continuation of subsequent treatment effects. We hypothesized that modified Tai Chi exercises could improve physical function and quality of life in patients with KOA.

MATERIALS AND METHODS

Trial Design

This parallel, single-blind, randomized controlled trial compared the effect of Tai Chi exercises and wellness education on the physical function and quality of life in older women with KOA. The participants were randomly assigned to the Tai Chi or control groups using a computer-generated random number. This study was approved by the Nanjing Sport Institute Ethics Committee, and all the patients submitted informed consent to participate in the study.

Participants

The participants were recruited in a community free clinic through WeChat public account promotion, advertisements, and recommendations from a community chronic disease management center. For interested respondents, we conducted a simple screening; subjects who met the KOA standard underwent a radiographic examination after signing the informed consent form to further ensure that they met the requirements of KOA.

Primary inclusion criteria for participants were: (1) women 60–75 years of age; (2) clinical radiographic diagnosis of KOA, and reported a 1–2 year course of disease; (3) pain symptoms for at least 6 months; (4) Kallgren-Lawrence (K/L) grading scale (0–3) for KOA; radiographs showing the knee space narrowing, with no large loose bodies in the joints; (5) no history of Tai Chi exercises; and (6) having signed the informed consent form.

Exclusion criteria for participants were: (1) severe cardiac, hepatic, and renal diseases preventing relaxed exercises; (2) knee pain or deformity or inconveniences in the spine, hips, ankles, and feet; (3) other diseases such as knee tumors, tuberculosis, infections, rheumatoid conditions, etc.; (4) individuals having undergone hip, knee, and ankle surgeries within 6 months before treatment; (5) having taken medicines for knee conditions within 3 months before treatment and those treated by injections; and (6) subjects with consciousness disorders or inability to cooperate.

Interventions

The Tai Chi Group

The Tai Chi group participated in a 60-min session and repeated it three times a week for 12 weeks. Each session is conducted in the group within the community center, with a 10-min warm-up, 40-min Tai Chi practice, and cooling down for 10 min instruction by a professional Tai Chi master. The Tai Chi programs were adapted from the classical Yang style 24-form Tai Chi exercises. According to the characteristics of the subjects and the opinions of experts, to reduce sustained weight-bearing time of the knee joint and excessive knee flexion movements among traditional

24-form that included eight forms: (1) "Part the wild horse's mane;" (2) "Brush the knee and twist steps;" (3) "Step back to repulse monkey;" (4) "Grasp sparrow's tail on both sides;" (5) "Wave hands like clouds;" (6) "Golden pheasant stands with one leg;" (7) "Jade lady weaves shuttles;" and (8) "Apparent close-up." An emphasis was placed on the transfer of the body's center of gravity and multi-segment movement coordination of the trunk, incorporating regular breathing as part of the exercise and integrating it into the practice. After the 12 weeks, we encouraged patients to continue practicing Tai Chi and re-evaluated the participants in 3- and 6-months respectively.

The Control Group

The control group participated in the 12-week program (60-min per session, once per week). Each session consisted of 45-min health education, including disease prevention, health management, self-care, etc. Concerning the 15-min home-based self-exercise guidance, its content was light intensity resistance exercise and stretching of the lower limbs. The participants were encouraged to practice at home at least twice per week and maintain their original lifestyle habits. During the 12-week intervention period, the attendance was recorded as a check-in card method, and participants with an attendance rate of more than 80% received a gift after the experiment to assess the effectiveness of the intervention.

Outcomes

The outcome measures were assessed at baseline and 12-week, 3-month, and 6-month follow-up, including the subject's demographic and clinical characteristics and primary and secondary outcome measures. All the research measures were professional to avoid subjective errors; the same assessors conducted each test.

Primary Outcome Measures

The primary outcome measures were the change in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score at baseline and after treatment of 12-week. The WOMAC is a self-report questionnaire for KOA to assess pain, stiffness, and physical function. Its reliability was satisfactory, with ICCs of 0.86, 0.68, and 0.89 (Salaffi et al., 2003). It includes five items for pain (score range: 0–50), two items for stiffness (score range: 0–20), and 17 items for physical function (score range: 0–170).

Secondary Outcome Measures

Secondary outcome measures included physical function and quality of life. The Berg Balance Scale (BBS) and Time Up and Go test (TUG) was assessed as physical function. BBS was widely used in clinical testing of human static and dynamic balance ability; the reliability was high (0.98). It consists of 14 items; each item is scored from 0 (cannot be completed) to 4 points (normal completion) with a total score range of 0–56, where a higher score indicates a better balance (Downs et al., 2013). TUG is a quick and quantitative method to assess functional walking ability in which the participant was asked to rise from a 45-cm chair, walk 3 meters, turn around, walk back to the chair, and then sit (Podsiadlo and Richardson, 1991).

Health-related quality of life assessment was conducted using the MOS item Short-Form 36 (SF-36), Pittsburgh Sleep Quality Index (PSQI), Self-rating Anxiety Scale (SAS), and Self-rating Depression Scale (SAS). SF-36 is currently used widely to assess the general population's quality of life and evaluate clinical trial effects. It includes eight domains, internal consistency of each of the eight subscales was excellent (Cronbach's coefficient alpha range 0.64–0.93). Our study used Physical components summary (PCS) and Mental components summary (MCS) as evaluation indicators (Laeson, 1997). PSQI is a self-rated questionnaire to assess sleep quality and disturbances; its reliability was 0.87. It contains seven components, ranging from 0 to 21; the higher scores indicate poorer sleep quality (Buysse et al., 1989). SAS and SDS were used to assess anxiety and depression symptoms. It includes 20 items, with a 1–4 scale; a higher score indicates more severe symptoms. Cronbach's alpha for the SAS and SDS in this study was 0.83 and 0.73 (Dunstan et al., 2017; Dunstan and Scott, 2020).

Sample Size

According to G-power software, a two-sided *t*-test was used to estimate the sample size. When the effect size was 1.18, $a = 0.05$, and the power was 0.9, considering the 20% attrition rate, the total sample size was calculated to be at least 40 people.

Randomization and Blinding

Randomization included computer-generated numbers for random grouping, set random number seeding, and random number generation function Rv. Random numbers were generated from 0 to 40, using a visual sub-box for regional segmentation, randomly assigning individuals to the Tai Chi and the control groups according to 1:1 proportion. A random number was placed in a sealed opaque envelope, which was opened for each subject separately after signing the informed consent form. The study assessors who performed the outcome measures were blinded to group assignment and the grouping researchers were not participate in the outcome measurement.

Statistical Methods

All the analyses were based on the intention to treat. The demographic characteristics and baseline variables of the two groups were analyzed using the analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. *Post-hoc* tests were used to compare factor means for significant models for the missing data. Linear mixed models were used to test the changes in various observation indicators between the two groups over time. For intra-group comparisons, changes in outcome variables between baseline, post-intervention, and follow-up time intervals were estimated from the mixed model, stratified by group. For inter-group comparisons, the difference in outcome variables between the two groups at each time interval was estimated by the mixed model and the interactions between groups and time. We report 95% confidence intervals (95% CI) and significance levels for the difference and trend tests for between-group comparisons. The data analyses were carried out using SPSS 25.0 (IBM SPSS Inc., Chicago, USA). The study test level was set at $\alpha = 0.05$, and $p < 0.05$ was considered statistically significant.

RESULTS

Ninety-eight individuals were recruited; 58 individuals were excluded for various reasons. The main reasons for exclusion were a lack of inclusion criteria (n = 32), no radiographic diagnostic evidence for KOA (n = 12), time conflict (n = 8), and other reasons (n = 6). Of these individuals, 40 were qualified and were randomly assigned to the Tai Chi (n = 20) and control (n = 20) groups (see **Figure 1**).

Baseline Data

Table 1 presents baseline characteristics of participants, including age, BMI, course of the disease, K/L grade, comorbidities, and the outcome measures in the two groups. There were no significant differences between the Tai Chi and the control groups at baseline ($p > 0.05$).

Of the 40 randomized participants, 35 (87.5%) completed the follow-up assessment, including 18 (90%) in the Tai Chi group and 17 (85%) in the control group. **Figure 1** presents the reasons for withdrawing or not completing post-intervention testing. In the intervention period, the attendance rate of the Tai Chi group was 88%, with 81% in the control group. Common reasons for absenteeism were time conflicts and health-related issues.

Primary Outcomes

At 12 weeks, there was a significant difference between the two groups in the WOMAC score. Compared with the baseline, the WOMAC score in the Tai Chi group was significantly improved while there was no significant improvement in the control group. Compared with the control group, the Tai Chi group showed significant improvements in WOMAC pain (p = 0.001), stiffness (p = 0.002), and physical function (p = 0.001). At the 3-month follow-up, there were still differences in the WOMAC scores between the two groups. However, at the 6-month follow-up, there was no significant difference between the two groups (**Table 2**, **Figure 2**).

Secondary Outcomes

We compared the changes in balance function, quality of life, sleep status, anxiety, and depression in the two groups before and after 12 weeks. Compared with the control, the BBS score was higher in the Tai Chi group than the control group (p = 0.008), and the TUG time was significantly reduced by −0.52 s (p = 0.001). In SF-36, the Tai Chi group improved physiological function, which increased by 7.60 points (p = 0.001), with a 7.30-points increase in the mental health score (p = 0.001). The Tai Chi group had a more significant improvement in sleep quality (−3.71 points; p = 0.001). Between the SDS score and SAS score, SDS decreased by 5.37 points (p = 0.025); SAS decreased by 5.06 points (p = 0.002).

Adverse Events

During the 12-week intervention, we used a standard adverse event report form to monitor adverse events during the study, including the start and end time, frequency, symptoms, signs, description of the extent of adverse events, and whether corresponding measures were taken. Due to the nature of the experiment, thigh muscle soreness and other symptoms occurred after Tai Chi exercise, mainly caused by the accumulation of lactic acid, which was normal. Therefore, it was not considered an adverse event.

DISCUSSION

This study explored the effects of the modified Tai Chi exercise on the physical function and quality of life in older women with KOA. The results showed that 12-week Tai Chi exercises could significantly reduce pain, improve physical function and quality of life compared to the control group. It suggests that a modified Tai Chi exercises program was an effective treatment for elderly women with KOA. At the 3-month follow-up, our survey found that 65% of the Tai Chi group participants continued to do Tai Chi exercises after the end. Therefore, the intervention effect of modified Tai Chi exercise has been continued. The continuation of the intervention effect may be due to the modified Tai Chi being an easy-to-learn and very safe exercise. At the same time, the Tai Chi exercise effectively lessened pain in KOA patients, which stimulated the patient's enthusiasm for continuing to learn and practice after the intervention. But at the 6-month follow-up, we found that the continuation of the effect of Tai Chi intervention decreased significantly because only 35% of participants continued to exercise. It indicated that long-term adherence to exercise might be key to sustaining intervention effects.

KOA patients generally have pain, stiffness, and restricted activities early. A recent meta-analysis showed that Tai Chi could be an alternative and effective treatment method to reduce pain and stiffness in KOA patients and improve physical function (Yan et al., 2013). The study results showed that at 12 weeks, the WOMAC pain in the Tai Chi group improved by 32% (24% higher than the control group); stiffness improved by 39% (35% higher than the control group), the physical function improved by 32% (a 27% improvement compared to the control group); this suggests a significant beneficial effect of Tai Chi on improving physical function because a 25% to 30% improvement in the WOMAC score is considered clinically meaningful.

Although the biological effect mechanism of Tai Chi exercises on improving KOA is still unclear, Tai Chi, as a slow and gentle exercise, improves the patients' physical condition through many intermediate variables (Wang et al., 2010a). Tai Chi can trigger behavioral responses and change the sensitivity to pain by activating neuroendocrine and autonomic nerve functions, neurochemical and pain-relieving pathways (Irwin and Cole, 2011; Morgan et al., 2014). In addition, Tai Chi exercises can correct KOA patients with forceful posture and increase muscle strength to reduce pain. The pain-relieving effect of Tai Chi exercise may also be attributed to changes in the structure and activity of certain brain parts caused by Tai Chi exercises, such as the anterior cingulate gyrus and insular cortex (Gu et al., 2015). An investigative study showed that in people who received long-term Tai Chi exercise, increased cortical thickness in the inferior segment of the annular sulcus of the insular lobe was found, along with a decrease in the functional homogeneity of the left anterior cingulate cortex (Wei et al., 2013, 2014). Alterations in these brain regions may be related

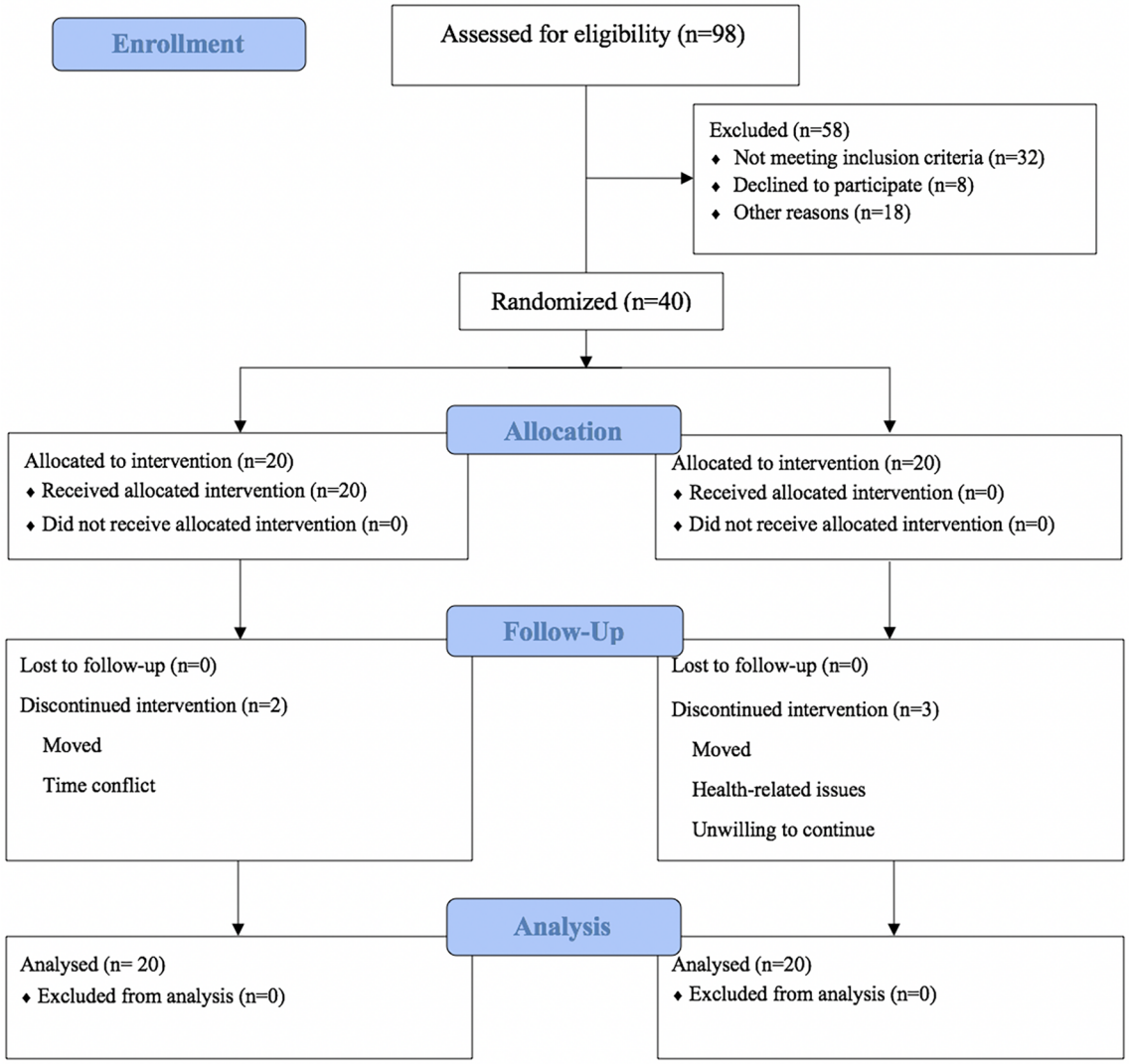


FIGURE 1 | Study flow chart.

to Tai Chi-mediated pain modulation mechanisms, thereby explaining the pain relief effects of Tai Chi exercise in patients with KOA.

With respect to balance control, we found that Tai Chi exercises effectively improved the balance function compared to the control group. This was similar to the results of a previous trial of the effect of Tai Chi on postural stability in Parkinson's patients (Li et al., 2012); these results support the benefit of Tai Chi exercise for improving balance function. During the practice, Tai Chi emphasizes the transfer of the body's center of gravity by taking the trunk axis; the limbs move around the trunk in three-dimensional directions of front and rear, left and right, and up and down (Yu and Yang, 2012). It breaks the original static balance of the body, allowing the patient to continue to contract the muscles during practice and control the posture and stability (Gatts and Woollacott, 2006). The level of balance ability is also related to brain function, and long-term Tai Chi exercise is beneficial to improving brain function. Long-term Tai Chi exercise resulted in increased cortical thickness in the right precentral gyrus and improved homogeneity of the posterior central gyrus (Wei et al., 2013). It is well known that the precentral gyrus of the brain is the primary motor cortex responsible for coordinating and planning the voluntary movements of skeletal muscles, while the postcentral gyrus is the main sensory area. Thus, increased cortical thickness in the right precentral gyrus and improved homogeneity of the postcentral gyrus may provide the brain with more concise information on how to coordinate muscles for better balance control (Wei et al., 2014).

Compared with other chronic diseases, KOA has a greater impact on patients' quality of life. Tai Chi Qigong showed its beneficial effects on KOA patients' quality of life and physical

TABLE 1 | Baseline characteristics of participants*.

Variable	Tai Chi group (n = 20)	Control group (n = 20)	P**
Mean age, years	64.15 ± 8.56	64.15 ± 8.56	0.967
Body Mass Index, kg/m^2	24.60 ± 5.64	24.37 ± 2.71	0.873
Course of disease, years	6.60 ± 2.01	5.60 ± 2.16	0.138
Radiograph score, n (%)			
K/L grade 1	7 (35)	7 (35)	
K/L grade 2	8 (40)	7 (35)	
K/L grade 3	5 (25)	6 (30)	0.924$^{\chi}$
Comorbidities, n (%)			
Hypertension	14 (43.8)	12 (33.3)	
Diabetes	10 (31.3)	15 (41.7)	
Osteoporosis	6 (18.8)	8 (22.2)	
COPD	2 (6.3)	1 (2.8)	0.672$^{\chi}$
WOMAC score			
Knee pain (0-50)†	21.22 ± 3.42	21.17 ± 3.81	0.970
Knee stiffness(0-20)†	10.27 ± 2.73	10.12 ± 3.27	0.876
Physical function (0-170)†	40.83 ± 5.23	40.23 ± 7.58	0.787
Balance function, Mean (SD)			
BBS (0-56)‡	52.27 ± 1.96	51.94 ± 2.07	0.625
TUG, seconds	10.13 ± 0.42	10.17 ± 0.51	0.769
Health-related quality of life			
SF-36 PCS (0-100)‡	58.33 ± 7.27	57.64 ± 6.15	0.766
SF-36 MCS(0-100)‡	57.38 ± 6.64	58.70 ± 5.04	0.515
Sleep quality			
PSQI (0-21)†	8.89 ± 4.28	9.47 ± 2.47	0.629
Anxiety and Depression			
SDS (20-80)†	42.55 ± 8.12	41.94 ± 5.84	0.800
SAS (20-80)†	39.94 ± 5.81	39.35 ± 3.80	0.726

*Values are shown as mean ± SD (Standard Deviation) unless otherwise indicated. **P values were calculated by t-test for continuous variables and by chi-square test for categorical variables. K/L, Kellgren-Lawrence scale; COPD, Chronic obstructive pulmonary disease; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; BBS, Berg balance scale; TUG, Time up go; SF-36, The MOS item short form health survey; MCS, Mental component summary; PCS, Physical component summary; PAQI, Pittsburgh sleep quality index; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale. †Lower scores indicated an improved state. ‡Higher scores indicated an improved state. $^{\chi}$Chi-squared test.*

function with no increased risks (Lee et al., 2009). As a potential form of postoperative rehabilitation exercise, Tai Chi exercise can effectively improve patients' quality of life after total knee arthroplasty without increasing risks (Li et al., 2019). Our research confirmed that SF-36PCS and MCS improved significantly after 12 weeks of treatment. The effect of Tai Chi on quality of life appears to be associated with improved mental health, including reductions in stress, anxiety, depression, mood disorders, and increased self-confidence (Wang et al., 2010b). In addition, Tai Chi exercises use movement in conjunction with meditative attention, which helps combine with breathing for skeletal muscle stretching and relaxation, physical coordination, and high concentration (Li et al., 2001). From a behavioral immunology perspective, studies have found that the effectiveness of Tai Chi exercise in improving quality of life appears to be associated with significantly reduced sympathetic nervous system activity. Through salivary cortisol measurement, Tai Chi exercise can relieve psychological stress by producing regulatory T cell mediators transforming growth factor-beta and interleukin 10 under specific antigen stimulation, thereby improving the quality of life (Esch et al., 2007).

Previous research has shown that older adults with moderate sleep disorders can improve their sleep quality in six months using low-to-moderate-intensity Tai Chi exercises (Li et al., 2004). For instance, Lü et al. (2017) found that 24-weeks of Tai Chi exercise can improve total sleep time and sleep duration, and daytime dysfunction in elderly women with KOA. Our study also confirmed this finding, with an overall PSQI score improvement of 3.72 points (42% improvement) in the Tai Chi group compared to the control group. Although Tai Chi has been shown to help with sleep problems, no direct research reports prove that Tai Chi can improve sleep by altering brain structure or reducing sleep discomfort and insomnia. But studies have shown that meditation, an important part of Tai Chi training, can help patients improve sleep-related areas of the brain (Tao et al., 2017). Tai Chi meditation increases hippocampal volume and gray matter density in the orbitofrontal cortex; Tai Chi exercise has the potential to improve sleep quality by inducing similar changes in the brain (Luders et al., 2009). A recent study also showed a significant increase in resting functional connectivity between the brain's bilateral hippocampus and prefrontal cortex after Tai Chi training (Tao et al., 2017). Although the changes in these brain regions caused by Tai Chi exercise are not directly similar to the brain changes observed in patients with sleep disorders, changes in related brain regions induced by Tai Chi exercise may be a possible mechanism for promoting sleep improvement. Therefore, Tai Chi exercise can be used as an important measure to improve the sleep quality of patients with knee OA.

The study found that psychological factors (such as mental health, depression, anxiety, etc.) may affect the response of KOA patients to exercise therapy and regulate pain

TABLE 2 | Primary and secondary outcomes.

Variable	Mean change from baseline*		Between-group difference (95%CI)**	
	Tai Chi (n = 20)	Control (n = 20)	Tai Chi vs. Control	$P^{\#}$
Primary outcome: WOMAC score				
Knee pain (0–50)†				
Post-test	14.55 ± 3.64	19.64 ± 4.06	−5.09 (−7.74,−2.43)	0.001
Follow-up 3 months	17.61 ± 2.22	20.58 ± 3.95	−2.97 (−5.16,−0.78)	0.009
Follow-up 6 months	18.94 ± 2.26	21.23 ± 5.22	−2.91 (−5.03, 0.45)	0.099
Knee stiffness (0–20)†				
Post-test	6.33 ± 1.81	9.94 ± 3.15	−3.60 (−5.36,−1.85)	0.001
Follow-up 3 months	7.94 ± 2.01	10.05 ± 2.94	−2.11 (−3.84,−0.38)	0.018
Follow-up 6 months	9.22 ± 2.66	10.05 ± 3.17	−0.83 (−2.84,1.17)	0.404
Physical function (0–100)†				
Post-test	27.72 ± 6.01	38.94 ± 6.32	−11.21 (−15.46,−6.97)	0.001
Follow-up 3 months	32.44 ± 7.92	39.76 ± 6.04	−7.32 (−12.18,−2.45)	0.004
Follow-up 6 months	34.77 ± 8.46	39.94 ± 5.57	−5.16 (−10.12,−0.20)	0.042
Secondary outcomes				
BBS (0–56)‡				
Post-test	53.94 ± 1.55	52.23 ± 1.98	1.70 (0.48, 2.93)	0.008
Follow-up 3 months	53.44 ± 1.46	52.17 ± 1.77	1.26 (0.15, 2.38)	0.027
Follow-up 6 months	52.72 ± 1.40	52.11 ± 1.49	0.60 (−0.39,1.60)	0.226
TUG (s)				
Post-test	9.58 ± 0.28	10.10 ± 0.52	−0.52 (−0.81, −0.23)	0.001
Follow-up 3 months	9.82 ± 0.43	10.15 ± 0.44	−0.32 (−0.60,−0.05)	0.019
Follow-up 6 months	10.05 ± 0.32	10.21 ± 0.42	−0.15 (−0.41,−0.09)	0.218
SF-36 PCS (0–100)‡				
Post-test	67.77 ± 6.90	60.17 ± 4.31	7.60 (3.61,11.59)	0.001
Follow-up 3 months	64.72 ± 5.54	59.35 ± 4.22	5.36 (1.96, 8.77)	0.003
Follow-up 6 months	60.83 ± 6.69	58.82 ± 4.85	2.01 (−2.03, 6.05)	0.319
SF-36 MCS (0–100)‡				
Post-test	66.88 ± 5.49	59.58 ± 4.67	7.30 (3.78,10.82)	0.001
Follow-up 3 months	63.72 ± 6.03	59.29 ± 5.03	4.42 (0.59, 8.26)	0.025
Follow-up 6 months	60.16 ± 6.79	58.82 ± 5.51	1.34 (−2.92, 5.61)	0.527
PSQI (0–21)†				
Post-test	5.16 ± 3.18	8.88 ± 2.31	−3.71 (−5.64,−1.79)	0.001
Follow-up 3 months	6.77 ± 3.54	9.29 ± 2.14	−2.51 (−4.54,−0.48)	0.017
Follow-up 6 months	7.72 ± 3.61	9.35 ± 1.69	−1.63 (−3.59, 0.32)	0.100
SDS (20–80)†				
Post-test	36.44 ± 7.70	41.82 ± 5.67	−5.37 (−10.05,−0.70)	0.025
Follow-up 3 months	38.05 ± 7.75	41.94 ± 6.08	−3.88 (−8.70, 0.92)	0.110
Follow-up 6 months	39.94 ± 7.88	42.47 ± 5.54	−2.52 (−7.24, 2.18)	0.284
SAS (20–80)†				
Post-test	33.05 ± 5.09	38.11 ± 3.72	−5.06 (−8.14,−1.97)	0.002
Follow-up 3 months	35.38 ± 4.44	38.76 ± 4.02	−3.37 (−6.29,−0.45)	0.025
Follow-up 6 months	36.66 ± 3.98	38.94 ± 3.99	−2.27 (−5.01, 0.47)	0.101

**Values are the mean ± SD (Standard Deviation). **Values are shown as mean (95% confidence interval). WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; BBS, Berg balance scale; TUG, Time up go; SF-36, The MOS item short form health survey; MCS, Mental component summary; PCS, Physical component summary; PAQI, Pittsburgh sleep quality index; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale. #Pvalues were calculated with repeated-measures analysis of variance. †Lower scores indicated an improved state. ‡Higher scores indicated an improved state.*

symptoms by magnifying pain and fear avoidance (Gilpin et al., 2015; Lee et al., 2018). The present study showed that the anxiety and depression of patients in the Tai Chi group improved after 12 weeks, possibly because long-term Tai Chi exercises relieved tension and resulted in more frequent relaxation and calmness; greater happiness was achieved through mental concentration and physical exercise (Hartman et al., 2000). Tai Chi exercise intervention altered cortical thickness and functional connectivity in several mood-related brain regions; increased thickness of the insula's right lower segment of the annular sulcus and improved functional specialization of the anterior cingulate cortex were observed in long-term Tai Chi exercisers (Wei et al., 2014). At the same time, resting-state functional connectivity between the ventromedial prefrontal cortex and the bilateral hippocampus was also increased (Tao et al., 2017). Increased functional connectivity between these brain regions may improve mood by associating current mood with previous events. Therefore, these brain changes induced by Tai Chi exercise may improve Tai Chi practitioners' ability to deal with anxiety and depression, thereby alleviating the cause of the patient's mood disorders.

Our study has several potential limitations, which should be resolved in future research. First, the results might be biased due to the small sample size. Therefore, future research should enroll more subjects. Second, the participants in this study consisted

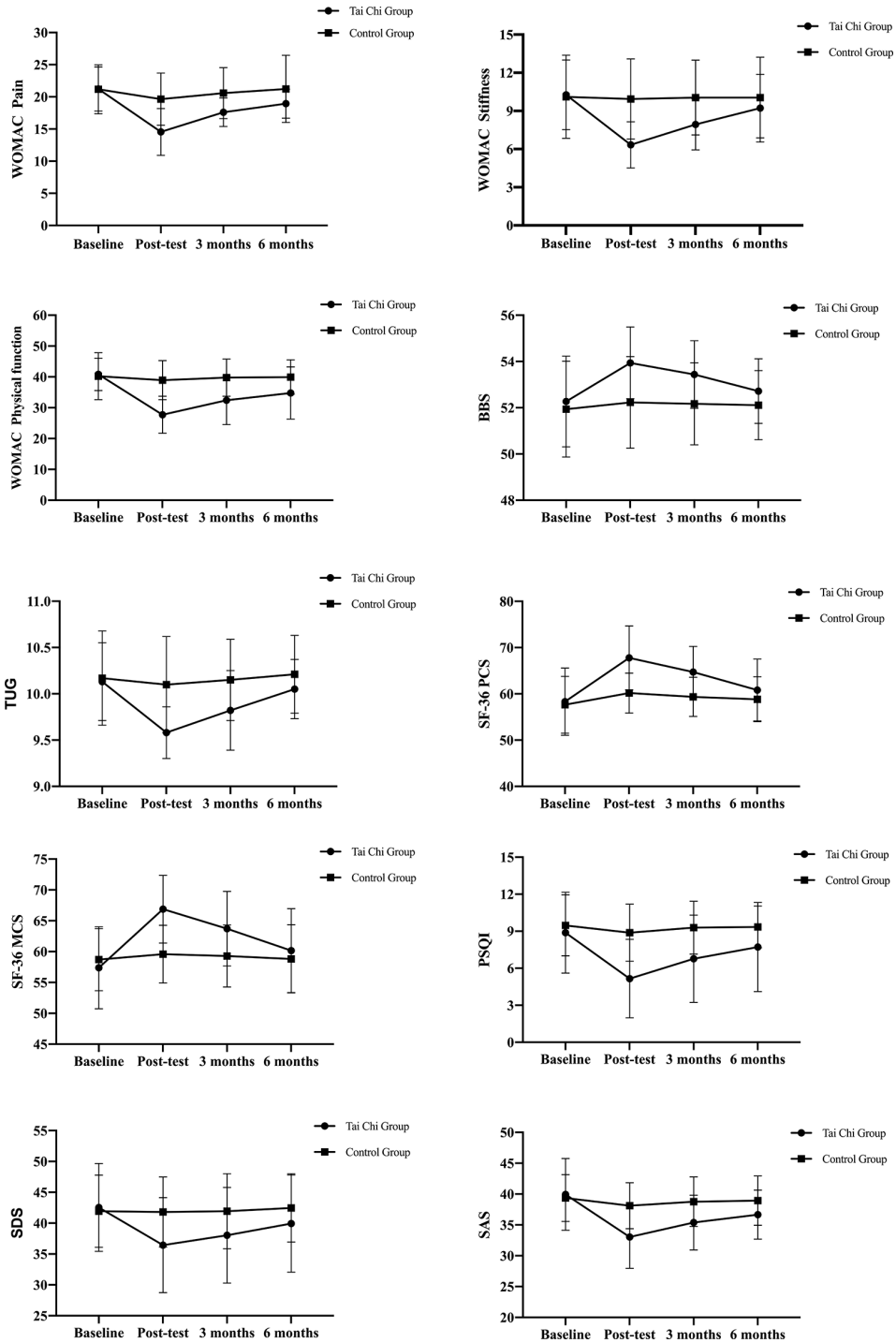


FIGURE 2 | The changes in the indicators of the two groups at Baseline, 12 weeks, follow-up 3 months, and 6 months over time. The value is the mean ± standard deviation (SD); error bars show the 95% confidence interval. WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; BBS, Berg balance scale; TUG, time up go; SF-36, The MOS item short-form health survey; MCS, Mental component summary; PCS, Physical component summary; PSQI, Pittsburgh sleep quality index; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale.

of older women with KOA, which limits the generalizability of the findings to other populations with KOA. Finally, a multi-subjective evaluation scale for the measure indicators in this study might have resulted in bias in understanding, leading to potential overestimation of the intervention effects.

CONCLUSION

This study suggests that the modified Tai Chi exercise is effective in improving physical function and quality of life in elderly women with KOA. Furthermore, long-term adherence to Tai Chi exercise can be significantly beneficial to the continuity of the effect, which provides a basis for guiding patients to follow-up exercises. The modified Tai Chi exercise can be widely used in the treatment of clinical knee osteoarthritis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Nanjing Sport Institute. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS, LW, KC, PX, AC, and XL designed the study. JS, XinW, BC, AD, and MS collected the data. JS and QL analyzed the data. TY, XiaW, AC, and XL provided advice related to the study. All authors contributed to the article and approved the submitted version.

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Traditional Chinese Exercises on Pain and Disability in Middle-Aged and Elderly Patients With Neck Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: With the change of life and work style, more middle-aged and elderly individuals are suffering from neck pain. In China, traditional Chinese exercises (TCEs) are widely used in the management of neck pain, such as Tai Chi, Qigong, Yijinjing, Baduanjin, Liuzijue, and Five-animal exercises. However, the evidence of TCEs for neck pain maintains controversial. Therefore, the current systematic review was conducted to evaluate the effects of TCEs on pain and disability of middle-aged and elderly patients with neck pain.

Methods: A comprehensive literature search was performed in six electronic databases from their inception to January 2022 for randomized controlled trials of TCEs for neck pain. The methodological quality of the included studies was assessed by PEDro scale. The subgroup analysis was conducted based on different TCEs. The I^2 statistic was applied to assess the heterogeneity.

Results: Twenty-one studies were included in our review, which were conducted in China, United States, and Germany between 2003 and 2021. Most (86%) of them exceeded the cut off score 6. TCEs included Baduanjin, Yijinjing, Tai Chi, Qigong, and Five-animal exercises. The aggregated results indicated that TCEs showed positive complementary effects in relieving pain (*SMD*, 1.12; 95% *CI*, 0.78–1.45; $p < 0.00001$), especially Baduanjin exercises. Baduanjin exercises also showed beneficial complementary effects in improving flexion (*SMD*, 0.65; 95% *CI*, 0.28–1.03; $p = 0.0006$) and extension (*SMD*, 0.66; 95% *CI*, 0.12–1.19; $p = 0.02$) of the neck. In addition, the aggregated results indicated that TCEs alone showed beneficial effects in improving disability (*SMD*, 0.74; 95% *CI*, 0.40–1.08; $p < 0.0001$) and relieving pain (*SMD*, 0.81; 95% *CI*, 0.50–1.13; $p < 0.00001$) compared with waiting list. The follow-up effects of TCEs were still insufficient.

Conclusion: There was the positive evidence to support the clinical use of TCEs, as a complementary therapy, for middle-aged and elderly patients with neck pain,

especially Baduanjin exercises. However, the evidence supporting the effects of TCEs alone for the middle-aged and elderly patients with neck pain was limited due to the small sample size.

Systematic Review Registration: https://inplasy.com/inplasy-2022-4-0083/, identifier INPLASY202240083.

Keywords: traditional Chinese exercises, neck pain, disability, meta-analysis, complementary and alternative therapy

INTRODUCTION

Neck pain is a common musculoskeletal condition with a high incidence rate, and it is the fourth leading cause of years lived with a disability around the world (Vos et al., 2012). The estimated annual incidence of neck pain ranged between 10.4 and 21.3% (Hoy et al., 2010), with a higher incidence in middle-aged office workers and elderly population. In China, the incidence rate of neck pain was up to 24.66%, and it increases with age. The prevalence of neck pain was 34.94% among people over 60 years old (Xu, 2019). More than 60% patients with neck pain may experience the second neck pain within 1 year (Carroll et al., 2008). It places a significant burden on the patients with neck pain and social healthcare systems due to the treatment costs, work absenteeism, and reduced productivity (Cote et al., 2013). The study reported that 14.2% patients with neck pain have multiple episodes of work absenteeism within 2 years of their initial health claims due to neck pain (Van Eerd et al., 2011).

Health professionals and patients still face tremendous challenges on the management of neck pain due to a variety of treatment strategies and conflicting reports on its treatments (Cohen, 2015). Considering drug dependence and poor stability of the spine after neck surgery, more patients turn to choose complementary and alternative therapies for neck pain to relieve pain and improve quality of life. Exercises have been recommended to prevent and treat neck pain by the clinical guidelines (Bussières et al., 2016). Common exercise therapies for neck pain include range-of-motion exercise, aerobic exercise, supervised exercise, strengthening exercise, and yoga, which can possibly alleviate neck pain because of their ability to improve muscle strength, flexibility, and endurance as well as restore injured tissues (Jordan et al., 1997; Wolsko et al., 2003; Kose et al., 2007).

In China, traditional Chinese exercises (TCEs) are widely used in the treatment of neck pain and associated conditions, which include Tai Chi, Qigong, Yijinjing, Baduanjin, Liuzijue, and Five-animal exercises (Xie et al., 2021). TCEs take both body and mind into account, emphasize the coordination and unification of breathing and body movements under the guidance of consciousness, and exercise the muscles and joints of the whole body (Lan et al., 2013; Solloway et al., 2016). They may also improve balance, aerobic capacity, and regulate the cervical balance of dynamic and static mechanics, so as to improve neck function, control posture, and relieve pain (Kuo et al., 2021). The study also reported that the movements of TCEs are thought to relax the mind and body to dilate blood vessels and promote local blood circulation (Huston and McFarlane, 2016). As one of low to moderate-intensity mind-body exercises, TCEs may have similar health benefits with common exercise therapy, but experience lower energy metabolism. These traditional mind-body exercises are suitable for middle-aged and elderly patients with neck pain and mental health conditions. Some studies (von Trott et al., 2009; Lauche et al., 2016; Huang et al., 2020) reported the positive effects of TCEs in the management of neck pain. However, the previous review (Xie et al., 2021) showed that there was insufficient evidence to support the effects of TCEs in improving pain intensity and enhancing functional mobility in individuals with neck pain. The evidence of TCEs for neck pain maintains controversial.

Therefore, the current systematic review evaluated the effects of TCEs on pain and disability in middle-aged and elderly patients with neck pain. It provided evidence-based information for the clinical application of TCEs for neck pain.

METHODS

The systematic review was registered on the international platform of registered systematic review and meta-analysis. The registration number is INPLASY202240083.

Search Strategy

A computerized literature search was conducted to identify the potential eligible studies in the following electronic databases from their inceptions to January 2022: PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Degree and Conference Papers Database, and Chinese Science and Technology Periodical (VIP) Databases. The key searching terms were ("traditional Chinese exercises" OR "Tai Chi" OR "tai ji" OR "Baduanjin" OR "Yijinjing" OR "Qigong" OR "Liuzijue" OR "Five-animal exercises" OR "Wuqinxi") and ("neck pain" OR "cervical spondylopathy" OR "cervical pain"). Additional studies were identified by scanning the reference list of relevant reviews. The World Health Organization International Clinical Trials Registry Platform (ICTRP) and the Chinese Clinical Trial Registry (ChiCTR) were searched to identify the ongoing or unpublished studies. When necessary, the reviewers contacted the study authors. There were no restrictions on publication language or status.

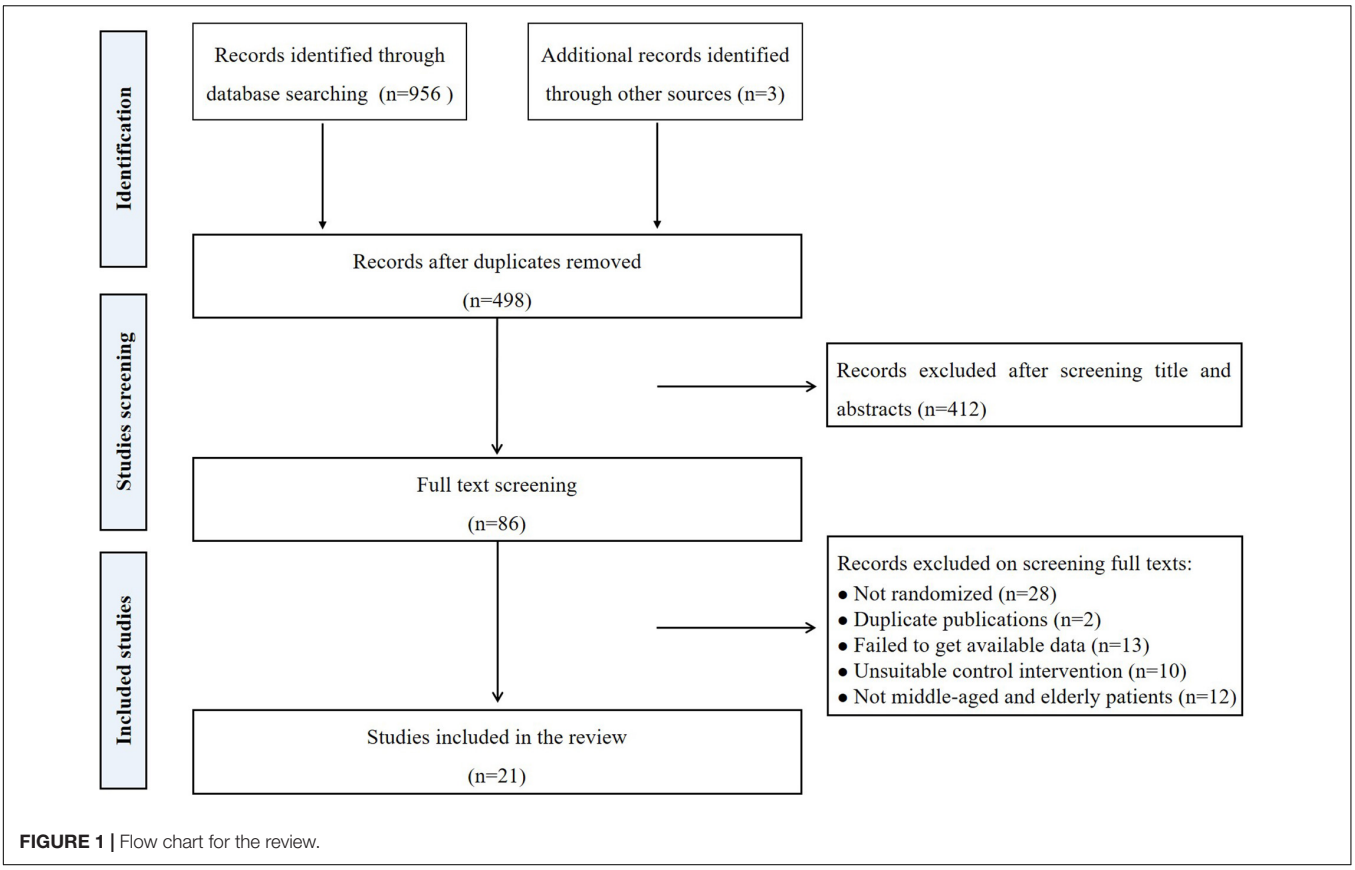


FIGURE 1 | Flow chart for the review.

Study Selection

According to the inclusion and exclusion criteria, the literature selection was performed by two reviewers independently. In this review, the inclusion and exclusion criteria were: (1) Types of study: randomized control trials (RCTs). (2) Types of participants: participants with a clinical diagnosis of neck pain, and the average age more than 40 years at least one group. There were no limitations on gender or nationality. (3) Types of interventions: TCEs were Tai Chi, Baduanjin, Yijinjing, Qigong, Liuzijue, and Five-animal exercises. The control interventions included waiting list, education, routine rehabilitation therapy, acupuncture, medicine, other modern exercise therapy, and any treatments without TCEs. (4) Types of outcomes: pain was measured by the visual analogue scale (VAS), functional mobility of the neck was assessed using the neck disability index (NDI), quality of life was assessed using the 36-item short form health survey (SF-36), and cervical range of motion such as flexion, extension, lateral-flexion, and rotation.

Trials that met any of the following criteria were excluded: (1) quasi-randomized RCTs and non-randomized trials, (2) duplicated publications, and (3) unavailable full text or missing data. Any disagreements were resolved by discussion between two reviewers.

Data Extraction

The data extraction was independently performed by two reviewers based on pre-defined criteria. The following data were collected: (1) basic information such as the name of the first author, year, and country of publication; (2) characteristics of the participants such as sample size and mean age; (3) information regarding study design such as interventions, outcomes, and follow-up duration. Only the first phase data were extracted in the crossover studies. Any disagreements were resolved by discussion between two reviewers.

Quality Assessment

Two reviewers independently assessed the methodological quality of the included trials by the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale is a multi-item scale consisting of 11 items to measure the methodological quality of RCTs of physiotherapy interventions. The PEDro scale includes: (1) study eligibility criteria specified, (2) random allocation of subjects, (3) concealed allocation, (4) measure of similarity between groups at baseline, (5) subject blinding, (6) therapist blinding, (7) assessor blinding, (8) less than 15% dropouts, (9) intention-to-treat analysis, (10) between-group statistical comparisons, and (11) point measures and variability data. The PEDro score of 0–10 is obtained by summation (item 1 is not scored), and a cut point of 6 indicates high-quality studies. The PEDro score has been demonstrated to be valid and reliable for assessing methodological quality of physiotherapy RCTs (Maher et al., 2003; de Morton, 2009). Any disagreements were resolved by obtaining the consensus of all reviewers.

TABLE 1 | Randomized controlled trials evaluating the effects of traditional Chinese exercises for neck pain.

Study	Sample size	Mean age (years)	Duration (weeks)	Follow-up (weeks)	Main outcomes	Experimental group intervention	Control group intervention
Traditional Chinese exercises alone for neck pain							
von Trott et al. (2009), United States	38 39 40	75.9 ± 7.6 76.0 ± 7.2 75.7 ± 7.6	12	24	VAS, NPAD, ADS, SF-36	Qigong (45 min/session, 24 sessions, 12 weeks)	(1) Exercise (45 min/session, 24 sessions, 12 weeks) (2) Waiting list
Rendant et al. (2011), United States	42 39 41	44.7 ± 10.8 44.4 ± 10.9 47.8 ± 10.3	24	/	VAS, NPAD, SF-36	Tai Chi (18 sessions, 24 weeks)	(1) Exercise (18 sessions, 24 weeks) (2) Waiting list
Lin (2015), China	25 25	40.33 ± 7.33 39.98 ± 8.34	10	24	VAS, NPQ, ROM	Traditional Chinese exercises (80 min/session, 50–60 sessions, 10 weeks)	Tuina (60 min/session, 40 sessions, 10 weeks)
Lauche et al. (2016), Germany	38 39 37	52.0 ± 10.9 49.2 ± 11.7 47.0 ± 12.3	12	24	VAS, NDI, SF-36, HADS FEW-16, PSS, PAS, MAIA	Tai Chi (75–90 min/session, 12 sessions, 12 weeks)	(1) Exercise (60–75 min/week, 12 sessions, 12 weeks) (2) Waiting list
Zhou et al. (2017), China	32 33	59.71 ± 4.84 60.12 ± 4.56	10	/	NDI	Five-animal exercises (40 min/session, 30 sessions, 10 weeks)	Traction (20 min/session, 30 sessions, 10 weeks)
Traditional Chinese exercises as complementary therapy for neck pain							
Xiao et al. (2003), China	26 18	52 50	30 days	/	VAS	Traditional Chinese exercises (30–40 min/session, 60 sessions, 30 days) plus Chinese herb (2 sessions/days, 60 sessions, 30 days)	Chinese herb (2 sessions/days, 60 sessions, 30 days)
He (2014), China	30 30	43.23 ± 8.01 41.5 ± 7.45	12	/	VAS, NDI, SAS, SDS	Baduanjin (50–60 min/session, 84 sessions, 12 weeks) plus Tuina (40 min/session, 10 sessions, 2 weeks)	Tuina (40 min/session, 10 sessions, 2 weeks)
Hu et al. (2014), China	125 125	44.55 ± 12.42 45.02 ± 12.2	24	/	VAS, NDI, SF-36	Traditional Chinese exercises (40 min/session, 12 sessions, 12 weeks)	Waiting-list
Cai et al. (2015), China	30 30	50.8 ± 8.0 49.9 ± 8.0	60 days	/	VAS	Baduanjin (30 min/session, 120 sessions, 60 days) plus medicine, traction, and physical therapy (15–20 min/session, 120 sessions, 60 days)	Medicine, traction, and physical therapy (15–20 min/session, 120 sessions, 60 days)
Feng and Qin (2017), China	50 50 50	45.55 ± 7.33 50.22 ± 4.68 48.67 ± 6.56	4	12	VAS	Baduanjin (20 min/session, 48 sessions, 4 weeks) plus massage (20 min/session, 24 sessions, 4 weeks)	(1) Massage (20 min/session, 24 sessions, 4 weeks) (2) Massage (20 min/session, 24 sessions, 4 weeks) plus exercise (10 min/session, 48 sessions, 4 weeks)
Cai et al. (2018), China	36 33	57.49 ± 6.13 55.26 ± 4.75	24	/	NPQ, NPRS, PCS, MCS	Baduanjin (30 min/session, 240 sessions, 24 weeks) plus education (2 sessions, 24 weeks)	Education (2 sessions, 24 weeks)
Zheng (2018), China	30 30	45.32 ± 6.11 46.19 ± 6.39	12	/	VAS, ROM	Yijinjing (20 min/session, 144 sessions, 12 weeks) plus acupuncture (6–12 sessions)	Acupuncture (6–12 sessions)
Jiang et al. (2019), China	30 30	42.87 ± 8.80 44.00 ± 9.54	20 days	/	Cervical Arc Chord Distances	Five-animals exercise (2 sessions/day, 40 sessions, 20 days) plus routine rehabilitation (25 min/session, 20 sessions, 20 days)	Routine rehabilitation (25 min/session, 20 sessions, 20 days)
Wu et al. (2019), China	35 33	57.80 ± 5.61 56.30 ± 5.32	8	/	NDI, ROM, VAS	Baduanjin (30–40 min/session, 3–5 sessions/week, 8 weeks) plus conventional treatment (8 weeks)	Conventional treatment (8 weeks)
Chen et al. (2020), China	48 46	38.7 ± 8.4 40.5 ± 8.6	12	/	VAS, PPI	Qigong (30 min/session, 60 sessions, 12 weeks) plus acupuncture (4 weeks)	Acupuncture (4 weeks)

(Continued)

TABLE 1 | (Continued)

Study	Sample size	Mean age (years)	Duration (weeks)	Follow-up (weeks)	Main outcomes	Experimental group intervention	Control group intervention
Huang et al. (2020), China	24 24	38.97 ± 2.37 40.26 ± 2.09	8	/	VAS, ROM	Baduanjin (10 min/session, 144 sessions, 8 weeks) plus Tuina (20 min/session, 24 sessions, 8 weeks)	Tuina (20 min/session, 24 sessions, 8 weeks)
Xie (2020), China	42 42	56.34 ± 6.45 55.98 ± 6.71	12	/	NPQ, MPQ	Baduanjin (5–8 sessions/day, 12 weeks) plus acupuncture (30 min/session, 24 sessions, 12 weeks) and medicine	Acupuncture (30 min/session, 24 sessions, 12 weeks) and medicine
Chen (2021), China	30 30	39.27 ± 9.40 40.00 ± 7.89	4	/	VAS, NDI, ROM	Baduanjin (12 sessions, 4 weeks) plus electroacupuncture (20 min/session, 12 sessions, 4 weeks)	Electroacupuncture (20 min/session, 12 sessions, 4 weeks)
Xu et al. (2021), China	30 30	54.93 ± 11.21 55.27 ± 9.84	4	/	VAS	Baduanjin (56 sessions, 4 weeks) plus acupuncture (20 min/session, 12 sessions, 4 weeks)	Acupuncture (20 min/session, 12 sessions, 4 weeks)
Yang et al. (2021), China	28 27	49.62 ± 7.83 46.45 ± 9.91	2	/	VAS, HAMA	Baduanjin (5 min/session, 42 sessions, 2 weeks) plus physiotherapy and education	Physiotherapy and education
Zhang (2021), China	40 40	43.21 ± 6.24 42.42 ± 6.25	/	/	VAS, PSQI	Baduanjin (40–60 min/session) plus routine rehabilitation	Routine rehabilitation

ADS, Allgemeine Depressions-skala; FEW-16, Questionnaire for Assessing Subjective Physical Well-being; HADS, Hospital Anxiety and Depression Scale; HAMA, Hamilton Anxiety Scale; PCS, Physical Component Summary; ROM, Range of Motion; MAIA, Multidimensional Assessment of Interoceptive Awareness Instrument; MCS, Mental Component Summary; MPQ, McGill Pain Questionnaire; NDI, Neck Disability Index; NPAD, Neck Pain and Disability Scale; NPQ, Northwick Park Neck Pain Questionnaire; NPRS, Numerical Pain Rating Scale; PAS, Postural Awareness Scale; PPI, Present Pain Intensity; PSS, German Version of the Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-Rating Anxiety Scale; SDS, Self-rating Depression Scale; SF-36, 36-Item Short Form Health Survey; VAS, Visual Analogue Scale.

Data Synthesis and Analysis

The meta-analysis was conducted using the RevMan version 5.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). For the continuous outcomes, the between-groups mean differences of the studies were converted to the standardized mean difference (*SMD*) with 95% confidence intervals (*CIs*) in the meta-analysis. A random effects model was used for better dealing with the clinical heterogeneity. The heterogeneity was evaluated using the I^2 statistic: $I^2 > 30\%$ suggests moderate heterogeneity, $I^2 > 50\%$ represents substantial heterogeneity, and $I^2 > 75\%$ considerable heterogeneity. The subgroup analysis was conducted based on different TCEs and control interventions. The risk of publication bias was assessed by funnel-plot if more than nine trials were included in the meta-analysis. Results were considered statistically significant for $p < 0.05$.

RESULTS

Search and Selection

In our initial search, a total of 959 articles were found. A total of 461 of them were duplicates and thus excluded. A total of 412 studies were excluded after screening the titles and abstracts. After screening the full texts, 21 studies were included in our review. The detailed process was showen in **Figure 1**.

Characteristics of the Included Studies

A total of 1,770 participants with a mean age of 49.59 ± 9.27 years were included in eligible 21 RCTs, which were conducted in China, United States, and Germany from 2003 to 2021. Sixteen studies used TCEs as a complementary therapy for neck pain. Five studies used TCEs alone for neck pain. In the included studies, TCEs included Baduanjin, Yijinjing, Tai Chi, Qigong, and Five-animal exercises. TCEs were combined with acupuncture, Tuina, routine rehabilitation, and medicine for neck pain in the included studies. The exercise duration was between 20 days and 24 weeks. The time of each exercise was between 5 and 90 min. The exercise ranged from 12 to 240 sessions. The follow-up time ranged from 12 to 24 weeks. The control intervention included waiting list, education, traction, acupuncture, Tuina, routine rehabilitation, medicine, and other exercises. The main outcomes included neck pain, neck disability, quality of life, and cervical range of motion. The main characteristics of all included RCTs were shown in **Table 1**.

Methodological Quality

Based on the PEDro scale, most (86%) of the included studies have good methodological quality with the scores ranging from 6 to 7 points. The most common flaws were blinding methods in these studies. Blinding of subjects and therapies were absent in all included RCTs. Only 2 RCTs describe concealed allocation in details (von Trott et al., 2009; Lauche et al., 2016). The assessor blinding was performed in 4 included studies (Hu et al., 2014; Lauche et al., 2016; Cai et al., 2018; Yang et al., 2021). In addition,

TABLE 2 | PEDro scale of quality for the included studies.

Study	Eligibility criteria	Random allocation	Concealed allocation	Similar at baseline	Subjects blinded	Therapists blinded	Assessors blinded	< 15% dropouts	Intention-to-treat analysis	Between-group comparisons	Point measures and variability data	Total
Traditional Chinese exercises alone for neck pain												
von Trott et al. (2009)	1	1	1	1	0	0	0	1	1	1	1	7
Rendant et al. (2011)	1	1	0	1	0	0	0	1	1	1	1	6
Lin (2015)	1	1	0	1	0	0	0	1	1	1	1	6
Lauche et al. (2016)	1	1	1	1	0	0	1	0	1	1	1	7
Zhou et al. (2017)	1	1	0	1	0	0	0	1	0	1	1	5
Traditional Chinese exercises as complementary therapy for neck pain												
Xiao et al. (2003)	1	1	0	1	0	0	0	1	1	1	1	6
He (2014)	1	1	0	1	0	0	0	1	1	1	1	6
Hu et al. (2014)	1	1	0	1	0	0	1	1	0	1	1	6
Cai et al. (2015)	1	1	0	1	0	0	0	1	1	1	1	6
Feng and Qin (2017)	1	1	0	1	0	0	0	0	0	1	1	4
Cai et al. (2018)	1	1	0	1	0	0	1	1	1	1	1	7
Zheng (2018)	1	1	0	1	0	0	0	1	1	1	1	6
Jiang et al. (2019)	1	1	0	1	0	0	0	1	1	1	1	6
Wu et al. (2019)	1	1	0	1	0	0	0	1	1	1	1	6
Chen et al. (2020)	1	1	0	1	0	0	0	1	1	1	1	6
Huang et al. (2020)	1	1	0	1	0	0	0	0	0	1	1	4
Xie (2020)	1	1	0	1	0	0	0	1	1	1	1	6
Chen (2021)	1	1	0	1	0	0	0	1	1	1	1	6
Xu et al. (2021)	1	1	0	1	0	0	0	1	1	1	1	6
Yang et al. (2021)	1	1	0	1	0	0	1	1	1	1	1	7
Zhang (2021)	1	1	0	1	0	0	0	1	1	1	1	6

Criteria (2–11) were used to calculate the total PEDro score. Each criterion was scored as either 1 or 0 according to whether the criteria was met or not, respectively.

four trials rated the intention-to-treat negative (Hu et al., 2014; Feng and Qin, 2017; Zhou et al., 2017; Huang et al., 2020), and three studies showed > 15% dropouts (Lauche et al., 2016; Feng and Qin, 2017; Huang et al., 2020). Other items were scored positive in the included studies. The detailed scores were shown in **Table 2**.

Pain

As a complementary therapy, fifteen studies reported the complementary effects in relieving pain of TCEs for neck pain. Nine studies were included in the meta-analysis. The aggregated results indicated that the TCEs showed positive complementary effects in relieving pain (*SMD*, 1.12; 95% *CI*, 0.78–1.45; $p < 0.00001$, **Figure 2A**), especially Baduanjin (*SMD*, 1.19; 95% *CI*, 0.61–1.78; $p < 0.0001$, **Figure 2A**) and Yijinjing (*SMD*, 1.02; 95% *CI*, 0.39–1.65; $p = 0.002$, **Figure 2A**).

As an independent therapy, four studies reported the effects in relieving pain of TCEs for neck pain. All of them were included in the meta-analysis. The aggregated results indicated that TCEs alone showed better effects in improving pain (*SMD*, 0.81; 95% *CI*, 0.50–1.13; $p < 0.00001$, **Figure 3A**) compared with waiting list. But the aggregated results did not show better effects of TCEs alone in relieving pain compared with other exercises (*SMD*, 0.07; 95% *CI*, –0.18 to 0.33; $p = 0.58$, **Figure 3A**).

Disability

As a complementary therapy, six studies reported the complementary effects in improving disability of TCEs for neck pain. Four of them were included in the meta-analysis.

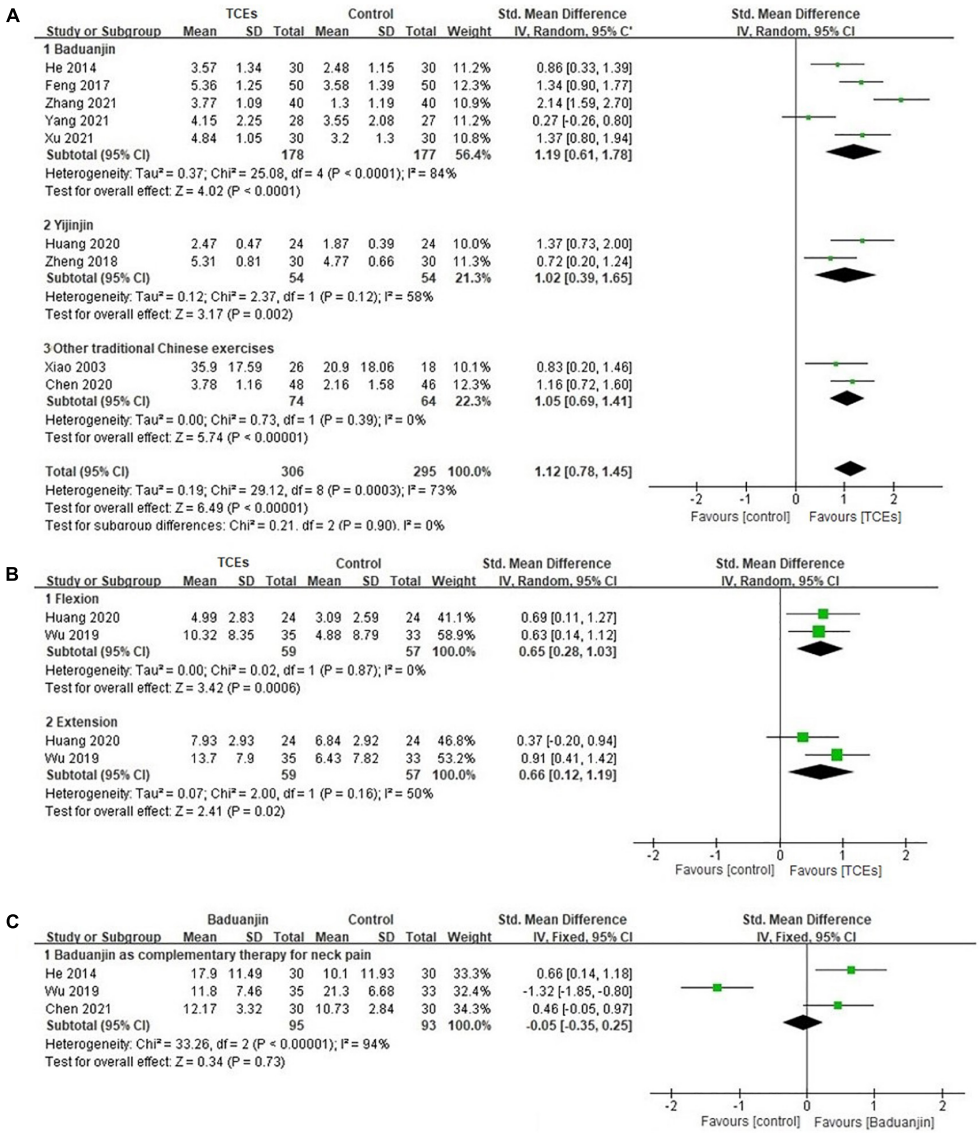


FIGURE 2 | Forest plot of the complementary effects of traditional Chinese exercises (TCEs) for neck pain: **(A)** Pain, **(B)** range of motion, and **(C)** disability.

Baduanjin exercises showed beneficial effects in improving flexion (*SMD*, 0.65; 95% *CI*, 0.28–1.03; $p = 0.0006$, **Figure 2B**) and extension (*SMD*, 0.66; 95% *CI*, 0.12–1.19; $p = 0.02$, **Figure 2B**) of the neck. However, the aggregated result did not show that Baduanjin exercises had better complementary effects in improving disability (*SMD*, –0.05; 95% *CI*, –0.35 to 0.25; $p = 0.73$, **Figure 2C**).

As an independent therapy, the aggregated result showed beneficial effects of TCEs in improving disability of patients with neck pain (*SMD*, 0.74; 95% *CI*, 0.40–1.08; $p < 0.0001$, **Figure 3B**).

Quality of Life

In the included studies, only three studies reported the effects of TCEs on quality of life in patients with neck pain. In the meta-analysis, the aggregated result did not show better effects of TCEs alone on quality of life in patients with neck pain (*SMD*, 0.03; 95% *CI*, –0.34 to 0.39; $p = 0.89$, **Figure 3C**). Hu et al. (2014) reported that 24-weeks TCEs showed potential effects in quality of life in patients with neck pain, especially for mental health.

The Follow-Up Effects

In the follow-up effects, the aggregated results indicated that TCEs alone showed beneficial effects in relieving pain (*SMD*, 0.69; 95% *CI*, 0.39–1.00; $p < 0.00001$, **Figure 3D**). Feng and Qin (2017) reported that participants in Baduanjin group experienced less pain recurrence compared with massage group (7.14% vs. 20.83%) after 3 months follow-up.

Publication Bias

The funnel plots for TCEs for neck pain in relieving pain including 9 RCTs, respectively, in **Figure 4**. The publication bias was small because the spots were substantially symmetric.

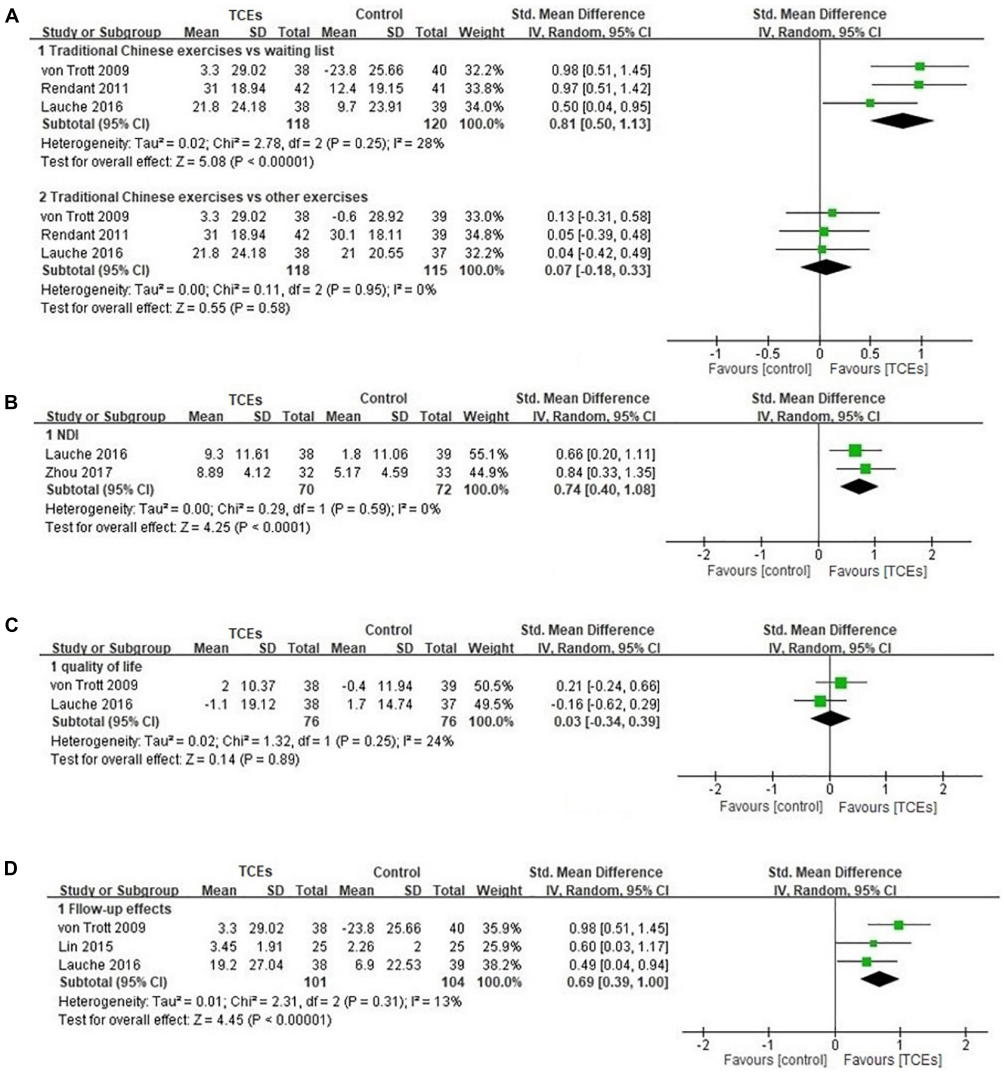


FIGURE 3 | Forest plot of the effects of traditional Chinese exercises (TCEs) alone for neck pain: **(A)** Pain, **(B)** neck disability index (NDI), **(C)** quality of life, and **(D)** follow-up effects on pain.

Adverse Events

TCEs are considered to be safer movements, but there were some minor adverse events such as nausea, aching muscles, muscle tension, and falls and abrasions (von Trott et al., 2009; Lauche et al., 2016).

DISCUSSION

The current systematic review and meta-analysis were conducted to evaluate the effects of TCEs for neck pain. The peak prevalence of neck pain usually is occurred in the middle-aged and elderly populations; thus the average age of included participants was limited (more than 40 years). In most included studies, TCEs were used as a complementary therapy for neck pain. There are encouraging results suggesting that TCEs have complementary effects in improving pain of middle-aged and elderly patients with neck pain, especially Baduanjin exercises. Baduanjin exercises also showed beneficial effects in improving the range of cervical motion of middle-aged and elderly patients with neck pain. However, Baduanjin exercises did not show better complementary effects in improving disability of patients with neck pain, which may be related to fewer included studies. There was not enough evidence on the follow-up effects of TCEs for middle-aged and elderly patients with neck pain. As a complementary therapy, TCEs may provide more improvements in cervical balance, postural control, and blood circulation to relieve pain (Huston and McFarlane, 2016; Kuo et al., 2021). In addition, the middle-aged and elderly individuals could have similar health benefits through low to moderate-intensity TCEs, but experience lower metabolic energy.

As an independent therapy, the results supported the positive effects in relieving pain of TCEs alone compared with waiting list, but no significant differences were shown for effects of TCEs

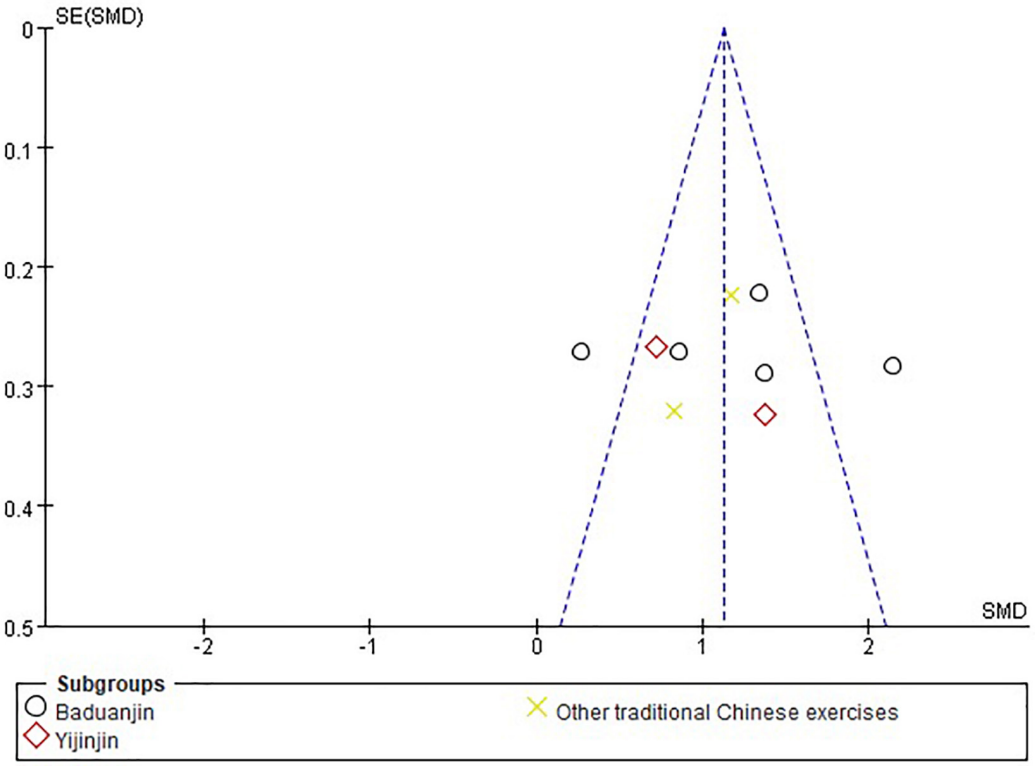


FIGURE 4 | The funnel plots of the complementary effects of TCEs for neck pain in relieving pain.

alone in relieving pain compared with other exercises. It indicates that TCEs may be similar as exercise therapy in relieving neck pain. Guidelines recommend exercise therapy as the first-line non-pharmacological therapy for neck pain (Bussières et al., 2016). Compared with common exercise therapy, TCEs have lower energy metabolism and similar health benefits. However, the mechanism of TCEs in the treatment of neck pain is not clear. They may also improve aerobic capacity and regulate the cervical balance of dynamic and static mechanics, so as to improve neck function, control posture, and relieve pain (Kuo et al., 2021). TCEs combined deep breathing with physical movements, and may have an influence on negative emotions. A study suggested that TCEs may reduce pain-related symptoms by improving cognitive appraisal outcomes such as anxiety and depression (Hall et al., 2016). Negative emotions usually originate from the chronic musculoskeletal pain. However, most included studies did not focus on mental health of patients with neck pain. Thus, TCEs did not show better effects in quality of life in middle-aged and elderly patients with neck pain. In our review, the aggregated result showed beneficial effects of TCEs in improving disability of middle-aged and elderly patients with neck pain, but it was based on the small sample size. In further studies, more high-quality evidence will be needed to support the effects of TCEs alone for middle-aged and elderly patients with neck pain.

The previous systematic review reported that there was insufficient evidence to support the clinical use of TCEs in improving pain intensity and enhancing functional mobility and quality of life in individuals with neck pain (Xie et al., 2021). However, there were only six studies of TCEs for neck pain published in English. TCEs were widely used for musculoskeletal pain in China; however, the studies published in China were excluded in their review. Therefore, there was a significant publication bias in their results. These Chinese studies of TCEs for neck pain were included in our review. TCEs usually were used as a complementary therapy for neck pain in China. In our review, the included studies used TCEs plus routine rehabilitation, acupuncture, Tuina, or medicine for neck pain. Therefore, the complementary effects and independent effects of TCEs for neck pain were evaluated separately in our review. In addition, the subgroup analysis was conducted based on different TCEs in our meta-analysis. The previous systematic review also showed similar results with our review. Li et al. (2021) reported that TCEs could effectively relieve the clinical symptoms of patients with musculoskeletal pain. Therefore, there was more powerful evidence of TCEs for neck pain in our review.

Limitation

There are several limitations in this review. First, a rigorous search strategy was applied in our review, but there may be some uncertainty bias in location and publication (Moncrieff et al., 1998). Second, only RCTs were included in our review, but it was impossible to blind the patients and therapists in the studies of TCEs. The blinded outcome assessors and concealed allocations could partly compensate for these flaws, but only

two trials used concealed allocation and four studies blinded the outcome assessors. Third, the subgroup analysis based on different TCEs was only conducted on the complementary effects in relieving pain. In other outcomes, detailed subgroup analysis was not performed due to insufficient eligible studies. Forth, our results may be affected by the different style, frequency, duration, and session of TCEs. Further reviews should focus on the parameters of TCEs if there are enough eligible studies. Fifth, the result of this review may be influenced by the type of neck pain, but the subgroup analysis could not be conducted due to few included studies. However, it is certain that the neck pain originates from the cervical degenerative diseases in most included studies. Finally, it was suspicious that most included studies conducted in China had non-participants dropout.

CONCLUSION

The current systematic review demonstrated that there was the positive evidence to support the clinical use of TCEs, as a complementary therapy, in relieving pain of middle-aged and elderly patients with neck pain, especially Baduanjin exercises. However, the evidence supporting the effects of TCEs alone in improving pain and disability of middle-aged and elderly patients with neck pain was limited due to the small sample size. The follow-up effects of TCEs were still insufficient.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LK, JR, XZ, and MF conserved and designed the study. TH and JR performed the literature search. JR and SF identified and selected the studies. LK and XZ assessed the methodological quality and extracted data. LK, XZ, and MF performed data synthesis and analysis. LK, JR, SF, XZ, and MF wrote the draft manuscript. All authors contributed to the article and approved the submitted version.

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STUDY PROTOCOL
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Tai Chi Quan Versus Physical Therapy on Pain and Cognitive Performance for Elderly People With Chronic Low Back Pain: Study Protocol for a Randomized Controlled Trial

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Objectives: Chronic low back pain has become a major cause of global disability and caused a huge economic burden to society. Physical therapy is a vital strategy for rehabilitation of chronic low back pain. Although several trials have shown that Tai Chi Quan is a beneficial treatment, the comparative effectiveness of Tai Chi Quan versus physical therapy is unknown. We are conducting a randomized controlled trial to assess the effectiveness of Tai Chi Quan versus that of physical therapy in treating chronic low back pain.

Methods: We will perform a single-blind randomized controlled trial on elderly people with chronic low back pain. 138 participants will be randomly assigned to the Tai Chi Quan group (60-min classes, three times per week for 12 weeks) or physical therapy group (10 min of evaluation and warm-up, 40 min of therapist-directed exercise therapy, and 10 min of relaxation, three times per week for 12 weeks) with an allocation of 1:1. The participants will be followed up for 40 weeks for the study of long-term effects. The primary outcomes include pain intensity and back-related function at 12 weeks. Secondary outcomes include lumbar quantitative sensory testing, balance, cognitive function, psychosocial function, cost-effectiveness, compliance and adverse events. We will perform the intention-to-treat analysis for withdrawal and missing data.

Discussion: The study will be the first randomized trial with comparative-effectiveness of Tai Chi Quan and physical therapy for chronic low back pain. Standardized protocol, large sample size, and comprehensive outcomes are important features in this trial. This

study aims to determine the feasibility and effectiveness of Tai Chi Quan for low back pain. The results of this study will be beneficial for elderly people with low back pain and medical rehabilitation personnel.

Clinical Trial Registration: www.chictr.org.cn, identifier ChiCTR2000029723.

Keywords: chronic low back pain, traditional Chinese exercise, physical therapy, cognition, randomized controlled trial

INTRODUCTION

Low back pain (LBP) is a common pain syndrome between the lower rib margins and buttock creases and occurs at all ages (Hartvigsen et al., 2018). When LBP lasts more than 3 months, it is called chronic low back pain (CLBP), which is more common in women and the elderly (Hoy et al., 2012). By 2017, LBP has prevailed as one of the leading causes of global years lived with disability (YLD) and non-fatal health loss (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2018), and YLD increased by 54% between 1990 and 2015, especially in low- and middle-income countries (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). The prevalence of LBP is more than 80%, of which CLBP accounts for 23%, and the disability rate is 11–12% (Brinjikji et al., 2015; Maher et al., 2017). The prevalence of LBP ranged from approximately 28 to 51% in 28 countries (Maher et al., 2017). A systematic review of 35 studies found that the prevalence of LBP ranged from 21 to 75% among approximately 130,000 people aged over 60 years, and the majority of patients had functional disabilities and limitations of physical capacity (de Souza et al., 2019). Owing to changes in social environment and lifestyle, physical inactivity and sedentarism have become worldwide issues and important predictors of poor health (Panahi and Tremblay, 2018), and the incidence of adolescents with LBP shows an increasing trend (Shim et al., 2014). People with CLBP suffer from unpleasant nociceptive sensation and limited activities, are often absent from work and have low quality of life (Deyo et al., 2014). The cost of LBP ranked sixth in the overall burden of diseases ("Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013 Collaborators, 2015). Studies have pointed that LBP forces older people to leave work and retire early; this situation results in huge indirect costs (mainly lost productivity and household income) (Ferreira et al., 2010). People who retire early because of LBP earn approximately 87% less than people who work full time (Schofield et al., 2011). In 2018, the World Health Organization has identified research on 'reducing disabling LBP' as one of its global health priority programs (Buchbinder et al., 2018). LBP is of urgent global public health concern.

The non-invasive management for CLBP usually includes medication, physical therapy (PT) and education about being physically active (Qaseem et al., 2017). PT consists of movement therapy (such as aerobic exercise, whole body vibration exercise, and core stability exercise), manual therapy (such as massage, spinal manipulation, spinal mobilization, and nerve mobilization) and modality therapy (such as electrotherapies, laser therapy, and superficial heat therapy), and the international guidelines for LBP have provided a specific set of recommendations for these three sections (de Campos, 2017; Qaseem et al., 2017; George et al., 2021). Movement therapy has been recognized as a core part of LBP treatment (R. Wang et al., 2020). A systematic review have shown that guided and personalized exercise programs can effectively improve CLBP (Hayden et al., 2005). In clinical randomized controlled trials (RCTs), PT is often compared with other LBP interventions, and cost-benefit analyses are performed. Saper et al. founded that yoga and PT are effective for CLBP after 12-week intervention, and yoga is not inferior to PT in terms of improving lumbar function and relieving pain (Saper et al., 2017). Vibe et al. compared the effects of cognitive function therapy with those of PT for CLBP and showed that PT fully reflects the emphasis on exercise therapy and the importance of classified diagnosis and treatment (Vibe Fersum et al., 2013). Pengel et al. used physiotherapist-directed exercise interventions in patients with LBP, and their pain and physical function scores were significantly better than those of the placebo group after 6 weeks (Pengel et al., 2007). PT plays an important role in musculoskeletal disorders. The national PT referral rate for LBP patients aged 45 to 59 years in the United States between 1997 and 2010 was estimated to be about 36.5%, and the rate was approximately 19% for LBP patients aged 60 and above (Zheng et al., 2017). In the Chinese clinical setting, patients with chronic pain are mostly managed by rehabilitation therapists, and those with high incomes are particularly likely to choose individualized therapists. Although therapist-directed PT is effective in resolving the problems of patients, the cost of PT is considerable for most low- and middle-income people with CLBP. At present, health care staff and patients are looking forward to a long-term effective alternative treatment with lower economic burden.

As a traditional exercise therapy, Tai Chi Quan (TCQ) has been widely used in researching health promotion interventions for posture balance and fall and chronic diseases (Liu et al., 2012; X. Wang et al., 2015; Zhi-lei and Dong, 2018). A systematic review has demonstrated the safety and reliability of the clinical application of TCQ (Wayne et al., 2014). In 2017, the clinical guideline issued by the American College of Physicians strongly recommended TCQ for CLBP (Qaseem et al., 2017). TCQ is considered an active therapy and a coordinated movement in which a practitioner needs to concentrate and coordinate breathing. TCQ involves circular and curved movements,

emphasizes the twisting of the waist and hips and drives the limbs into diagonal spiral movements. The forward and backward, left and right and oblique steps can improve the flexibility and stability of the joints (Li, 2014). In recent years, some important achievements about TCQ have been made in health promotion and disease intervention (Li et al., 2012, 2018; C. Wang et al., 2016). In 2011, an RCT of TCQ for persistent LBP found that 10 weeks of TCQ exercise improves pain levels and pain-related disability (Hall et al., 2011). In 2013, Another RCT showed that 6 months of TCQ is effective in reducing pain symptoms and can be used as an alternative therapy (Sun, 2013).

Tai Chi Quan can significantly improve core stability and muscle strength, thereby reducing the risk of falls in patients with CLBP (Lomas-Vega et al., 2017). Sleep problems are common among people with CLBP, and insomnia can increase the risk of CLBP (Skarpsno et al., 2020). A meta-analysis showed that TCQ has a significant beneficial effect on the sleep quality of the elderly (Du et al., 2015). The intensity of TCQ practice depends on time, speed and experience. For the elderly with CLBP, simplified TCQ is easy to learn and can improve balance, coordination and spinal stability. Compared with the waiting group and the usual care group, TCQ from 10 to 28 weeks had a better effect on lumbago (Kong et al., 2016). However, few studies have investigated the long-term follow-up effects of TCQ on CLBP. Although PT is the main management method for LBP rehabilitation, it is expensive in terms of manpower and financial resources. As an easy to learn and low- cost exercise therapy, TCQ is expected to be accepted as an alternative therapy by a large number of patients with CLBP. However, previous studies had some deficiencies, such as short intervention time, lack of follow-up observation and economic analysis, and evidence supporting the application value of TCQ in patients with CLBP remains insufficient. Therefore, we propose a detailed protocol to study the comparative effectiveness of TCQ classes versus grouped-PT for people with CLBP. Our primary hypothesis is that TCQ and grouped-PT have a significant clinical effect on CLBP. The secondary hypothesis is that TCQ is not inferior to PT in terms of improving outcomes. The third hypothesis is that TCQ has a longer-term effect than PT.

STUDY DESIGN AND METHODS

Study Design

The study is a single-blinded RCT of TCQ classes or grouped-PT for patients with CLBP (**Figure 1**. Study flow diagram). Eligible participants will be randomly assigned into the Tai Chi Quan group (TCQG) or physical therapy group (PTG). Both groups will perform exercises for 60 min three times a week for a total of 12 weeks. After the program, 40 weeks of follow-ups will be conducted.

The coprimary outcomes after the interventions are maximum and average pain intensity measured using a numerical rating scale (NRS) (Williamson and Hoggart, 2005) and back-related function measured using the Roland Morris Disability questionnaire (RMDQ) (Roland and Morris, 1983). The secondary outcomes include lumbar quantitative sensory testing, balance, cognitive function, psychosocial function, cost-effectiveness, compliance and adverse events. Healthcare utilization data, including medical costs, drugs use and cost of TCQ and PT, are tracked to estimate whether TCQ would be more economical and beneficial than grouped-PT exercise. The outcomes and measurement timepoints are presented in **Table 1**.

The study setting is located in the Center of Sports Medicine and Rehabilitation, Shanghai Shangti Orthopaedic Hospital (SSOH), Shanghai, China. Each participant will sign a written informed consent. This study protocol has been approved by the Ethics Committee of the Shanghai University of Sport, China (Grant number 102772019RT039).

Sample Size

The sample size analysis is based on hypothesized change in RMDQ scores. For the primary outcome of change in pain intensity from baseline to week 12, we assume that two-sided α error prob is equal to 0.05 and power is 0.8. The minimal clinically important difference of the RMDQ is prespecified for 3 points (Jordan et al., 2006), and the effect size of RMDQ is in the range of 0.54–0.84 (Saper et al., 2017). We used G-Power Software (version 3.1.9.2, Germany) to estimate the total sample size with the method of *t*-tests-means (difference between two independent means measures in two groups). Considering the effect size of RMDQ is 0.54 and 20% attrition rate, we need a minimum of 138 participants in this study or 69 participants in each group to detect whether 12 weeks of TCQ and grouped-PT have a significant clinical effect on CLBP.

Participants

Randomization and Blinding

We will take a community randomized approach, and four communities will be assigned with an allocation of 1:1 through the random numbers generated by the analyst. Finally, two communities will be assigned to the TCQG, and two to the PTG. We will recruit participants in the corresponding community to practice TCQ or PT. Throughout the courses of the trial, all study assessors who are responsible for collecting outcomes will be blinded to the hypotheses and allocation. Meanwhile, we shall maintain separation between the assessors and assistants who are responsible for recruitment work and between the assessors and class instructors. In addition, participants should conceal their group status to the assessors. Participants have informed consent and are blinded impossibly without a placebo. Finally, all data analyst do not know group allocation and deal with coded data instead of the names of the participants.

Inclusion and Exclusion Criteria

Target participants will be mainly community-dwelling elderly people who are living in Shanghai. The specific inclusion and exclusion criteria are listed in **Table 2**. The participants will quit the study if they have been diagnosed with severe diseases (such as heart failure) or serious adverse events occur during the experiment. Besides, the participants will be allowed to voluntarily quit as result of any of their own reasons. We plan to execute the following ways to access our participants as many as possible: (1) Distributing study

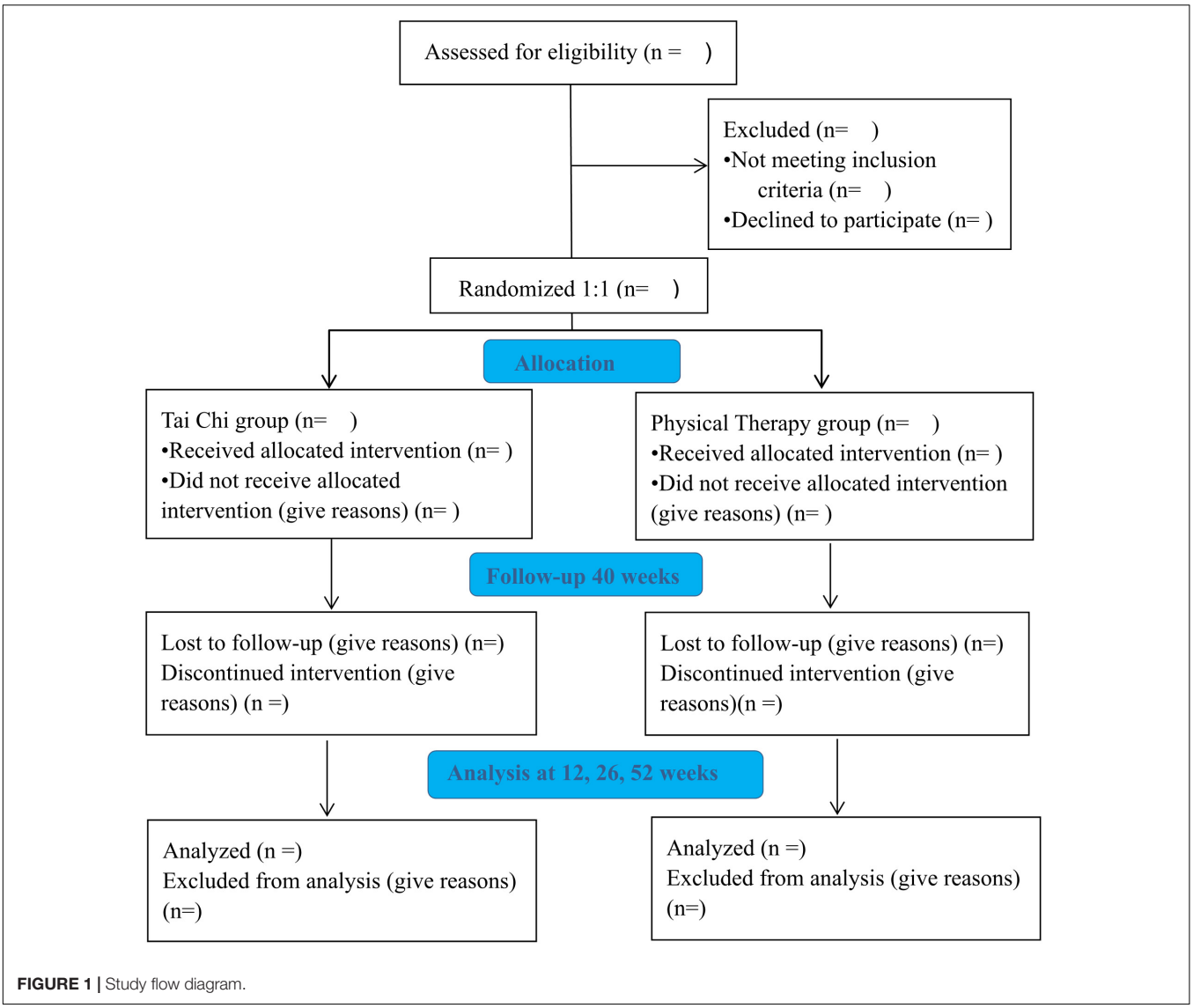


FIGURE 1 | Study flow diagram.

recruitment flyers in nearby four communities with permission; (2) Sending study recruitment presentations to community healthcare center staff to help introduce potential participants; and (3) Disseminating the recruitment information through electronic communications and anyone interested can contact the recruiter by telephone.

Intervention Conditions

Intervention Classes Locations

The participants randomized to TCQG will practice it at community health centers or residential activity center for non-profit organizations where the evidenced-based prevention of chronic diseases and health promotion activities are encouraged. PT intervention will take place at the Center of Sports Medicine and Rehabilitation of SSOH or community resident activity centers.

Tai Chi Quan Group

Tai Chi Quan is strongly recommended for treating CLBP (Qaseem et al., 2017). In our study, the TCQ program features eight modified movements, which combine Yang style and Cheng style, and reflect multiple directions around the central axis. In general, these movements revolve around the waist as the core, thereby activating the limbs. The movements include various steps (forward, backward and lateral), spatial orientation movements (performing each single movement in different directions) and complex movements (requiring coordination of eyes-heads-hand and increasing demands on attention and postural control) (Li, 2014). TCQ is a body–mind exercise, coordinating the movement of the limbs through lumbar winding movements (McAnulty et al., 2016). Therefore, TCQ may provide more stimulation for core muscles and improve the flexibility and stability of the spine. It may also enhance directly transferable skills in daily life, such as reaching and turning, going up/down stairs and walking.

TABLE 1 | Measurements timing for primary and secondary outcomes.

Outcomes variables	Baseline	Week 12	Week 26 (follow-up)	Week 52 (follow-up)
Primary outcomes				
NRS – the Maximum Pain	√	√	√	√
NRS – the Average Pain	√	√	√	√
RMDQ – Back-related Function	√	√	√	√
Secondary outcomes				
Lumbar quantitative sensory testing	√	√		
4-stage balance test				
Trial making tests	√	√	√	√
Stroop test	√	√	√	√
6-min walk test	√	√	√	√
Geriatric depression scale	√	√	√	√
Self-rating anxiety scale	√	√	√	√
Pain catastrophizing scale	√	√	√	√
Tampa scale for Kinesiophobia	√	√	√	√
Pittsburgh sleep quality index	√	√	√	√
Short-form 12	√	√	√	√
General perceived self-efficacy scale	√	√	√	√
Expenses for healthcare monthly	√	√	√	√
Expense for other diseases	√	√	√	√
Expense for low back pain	√	√	√	√
Global perceived effect		√		
Adherence		√		
Adverse Events		√		

NRS, numerical rating scale; RMDQ, Roland Morris disability questionnaire.

Protocol

The eight movements have been demonstrated in our published article (R. Wang et al., 2022). The eight movements combine forward and backward steps, left and right steps and diagonal steps with rotating waist. The consistent exercise schedule includes three parameters: frequency (three times a week), time (60 min per session) and content (10 min of warm-up, eight core forms and 5 min cool-down). Method of inhaling and exhaling will be integrated into the TCQ forms. During the initial 3 weeks, classes will focus on learning these eight forms. At the fourth week, participants will learn to unite the forms. In the last 8 weeks, classes will concentrate on practice. To ensure the best curative effect, we conduct TCQ classes for participants with qualified coaches who finished training delivered by senior TCQ professor before the intervention classes. Apart from a coach, each class is provided with an assistant to provide right action feedback to the participants.

Exercise Intensity Monitoring

Given that our participants are mainly elderly people, exercise intensity will be closely monitored throughout the study. During the learning phase, participants will be instructed to exercise at which their rating of perceived exertion (RPE) is characterized as being "light to moderate" (Scherr et al., 2013). In the last 8 weeks, the intensity progresses to "moderate" (equals to 4–6 scores). Exercise intensity will be assessed weekly by the class assistant. All participants need to record their weekly home exercise and adverse events on the given file after class (see **Supplementary Additional File 1**).

Physical Therapy Group

After physical examination and special lumbar tests, we will divide the group into four types (type 1: LBP with mobility deficits; type 2: LBP with movement control impairment; type 3: LBP with referred pain; type 4: LBP with radicular pain) according to the World Health Organization's International Classification of Functioning, Disability, and Health (Delitto et al., 2012) and the American Physical Therapy Association (APTA) clinical guideline of LBP (George et al., 2021). Different types of participants receive different types of exercises, such as position adjustment, flexibility exercise, stability exercise, specific trunk muscle activation exercise, McKenzie directional repetitive technique, and neural mobilization (see **Supplementary Additional File 2**). These exercise recommendations are based on the latest APTA guideline of LBP (George et al., 2021). The same therapist is responsible for in-group exercise for the same type of participants. The whole process will be implemented by the licensed therapist who have finished the prescribed training on the classification assessment and intervention, and recorded in the Classified Assessment and Intervention Form (see **Supplementary Additional File 3**).

Protocol

The exercise schedule includes three parameters: frequency (three times a week), time (60 min per session) and content (10 min of evaluation and warm-up, 40 min of therapist-directed exercise therapy, and 10 min of relaxation). Natural breathing is recommended during exercise.

TABLE 2 | Inclusion criteria and exclusion criteria.

Inclusion criteria	Exclusion criteria
Aged 50–80 years, can speak Chinese and complete the questionnaire survey.	Have practiced tai chi regularly for any reason within the past 6 months or who have practiced tai chi, yoga or qigong for nearly half a year to treat LBP.
Pain, at least 3 months, typically occurs in the area between the lower rib margins and the buttock creases, commonly accompanied by pain in one or both legs.	Have received guided physical therapy for LBP within half a year, including stretching, strength training, motor control training, and so on.
Have had back pain on at least half the time in the last 6 months.	Have specific causes or potential causes of LBP (e.g., sciatica, spinal stenosis, lumbar disk herniation, spondylolisthesis, recent vertebral fracture, and so on).
The average scores of numerical rating scale (in the range of 0–10) ≥3 and ≤8.	Have red flags of serious underlying systemic or visceral disease (e.g., inflammatory disorders malignancy, unexplained weight loss, infections, or recent trauma).
Back-related function scores of Roland-Morris disability questionnaire (in the range of 0–24) ≥5.	Pain in other parts of the body is greater than low back pain.
Have normal cognition or only mild cognitive impairment [the scores of Mini-Mental State Examination (in the range of 0–27) ≥24].	Had prior lumbar spine surgery.
Able to understand the learning process and complete the whole course.	Have history of drug and alcohol abuse.
Volunteer to participate the trial and sign an informed consent.	Have other disabling conditions that might confound treatment effects.
	Have moderate to severe depressive symptoms [the scores of Geriatric Depression Scale (in the range of 0–30) ≥21].
	Exercise is contraindicated.

Exercise Intensity Monitoring

For a more clinical setting, the 40 min of exercise intensity is controlled by the therapist's evaluation of the participant. According to RPE, moderate intensity aerobic exercise equals to 4–6 scores of the modified Borg Scale. Participants shall record their weekly home exercise and adverse events on given file (see **Supplementary Additional File 4**).

Specific Notes

Participants accept intervention after baseline data collection. For 12 weeks, both groups receive supervised exercise, keep normal lifestyle and is not subjected to additional CLBP treatment. All participants are able to keep their routine medical visits with physicians. The research staff records any changes made to treatment but do not change or recommend changes in medical therapy. Participants will receive 50 yuan after the baseline assessment, 100 yuan for the final assessment, and, respectively, 50 yuan for two follow-up visits. Ensure the attendance of each participant for 3-month intervention through sign-in and telephone supervision. Participants with an attendance of 80% or above will be rewarded with an extra 100 yuan. Some participants may be absent on some weekdays, so we will plan to take a make-up session on weekends based on the number of participants to ensure the optimal attendance.

DATA COLLECTION AND OUTCOME MEASUREMENTS

The outcomes and measurement timepoints are presented in **Table 1**. A demographic questionnaire which consists of participants' characteristics (sex, age, body mass index, education background, and so on) and history of LBP will be completed before the intervention.

Primary Outcome

Numerical Rating Scale–the Maximum and the Average Pain

We will use the NRS to measure the maximum and average pain intensity at 12 weeks. The NRS is an 11-point (from 0 to 10) scale, and a score of '0' or '10' means no pain or unbearable pain, respectively (Williamson and Hoggart, 2005; Maughan and Lewis, 2010). Participants will assess their scores according to pain experience. The NRS has an excellent test-retest reliability with an intraclass correlation coefficient (ICC) of 0.92 (Chiarotto et al., 2019).

Roland Morris Disability Questionnaire–Back-Related Function

Roland Morris Disability questionnaire is suitable for evaluating the short-term changes of back-related function after intervention. The questionnaire consists of 24 questions, involving eight facets of walking, standing, bending, lying, dressing, sleeping, self-care, and daily activities (Roland and Morris, 1983). 'Yes' (1 point) or 'No' (0 point) is answered to each question, and a high total score equates to poor back function. A reduction of 30% on RMDQ score from baseline is identified as minimal clinically important difference for CLBP (Jordan et al., 2006). The RMDQ has an excellent test-retest reliability with an ICC of 0.91 (Brouwer et al., 2004).

Secondary Outcomes

Lumbar Quantitative Sensory Testing

Pain threshold is a predicator of chronic pain and can be used to assess muscle sensitivity (Fischer, 1987). Patients with CLBP had lower pressure pain thresholds than healthy people (Farasyn and Meeusen, 2005; Giesbrecht and Battié, 2005). We will use a hand-held digital manometer (FDX 25 Digital Force Gage, 100× 0.1N) to evaluate pressure pain thresholds of lumbar and lower extremity muscles in elderly people with CLBP. And also, we will use Pathway sensory assessment system (Medoc Ltd., Israel) to evaluate hot pain thresholds and cold pain thresholds.

4-Stage Balance Test

The 4-stage balance test is recommended by Disease Control and Prevention to assess static balance in the elderly (CDC, 2017).

Participants start in sequence with standing with feet side-by-side, then standing with half step (he instep of one foot touches the toe of the other foot), standing in tandem stance (the heel of one foot touches the toe of the other foot), and standing on one foot. Participants try to hold each position without any support for 10 s measured with stopwatch. If participants failed in one of the positions, the test will be terminated. A total time of less than 30 s indicates high risk of falling.

Cognitive Performance

Cognitive decline is an important concern with aging process. Each elderly participant is expected to finish cognitive tests. The Trial making tests (TMT) mainly focus on memory and executive function (Llinàs-Reglà et al., 2017). TMT-A is carried out by participants using a pen to connect random distributed numbers 1 to 25 in sequence, and TMT-B is carried out by connecting distributed letters A to L in sequence. Record the completion time of TMT-A and TMT-B, respectively. The Stroop color- word test is used to evaluate attention control, executive function, and working memory (Washburn, 2016; W. Wang et al., 2021). Participants will response to the color which is congruent, incongruent, or irrelevant with the random word meaning (Hyodo et al., 2012). Record the response time and accuracy.

6-Min Walk Test

The 6-min walk test (6MWT) is in measuring the distance that a participant can quickly walk on a flat and hard surface in 6 min. The distance recorded in meters will reflect the functional exercise level of daily physical activities (Peppin et al., 2014).

Geriatric Depression Scale

The 15-item Chinese revision of the Geriatric Depression Scale (GDS) is suitable for assessing the level of elderly depression. According to the items on the scale, participants answer 'yes' or 'no' to describe their feelings in the last 2 weeks. The higher the score (closer to 15) is, the higher level of depression is (Park and Kwak, 2021). The GDS has an excellent internal consistency (Albiński et al., 2011).

Self-Rating Anxiety Scale

The Self-rating Anxiety Scale (SAS) is a self-reported scale, in which items tap affective and somatic symptoms. Each item of the scale is rated by participants according to their actual status within the past week, using a 4-point scale ranging from 1 (none or a little of the time) to 4 (most or all of the time) (Shimada et al., 2016). Higher score indicates greater severity of anxiety. The SAS has a satisfactory internal consistency with a Cronbach's alpha of 0.83 (Dunstan and Scott, 2020).

Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is designed to assess catastrophic thinking associated with pain among patients with chronic pain (Wheeler et al., 2019). Participants will self-report 13 items related to painful experiences and the answer will be rated on a 5-point Likert scale from 0 (not at all) to 4 (all the time). A total score above 30 indicates clinically relevant level of catastrophizing. The test-retest reliability is excellent with an ICC of 0.94 (Xu et al., 2015).

Tampa Scale for Kinesiophobia

The Tampa Scale for Kinesiophobia (TSK) is a 17-item self-report measure to assess pain-related fear and is used extensively in patients with persistent LBP (Roelofs et al., 2004). The scale is rated on a 4-ponit Likert scale from 1 (strongly disagree) to 4 (strongly agree). A high score indicates high level of the fear of activity or reinjury. The TSK has a good reliability with an ICC of 0.86 (Wei et al., 2015).

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) can be used in assessing sleep quality and disturbances. The index ranges from 0 to 21 and consists of 24 questions covering seven domains. The lower the index is, the better the sleep quality or the lower the disturbance in sleep is (Mollayeva et al., 2016). The PSQI has an excellent test-retest reliability with a correlation coefficient of 0.77 (Tsai et al., 2005).

Short-Form 12

The Short-Form 12 (SF-12) is a brief health-related quality of life questionnaire. The questionnaire measuring eight domains can be used in calculating physical and psychological scores (Ware and Sherbourne, 1992). It is widely used in community-based health surveys and outcome assessment of physical and mental illnesses. Low scores indicate poor health status. The SF-12 shows satisfactory internal consistency both in the physical component summary (Cronbach's alpha = 0.81) and mental component summary (Cronbach's alpha = 0.83) (Su and Wang, 2019).

General Perceived Self-Efficacy Scale

The scale has 10 items, each of which is scored in integers from 1 (completely incorrect) to 4 (completely correct) (Zotti et al., 2007). High scores indicate better confidence to handle various things. General Perceived Self-efficacy Scale (GSES) can be considered a predictive variable of outcomes and an outcome itself. We use it to reflect participants' confidence in their capability to increase self-management of chronic pain and perform daily coping tasks. The GSES has an adequate test-retest reliability with a correlation coefficient of 0.75 (Wu et al., 2004).

Expenses for Healthcare Monthly

To analyze the cost-effectiveness of TCQ and PT, we will collect participants' expenses for treating LBP or other diseases monthly since the start of the intervention. We expect that practicing TCQ will reduce the cost for treating chronic diseases and improve quality of life.

Global Perceived Effect

Global Perceived Effect (GPE) numerical rating scale consists of seven choices (from 1 to 7 points), each representing the overall improvement in the participants' symptoms after they completed the trial (Kamper et al., 2010). A good improvement indicates a high score. It can be useful in understanding the strengths and shortcomings of outcome measures for research. The participants will be asked to rate the degree of improvement or aggravation in their conditions since the beginning of the intervention. The GPE has an excellent test-retest reliability with an ICC of 0.90 (Kamper et al., 2010).

We will record the number of classes the participants attend and the reasons for absence. In addition, adverse events, which are related to interventions and home exercise, will be recorded (see **Supplementary Additional Files 1, 4** for details).

DATA MANAGEMENT AND ANALYSIS

Data Management

After recruitment, the researchers will replace the participants' names with numerical codes in order to protect their privacy. Their data will be collected at baseline and week 12, 26, and 52, respectively. Two professional data workers are responsible for entering their paper files into the same database and cross-checking them for data's accuracy. Eventually, all paper files and encrypted electronic files will be kept and backed up by the researcher leader. These files will be maintained in storage for 3 years after completion of the study.

Data Analysis

Intention-to-treat analysis will be performed regardless of adherence. Microsoft excel 2016 and IBM SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, United States) will be used in data analysis. Continuous variables (e.g., age, body mass index, NRS score, and RMDQ score) will be represented as mean ± standard deviation and be compared using analysis of the independent samples *t*-test. We will use the chi-squared test to analyze the categorical variables (e.g., gender, marital status, smoking, and exercise habits) between the TCQ group and PT group. The baseline demographics characteristics differences between groups will be compared using analysis of *t*-test, variance (ANOVA) or chi-squared tests. If potential confounding factors including gender, age, body mass index, smoking, exercise habits, etc., are present, we will prespecified an adjusted analysis, by using multiple linear regression. At the same time, missing values at week 12, 26, and 52 will be imputed using the multiple imputation.

The co-primary outcomes are the measurement of minimal clinically important difference in NRS and RMDQ scores in two groups after the 12-week intervention, and the paired-sample *t*-test will be carried out for the comparison of the differences. For secondary outcomes, the difference of continuous variables between groups will be compared using the analysis of independent-samples *t*-test. Expenses for LBP or other disease will be explored for cost-benefit analysis. Participants' global perceived effect, adherence, and health-related quality of life will be compare using appropriate regression. The Fisher exact test will be used to compare adverse events. For the follow-ups phase, two-way repeated-measures analysis of variance (group × time) will be carried out to assess the differences of the primary outcomes (NRS score and RMDQ score) between the two groups. In all analyses, a *P*-value of <0.05 will be considered statistically significant.

Data Monitoring

The study will be supervised by the Ethics Committee of the Shanghai University of Sport, whose members did not have any conflict of interest with this study. The principal investigators have access to all results and make the final decision to terminate the study. And also, they will grant project members the right to disseminate the results of this trial by publishing papers.

DISCUSSION

Finding an effective and inexpensive treatment for CLBP is valuable. Compared with the conventional non-invasive intervention for CLBP, TCQ is convenient and can be performed indoors and outdoors and by a single person or groups. For people of all ages, TCQ has the dual benefits of physical and mental conditioning. In this project, we will conduct an RCT to compare the effectiveness of TCQ with that of PT for CLBP. The TCQ practice program consists of eight movements for enhancing spinal stability and muscle strength of the waist and will be taught by professional teachers. Classification assessment and grouped-PT practice program based on patients' functional performance and pain symptoms is carried out by licensed therapists. The intervention duration is 12 weeks, and 40 weeks of follow-ups is performed for the observation of long-term efficacy.

The strengths of this protocol are as follows. First, it will be the first RCT to compare modified TCQ with grouped-PT in patients with CLBP. The results of this trial will complement research in TCQ for LBP. Second, the 12-week intervention period and 40-week follow-up will be helpful in comparing the short- and long-term benefits of TCQ and PT. Third, by analyzing the medical expenses of the participants, the study will investigate whether TCQ has the benefit of saving medical costs. In addition, the study with large sample size will provide robust evidence of whether TCQ, rather than PT, can be a simple, effective, inexpensive and durable alternative therapy for chronic diseases. However, several potential limitations have been observed. First, all participants will not be blinded, and the recruitment criteria are limited to participants aged 50–80 years and without severe CLBP. Thus, the findings of study may not be appropriate for other age groups.

In conclusion, the purpose of this study is to estimate the effectiveness of TCQ in relieving pain intensity and improving back-related function and cognitive function on the basis of comparison with PT. The findings of this study will provide substantial evidence for TCQ as an effect alternative treatment for elderly people with CLBP.

ETHICS STATEMENT

This study protocol has been approved by the Ethics Committee of the Shanghai University of Sport, China (number: 102772019RT039). A written informed consent will be obtained from each study participant. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

X-QW had substantial contributions to the conception of the study. X-QW, DZ, LW, JL, JZ, YJ, YS, and

RW designed the randomized controlled trial. RW, YS, H-YH, Z-WD, L-MW, K-YZ, and SK conducted the research. RW wrote the original draft of the manuscript. X-QW and RW participated in the revision of the draft. SK as one of the co-authors agreed to publish her images presented in **Supplementary Additional File 2**. All authors read and approved the final submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.900430/full#supplementary-material

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REVIEW
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Exercise for Stroke Rehabilitation: A Bibliometric Analysis of Global Research From 2001 to 2021

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Objective: To make a bibliometric analysis of global trends in research into exercise interventions for stroke between 2001 and 2021.

Method: This study did the systematic literature from 2001 to 2021 in Web of Science Core Collection. CiteSpace software was used to analyze the relationship of publications with countries, journals, authors, references, and keywords.

Results: A total of 3,484 publications were obtained in the bibliometric analysis. The number of publications increased gradually over the period. The United States have the most number of publications. The journal *stroke* had the most citations per paper (106.95) and the highest impact factor (IF 2020, 7.194). The most high frequency keywords are "stroke," "rehabilitation," and "recovery," the top of burst key words are "health," "speed," and "aerobic exercise".

Conclusion: These findings provide the trends of exercise for stroke s and provided the potential research frontiers in the past 20 years. It will be a useful basis for further research into focus issues, cooperators, development trends.

Keywords: stroke, rehabilitation, bibliometric analysis, exercise, global trend

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INTRODUCTION

Stroke is a kind of cerebrovascular diseases, and its main clinical manifestations are cerebral ischemia and hemorrhagic injury. In 2017, there were about 104.2 million stroke survivors and 11.9 million new cases of stroke worldwide (Gbd 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). On a global scale, stroke is the second leading cause of death and the third leading cause of disability (Johnson et al., 2016). The prevalence of stroke and mental illnesses is estimated to result in continued economic cost worth $240.67 billion by 2030 (Ovbiagele et al., 2013). Stroke not only affects the long-term functional disability but also increases the economic burden on families and the healthcare system (Prince et al., 2015). Therefore, low-cost and easily accessible treatments with minimal side effects must be developed to address stroke.

According to the American Heart Association/American Stroke Association, exercise therapy is beneficial to stroke survivors (Ovbiagele et al., 2013). Many studies have reported that gait-oriented training, aerobic treadmill training, intensive mobility training, and physiotherapeutic interventions, can improve disability for stroke survivors (Hesse et al., 2003;

Eng and Tang, 2007; van de Port et al., 2007; Hesse, 2008; De Rooij et al., 2016). Several meta-analyses focus on specific exercise therapy for stroke, such as Tai Chi exercise (Wu et al., 2018), aerobic exercise (Wang et al., 2019), sling exercise (Chen et al., 2016), and traditional Chinese exercise (Chen et al., 2015). Various exercise therapies are used to treat stroke, but there is no clear evidence to support the superiority of any particular exercise intervention. Also, there are lack of systematic analysis of global research into exercise for stroke. Therefore, there is a need to summarize the progress of research into exercise therapy for stroke over recent decades, and to provide objective data on which to base future research.

Bibliometric analysis has been considered as a quantitative statistical tool to describe the knowledge structure and keyword trends in specific research areas (Hicks et al., 2015). This type of study could offer readers the general aspects of research topic on distribution by country, institution, author, and journal. Bibliometric methods have been used in many research fields, including stroke (Feng et al., 2013) and exercise (Fares et al., 2017; Khatra et al., 2021). From the perspective of research progress, the number of clinical trials and papers on stroke rehabilitation has increased in the past years (Feng et al., 2013). Exercise as a therapeutic intervention in the treatment, rehabilitation, and prevention of illness (McCrory, 2006). However, no detailed bibliometric analysis has been conducted on the topic of exercise for stroke.

To address the shortage of quantitative analysis of exercise for stroke research, the present study aims to obtain the global scientific outputs of the research using exercise from 2001 to 2021 and quantitative information about the distribution of countries, institutions, journals, authors and visual information. This study will allow researchers to understand the hotspots and emerging trends of research on exercise and stroke.

METHODS

Search Strategy and Data Acquisition

Web of Science (WoS) contains 20,000 high-quality and influential academic journals related to 250 disciplines around the world. The database with comprehensive citation index records is conductive to data mining and co-citation analysis (Waqas et al., 2020). It is the authoritative data source for data extraction in bibliometric analysis, and has been used in many previous studies (Chen et al., 2012; Ellegaard and Wallin, 2015; Yan et al., 2020). It also had more accurate document type labeling than PubMed, Scopus (Yeung, 2019).

Publications on stroke and exercise research from 2001 to 2021 were retrieved and downloaded from the Science Citation Index Expanded (SCI-E) of WoS Core Collection (WoSCC). The search strategy was as follows: TI = (stroke OR apoplexy OR cerebrovascular accident OR cerebral hemorrhage OR hematencephalon OR encephalorrhagia OR cerebral ischemia) AND TI = (exercise OR train OR physical activity OR sport OR movement OR motion), language = English, and document type = article or review. A total of 3,484 publications were retrieved on 1 January 2022.

Knowledge Visualization Analysis

Publication records, including countries or regions, journals, authors, keywords, references, citations, citations per year, H-index, and impact factor (IF), were extracted from WoSCC. The H-index is a numerical indicator that evaluates the impact of scholars' or journals' publications and performance (Hirsch, 2005). IF reflects the average number of citations of a paper published in a journal and assesses the relative importance of the journal (Sharma et al., 2014). CiteSpace V was used in building knowledge network and citation paths (Chen et al., 2019). The publication records from WoSCC were input into CiteSpace, which generated collaborative networks (countries and authors), co-occurrence networks (keywords), and co-citation networks (references). The node represents the subject analyzed. Larger nodes denote greater number of occurrences or citations. A centrality index greater than 0 will be marked with a purple ring around the node, representing landmark works or theories (Waqas et al., 2020). Burst keywords or references indicates that the subjects frequently appear or are cited over a period, and represents those relevant topics have attracted considerable attention from researchers. Thus, they can be regarded as a research hotspot or research frontiers (Chen, 2006). Important themes, recent developments, and emerging trends in the field can be detected effectively based on these cues. The relationship between the publication outputs and IF was analyzed by Pearson correlation analysis in IBM SPSS Statistics 26. Statistical significance was considered at $P < 0.05$.

RESULTS

Publication Activity

Web of Science Core Collection yielded 3484 publications during the period of 2001–2021, with a total H-index of 125 and citations of 90,348 by citing 39,995 papers. Each paper was cited 25.93 times on average. In general, annual papers and citations presented a growing trend. The average number of citations per paper in WoSCC was 0.34 in 2001 and 28.88 in 2021. The vast majority of these papers were articles. In 2021, the number of articles was 343 and received 9,248 cumulative citations, about 9.03 and 5.27 times more than reviews, respectively (**Figure 1**).

Regional Trends

In accordance with the address of authors, 81 countries or regions contributed to these publications. The regions with the highest output of publications were in the United States, South Korea, China, Canada, and United Kingdom. Amongst the top 10 publication outputs, only China was a developing country, and others were developed countries. Switzerland, Austria, Singapore, Denmark, and Saudi Arabia were the top five countries and had a significant influence on global cooperation. These central nations are mainly developed countries, and they have also formed cooperative relations with several developing countries.

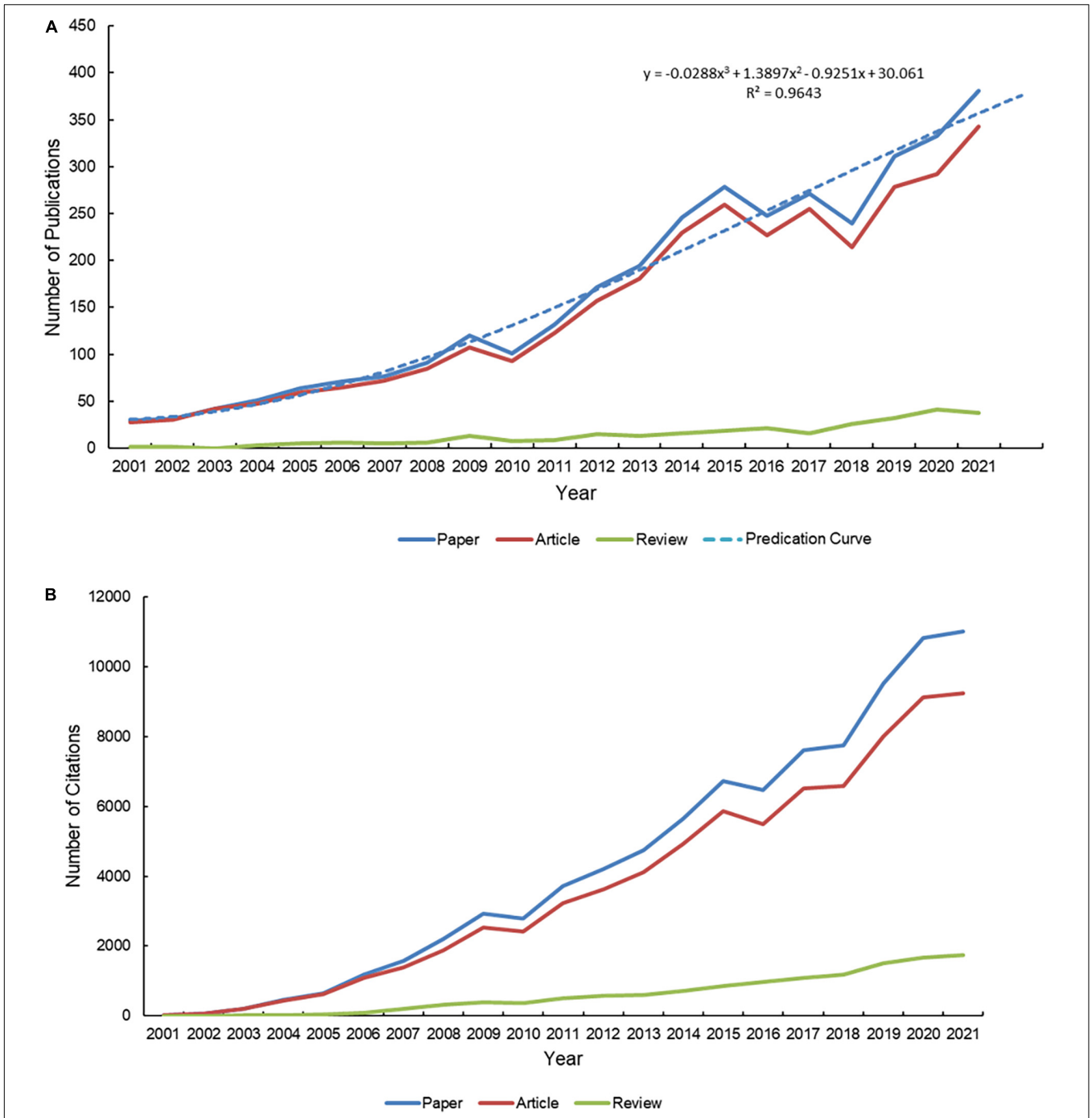


FIGURE 1 | Trends of publications and citations. **(A)** Trends of publication outputs and growth prediction from 2001 to 2021. **(B)** Trends of citations received by publications from 2001 to 2021.

In terms of publication output, none of the top five countries were considered important in the collaboration network (**Figures 2**, **3**).

Journal Characteristics

The papers were published in 584 academic journals. In the top 10 journals for publication output, *Journal of Physical Therapy Science* had the highest number of papers (175 publications), whereas *Disability and Rehabilitation* had the lowest number of papers (77 publications). Half of the journals were established in the United States, and all journals were based in developed countries. *Stroke* had the highest number of citations, citations per paper (106.95) and IF (2020, 7.194), occupying an important position in this field. The IF of these journals mainly concentrated in the range from 2 to 4, revealing that relevant papers

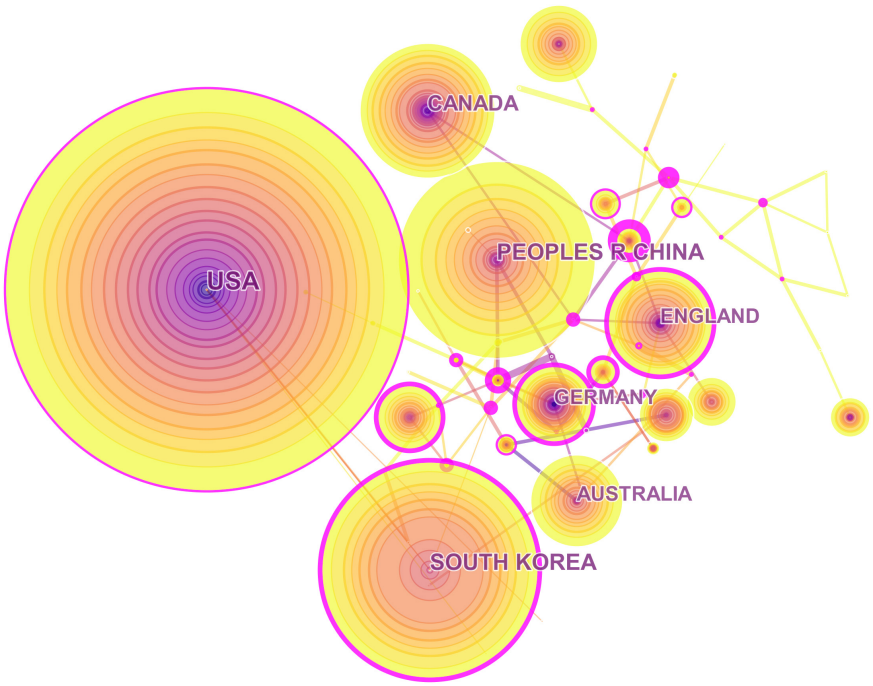


FIGURE 2 | Collaboration network of countries or regions.

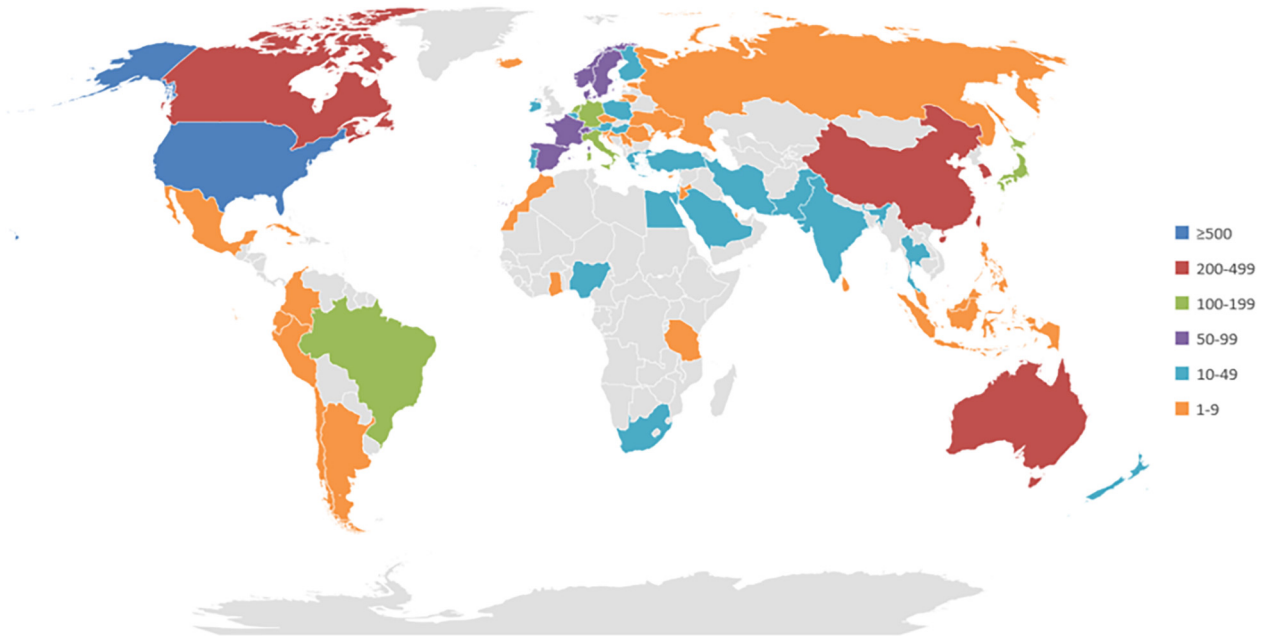


FIGURE 3 | World map of the total output of countries or regions.

published in high-IF journals present great challenges. Pearson correlation analysis revealed that publication outputs and IF had no significant correlation ($r = -0.198$, $p = 0.584$). In Journal Citation Reports, the majority of the top 10 journals belonged to the *Rehabilitation* category and were in Q1 (**Table 1**).

Figure 4 shows a dual-map overlay of all academic journals, mapping the citation paths of subject fields. The labels on the left of the dual-map represent the discipline covered by the citing journals, whereas those on the right indicate the discipline of the cited journals. Most journals were from neurology,

TABLE 1 | Top 10 journals based on publication outputs.

Rank	Journal	Papers	Country	Citations (WoS)	Citations per paper	IF (2020)	IF (5 years)	JCR categories	Quartile
1	Journal of Physical Therapy Science	175	Japan	1,880	10.74	0.392 (2014)	0.414	REHABILITATION (SCIE)	Q4
2	Neurorehabilitation and Neural Repair	160	United States	7,159	44.74	3.919	5.378	CLINICAL NEUROLOGY; REHABILITATION (SCIE)	Q2; Q1
3	Clinical Rehabilitation	145	United Kingdom	5,250	36.21	3.477	4.193	REHABILITATION (SCIE)	Q1
4	Archives of Physical Medicine and Rehabilitation	127	United States	7,432	58.52	3.966	4.489	REHABILITATION (SCIE); SPORT SCIENCES	Q1; Q2
5	Topics in Stroke Rehabilitation	125	United States	1,767	14.14	2.119	2.797	REHABILITATION (SCIE)	Q3
7	Journal of Neuroengineering and Rehabilitation	112	United Kingdom	3,447	30.78	4.262	5.218	ENGINEERING, BIOMEDICAL; NEUROSCIENCES; REHABILITATION (SCIE)	Q2; Q2; Q1
6	Stroke	108	United States	11,551	106.95	7.194	8.032	CLINICAL NEUROLOGY; PERIPHERAL VASCULAR DISEASE	Q1; Q1
8	Journal of Stroke Cerebrovascular Diseases	96	United States	875	9.11	2.136	2.185	NEUROSCIENCES; PERIPHERAL VASCULAR DISEASE	Q4; Q4
9	Neurorehabilitation	83	Ireland	891	10.73	2.138	2.501	CLINICAL NEUROLOGY; REHABILITATION (SSCI); REHABILITATION (SCIE)	Q4; Q2; Q3
10	Disability and Rehabilitation	77	United Kingdom	1,127	14.64	3.033	3.298	REHABILITATION (SSCI); REHABILITATION (SCIE)	Q1; Q1

sports, ophthalmology, medicine, medical, and clinical field, called research frontier. Cited papers were mainly published in molecular, biology, genetics, health, nursing, medicine, sports, rehabilitation, psychology, education, and social journals, called knowledge base.

Author Analysis

A total of 12,130 authors published these papers. **Figure 5** shows the collaboration network of authors. Amongst the top prolific authors, Eng J. J. ranked the first (36 publications), followed by Bernhardt J. (34 publications), Kwakkel G. (29 publications) and Teixeira-Salmela L. F. (29 publications). Eng J. J. was based at the University of British Columbia. He led their research team to design the Graded Repetitive Arm Supplementary Program that helped improve the recovery of stroke survivors' arm function and conducted a study on the use of robotic exoskeleton for walking training early after stoke. However, the link between nodes was sparse, and the centrality for cooperation was 0, indicating that the cooperation between various authors in this field was not very sufficient.

Keyword Co-occurrence

Keywords with high frequency of occurrence and high value of centrality reveal the research hotspots in the past 20 years, and those with strong citation bursts can predict future research frontiers. By the end of 2021, "stroke," "rehabilitation" and "recovery" were the top three high-frequency keywords. In terms of centrality, "brain" ranked the first, followed by "activation" and "mechanism" (**Figure 6**). The top 40 keywords obtained based on the times of occurrence and centrality were divided into eight themes (diseases, treatment, body region, outcome, evaluation, population, research design, and mechanism) (**Table 2**). Amongst the burst keywords, "health," "aerobic exercise," "speed," "motor," "stroke rehabilitation," "mobility," "health care professional," "impact," "risk," and "mortality" were cited frequently until 2021 (**Figure 7**).

Reference Co-citation

A timeline map of co-citation references with 19 clusters is shown in **Figure 8**. Each cluster was composed of papers with similar topics, named by nominal terms extracted from keywords in these co-cited papers. Cluster #0 (plasticity) was the largest, followed by cluster #1 (rct-rehabilitation-stroke interventions-upper extremity-motor recovery-behavior) and cluster #2 (sensorimotor impairments). Cluster #18 (movement training) appeared the earliest. Cluster #3 (physical activity) gradually attracted people's attention in recent years. The most cited reference (physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association) belonged to cluster #3 (physical activity) (**Table 3**).

Landmark Publication

Table 4 demonstrates the top five publications with the highest citation frequency. The paper by Wolf et al. (Effect

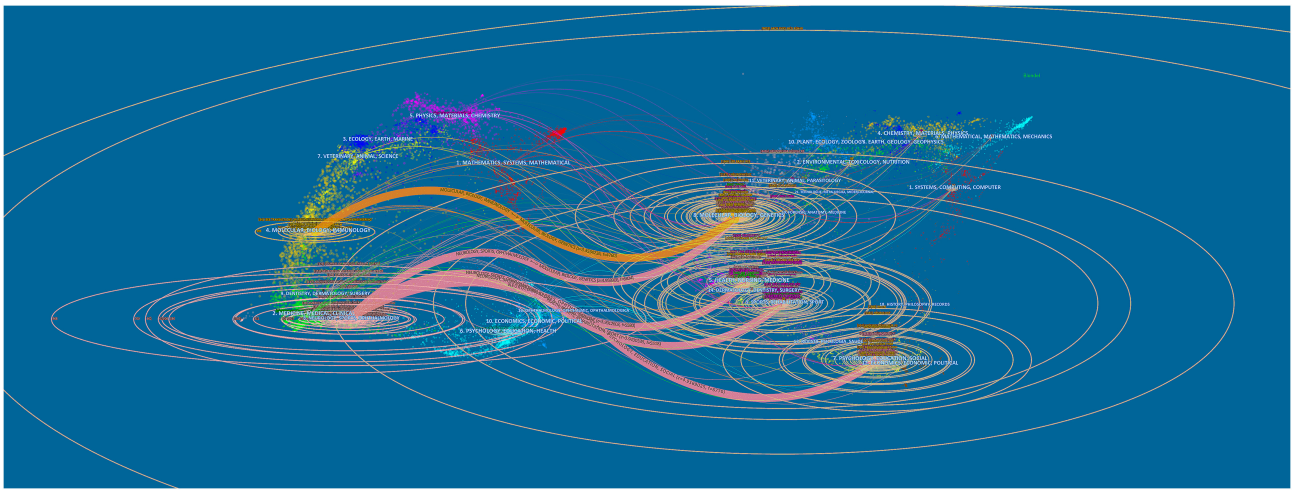


FIGURE 4 | The dual-map overlay of journals.

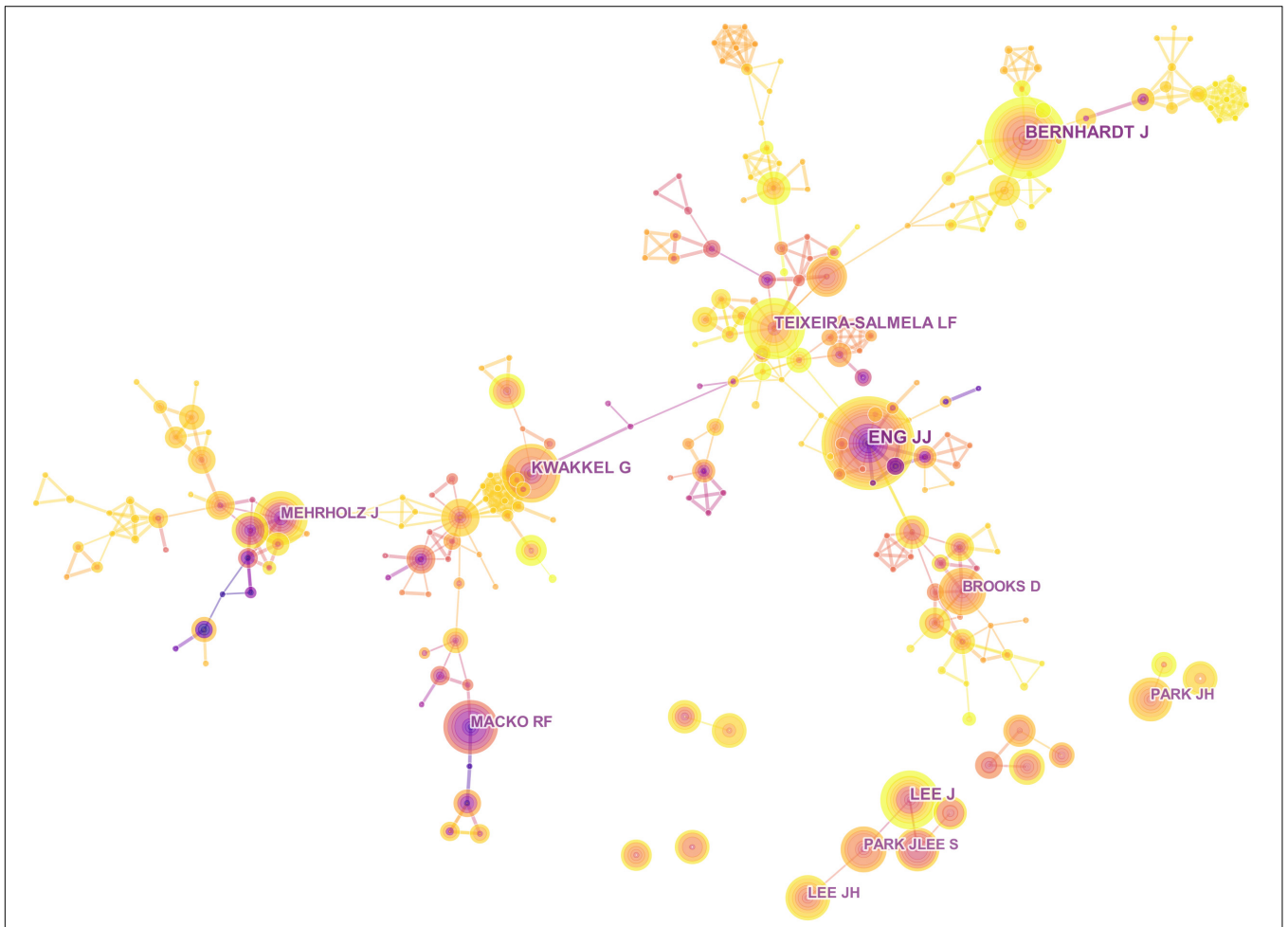


FIGURE 5 | Collaboration network of authors.

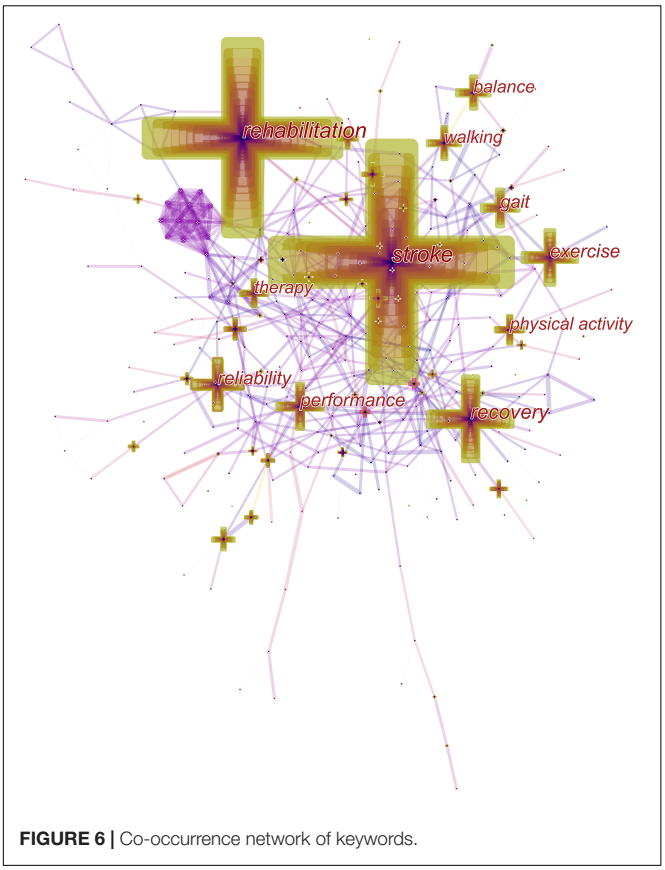


FIGURE 6 | Co-occurrence network of keywords.

of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial) was the most cited. It was published in JAMA and had relatively high average annual citations and the highest IF. The top two papers in **Table 4** were also the top two references in **Table 3**. A majority of papers had the same first author and corresponding author and were published before 2010.

In summary, the number of publications related to this research keeps increasing every year. Different countries have shown different international influences in this research field. The results also revealed some core journals and potential collaborators. The analysis of keywords and references indicated research status and hot spots, as well as emerging trends.

DISCUSSION

Global Trends of Exercise for Stroke Research

To our knowledge, this is the first bibliometric analysis of exercise for stroke based on WoSCC. We used the CiteSpace tool to obtain 3,484 published papers and show the continuous scholarly work in this field of exercise for stroke between 2001 and 2021. The results show that the number of publications increased gradually annually. The rapid growth of publications does not indicate that these papers have high quality; it only indicates that many researchers pay more attention to exercise for stroke. The top 10 journals did not have high IF. The journals with extremely high IF, such as Lancet, Nature did not publish the topic articles. Maybe, we think that this field has some innovative and breakthrough discoveries. According to the results, the United States has a positive sense of collaboration and plays an important role in the field of exercise for the research. There was strong positive correlation between the GDP of countries and stroke publication output (Salhab et al., 2018). We think that the strong economic foundation and larger number of stroke survivors have endowed the United States with important role in the research.

Research Focuses on the Exercise for Stroke Research

According to the co-occurrence network of keywords, the keywords with the highest frequency are "stroke," "rehabilitation," and "recovery"; that is to say, how to recover or rehabilitate the patients with stroke is still a hot topic in the field of exercise for stroke. **Figure 7** shows that the burst keywords were detected by CiteSpace V. According to these data, we could know the frontiers of exercises for the research. The top burst keywords are "health," "aerobic exercise," and "speed," indicating potentially emerging trends. The three research trends are as follows:

1. Health: there are different kinds of interventions for different health problems in stroke survivors. Physical exercises combined with cognitive training produced greater benefits on cognitive function in survivors with vascular cognitive impairment (Johnson et al., 2018; Bo et al., 2019). Chinese traditional exercises could help reduce symptoms of anxiety and stress and improve the sleep of

TABLE 2 | Research keywords by theme.

Theme	Keywords
Disease	Stroke, impairment, hemiparesis, cerebrovascular accident, coronary artery disease, lesion, cerebrovascular disorder
Treatment	Exercise, gait, walking, therapy, physical activity, balance, physical rehabilitation, strength, locomotion
Body region	Upper extremity, upper limb, arm, activation
Outcome	Rehabilitation, recovery, performance, follow-up, quality of life, mortality
Evaluation	Reliability, validity
Population	Individual, people
Research design	Randomized controlled trial
Mechanism	Brain, cortex, mechanism, cortical reorganization, reorganization, plasticity

Keywords	Year	Strength	Begin	End	2001 - 2021
health	2001	12.7121	2017	2021	
aerobic exercise	2001	10.6039	2017	2021	
speed	2001	5.2858	2018	2021	
motor	2001	7.4585	2019	2021	
stroke rehabilitation	2001	6.2121	2019	2021	
mobility	2001	9.0585	2019	2021	
health care professional	2001	12.1833	2019	2021	
impact	2001	3.7701	2019	2021	
risk	2001	4.1256	2019	2021	
mortality	2001	5.734	2019	2021	

FIGURE 7 | Burst keywords with frequent citations until 2021.

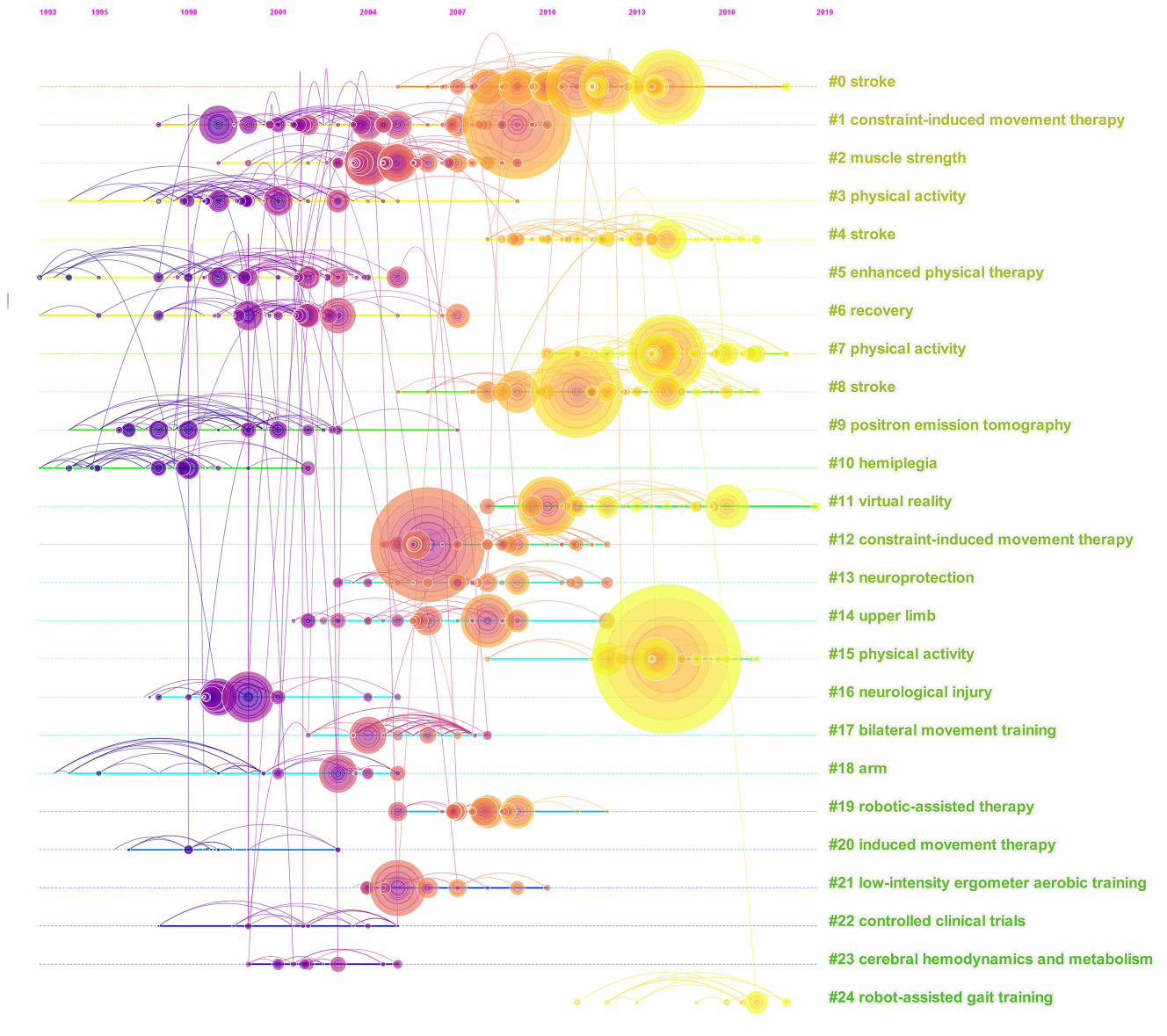


FIGURE 8 | Timeline view of references.

TABLE 3 | The top five references based on the number of citations.

Rank	Title	First author	Corresponding author	Document type	Year	Country	Journal	IF (2020)	Citations (WoS)
1	Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association	Billinger, S. A.	Billinger, S. A.	Review	2014	United States	Stroke	7.914	577
2	Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial	Wolf, S. L.	Wolf, S. L.	Article	2006	United States	JAMA	56.274	1,211
3	Motor recovery after stroke: a systematic review	Langhorne, P.	Langhorne, P.	Review	2009	United Kingdom	Lancet Neurology	44.182	1,053
4	Stroke Care 2 Stroke rehabilitation	Langhorne, P.	Langhorne, P.	Article	2011	United Kingdom	Lancet	79.323	1,161
5	What is the evidence for physical therapy poststroke? A systematic review and meta-analysis	Veerbeek, J. M.	Kwakkel, G.	Review	2014	Netherlands	PLoS One	3.24	519

TABLE 4 | The top five papers based on the number of citations.

Rank	Title	First author	Corresponding author	Document type	Year	Country	Journal	IF (2020)	Citations (WoS)	Citations per year
1	Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke - The EXCITE randomized clinical trial	Wolf, S. L.	Wolf, S. L.	Article	2006	United States	JAMA	56.274	1,211	134.07
2	Primary prevention of ischemic stroke – a guideline from the American Heart Association/American Stroke Association stroke council: cosponsored by the atherosclerotic peripheral vascular disease interdisciplinary working group; cardiovascular nursing council; clinical cardiology council; nutrition, physical activity, and metabolism council; and the quality of care and outcomes research interdisciplinary working group – the American academy of neurology affirms the value of this guideline	Goldstein, L. B.	/	Review	2006	/	Stroke	7.914	756	50.40
3	Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke	Lum, P. S.	Lum, P. S.	Article	2002	United States	Archives of Physical Medicine and Rehabilitation	3.966	712	37.47
4	Effects of augmented exercise therapy time after stroke – A meta-analysis	Kwakkel, G.	Kwakkel, G.	Review	2004	Netherlands	Stroke	7.194	646	38.00
5	Physical activity and exercise recommendations for stroke survivors a statement for healthcare professionals from the American Heart Association/American Stroke Association	Billinger, S. A.	Billinger, S. A.	Review	2014	United States	Stroke	7.914	574	82

the patients with stroke (Taylor-Piliae et al., 2021). Stroke was closely related to cardiovascular health; the effect of intensity and duration of exercise on cardiorespiratory fitness in patients with stroke could be a good topic in future research (Langhammer et al., 2014; Johnson et al., 2018; Luo et al., 2020).

2. Aerobic exercise: aerobic exercise not only has a positive effect on mood, quality of life, and aerobic capacity in patients with early stroke, but also changes the metabolomic profiles in patients with chronic stroke (Pang et al., 2013; Gezer et al., 2019). The evidence and mechanism of the effect of aerobic exercise in patients with stroke have been studied. For example, moderate forced exercise could reduce lesion volume and protect perilesional tissue against oxidative damage and inflammation in early-initiated (24–48 h post-stroke) (Austin et al., 2014).
3. Speed: walking speed can predict and influence functional recovery in patients with stroke. For example, walking speed exercise can improve cognitive function in patients with chronic stroke (Kim and Yim, 2017). Aerobic exercise has a positive effect on gait speed in individuals who have had a left-side stroke (Catapani et al., 2021). Walking speed could be used as an evaluation index and exercise protocol for stroke survivors. There is no mechanistic measure to explain the changes in walking speed during neurologic recovery. A multi-modal approach is necessary for stroke rehabilitation (Wonsetler and Bowden, 2017).

According to the top five references based on the number of citations, we can determine the potentially useful references for exploring the knowledge base of research frontiers. The American Heart Association's Stroke Council's Scientific Statement Oversight Committee and Manuscript Oversight Committee provided that the management of stroke survivors could benefit from physical activity and exercise prescription in daily life (Billinger et al., 2014). Many kinds of trials showed that a broad range of interventions could help stroke survivors to recover movement and related function, including constraint-induced movement therapy, electromyographic biofeedback, mental practice with motor imagery and robotics (Langhorne et al., 2009). Patents with different kinds of stroke need different exercise therapy. For example, amongst patients who had their first stroke 3–9 months previously, constraint-induced movement therapy could be an effective method to improve paretic arm function (Wolf et al., 2006). Physical therapy poststroke and intensive high repetitive task-oriented and task-specific training can be used for all phases poststroke (Veerbeek et al., 2014). Therefore, we think that the time point of recovery needs to be focused in the future research, and lager clinical trials with sufficient statistical power are needed to be obtained (Langhorne et al., 2011).

Strengths and Limitations

This is the first bibliometric analysis to summarize the progress and trends of exercise for stroke in the past 20 years on the basis of WoS data. To gain integrated and diverse data, our study included 3,484 publications, and these papers were published in 584 academic journals. Furthermore, this bibliometric analysis not only contained publications, journals, citations, collaboration network of authors, countries, and regions; it also included burst keywords, research keywords by theme, co-occurrence network of keywords, and the top five references and papers on the number of citations.

However, this study has some limitations. Firstly, our study did not search other academic databases, such as PubMed, Embase, and Cochrane Library. Secondly, the variety of languages was limited. The study selected English as the inclusion criterion, papers with other languages were excluded. This could result in publication bias. Thirdly, there was no accurate identification and separation of the interconnections amongst authors, regions or countries, even though our study analyzed their collaboration network.

CONCLUSION

This study analyzed the trends of exercise for stroke and provided the potential research frontiers in the past 20 years, it can prove useful as a basis for developing improved exercise interventions for stroke. The topic of exercise interventions for stroke is becoming more and more popular amongst clinical workers and researchers. This analysis may enable research teams to collaborate in promoting the application of exercise therapy in the clinical management of stroke. Although this study has some limitations, it provides a useful basis for further research into hot topics, research focuses, cooperators, and development trends of exercise for the research.

AUTHOR CONTRIBUTIONS

XW and JW: research concept and design. LW and YD: collection and assembly of data and writing the manuscript. TS and ZL: data analysis and interpretation. WW, YZ, and RD: critical revision of the manuscript. YH, YM, and JW: final approval of the manuscript. All authors have read and approved the manuscript.

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SYSTEMATIC REVIEW
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Are Mind-Body Exercise Beneficial for Treating Pain, Function, and Quality of Life in Middle-Aged and Old People With Chronic Pain? A Systematic Review and Meta-Analysis

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Background: Aging is a significant risk factor in chronic pain development with extensive disability and greater health care costs. Mind-body exercise (MBE) has been scientifically proven to affect the pain intensity and physical health.

Objectives: To assess the effects of MBE modes (Tai Chi, yoga, and qigong) for treating chronic pain among middle-aged and old people, compared with nonactive and active treatment, as well as function, quality of life, and adverse events.

Methods: We searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Chinese Scientific Journals Full-Text Database (VIP) till March 2022. No restrictions were chartered within the year and language of publication. We included randomized controlled trials of MBE treatment in middle-aged and elderly people with chronic pain. The overall certainty of evidence was evaluated by using the GRADE approach.

Results: A total of 17 studies (n = 1,332) were included in this review. There was low-certainty evidence indicating that MBE had a moderate effect on reducing pain compared with the nonactive and active control group (standard mean difference (SMD): −0.64, 95% confidence interval (CI): −0.86 to −0.42, $P < 0.001$). Very-low-certainty evidence showed that the pooled SMD for the functional improvement was −0.75 (95% CI: −1.13 to −0.37, $P < 0.001$). Low-certainty evidence presented that no influence was observed in physical component summary (SMD: 0.23, 95% CI: −0.16 to 0.62, $P = 0.24$) and mental component summary (SMD: −0.01, 95% CI −0.39 to 0.36, $P = 0.95$).

Conclusion: Our results indicated that MBE was an effective treatment for reducing symptoms of middle-aged and elderly people with chronic pain compared with nonactive and active control groups. TC and qigong had obvious benefits for knee osteoarthritis in self-reported function, but the efficacy of chronic low back pain was uncertain. No significant benefit of MBE on quality of life in older adults with chronic pain was found. More high-quality RCTs should be conducted to explore the efficacy and mechanism of MBE on chronic pain in middle-aged and elderly people from various dimensions, such as affective and cognitive dimensions.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=316591, identifier CRD42022316591.

Keywords: mind-body exercises, chronic pain, old people, systematic review, meta-analysis

INTRODUCTION

Pain is currently defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage" (Raja et al., 2020). Chronic pain is pain that lasts 12 weeks or longer (Treede et al., 2019). In the United States alone, more than one in five adults experience chronic pain at an estimated cost of 560 billion dollars a year (Reuben et al., 2015; Yong et al., 2022).

Aging is a significant factor in the development of chronic pain (Tsang et al., 2008). With the gradually increasing trend of global aging, the prevalence of chronic pain is increasing in middle-aged and old people and has a connection with extensive disability and greater health care costs (Cho et al., 2015; Reid et al., 2015; Corsi et al., 2018; Sun et al., 2019; Li et al., 2021). One survey based on Chinese people revealed the prevalence of knee osteoarthritis (KOA) increased with age, surging after 55 years old (Chen et al., 2021). Low back pain (LBP), a leading risk factor for physical disability worldwide, affects nearly 20–25% of the population older than 65 years around the world (Vadalà et al., 2020). However, the clinical efficacy and side effects of pharmacologic treatment for elderly people with chronic pain as well as the potential effects are unclear (McLachlan et al., 2011; Al-Qurain et al., 2020). Hence, identifying effective nonpharmacological approaches for middle-aged and elderly people with chronic pain is urgent.

Over the past decades, complementary and alternative medicine (CAM) has become popular among patients with various medical conditions (Weeks, 2016). Mind-body exercise (MBE) has been included in categories of CAM practices. The United States established a professional National Center for Complementary and Alternative Medicine to train professional CAM researchers, conduct research on the rigorous scientific role of MBE, and communicate authoritative information to the public. With the advancement of research techniques, more forms of MBE have been scientifically proven to affect neural activity and physical health (Clarke et al., 2015). Tai Chi (TC), yoga, and qigong (e.g., Baduanjin and Wuqinxi), the three most popular MBE modes, involve a variety of movements, such as postures with stretching and relaxation of skeletal muscles, breath control, and meditative state of mind (Bower and Irwin, 2016; Zou et al., 2018). They have been used as a treatment for different chronic pain conditions (Teut et al., 2016; Wang et al., 2016, 2018; Liu et al., 2019) and are considered suitable for middle-aged and old people (Reid et al., 2015; Siu et al., 2021). However, results of these studies are mixed. For example, a previous study has shown that TC may effectively improve pain intensity in middle-aged and elderly patients with chronic LBP (CLBP) (Liu et al., 2019), but studies about other MBE modes have not shown similar results (Teut et al., 2016). Natalia et al. published a structured review in similar areas (Morone and Greco, 2007), which included the study lacked randomized controlled trials (RCTs). Conclusions about the efficacy of MBE for chronic pain in elderly people must be tentative. No systematic review had tried to investigate the effects of MBE on middle-aged and elderly people with chronic pain to obtain a deeper awareness of it as a bona fide CAM therapy for chronic pain. Only a few reviews have paid attention to the role of MBE in the treatment of adults with chronic pain (Lauche et al., 2013; Bai et al., 2015; Kong et al., 2016; Hall et al., 2017; Wieland et al., 2017; Zou et al., 2019), and most of these studies either focused on a single chronic pain condition (Lauche et al., 2013; Wieland et al., 2017; Zou et al., 2019) or investigated a single MBE mode (Bai et al., 2015; Kong et al., 2016; Hall et al., 2017). Due to language barriers and limited retrieval resources, most reviews did not include Chinese RCTs (Lauche et al., 2013; Hall et al., 2017; Wieland et al., 2017, Zou et al., 2019).

Thus, this study aimed to represent the first systematic review and meta-analysis of current evidence from RCTs to ascertain the effectiveness of the three most popular MBE modes (i.e., TC, yoga, and qigong) among middle-aged and elderly people with chronic pain. Moreover, we investigated the effects of MBE on quality of life (QOL) and subjective physical function. We hypothesized that MBE intervention may benefit pain, physical function, and QOL in middle-aged and elderly with chronic pain, and compared with qigong and yoga, TC may have a better therapeutic effect. Our study raised the level of evidence by performing a secondary analysis of published RCTs in this area representing an important addition to the literature. Results provided robust evidence and guidance to clinicians in the use of CAM for middle-aged and old people with chronic pain and better manage patients' expectations.

METHODS

Protocol and Registration

We prospectively registered the protocol in the PROSPERO database with registration number CRD42022316591. This systematic review and meta-analysis were reported in line with the PRISMA guidelines and are shown in **Supplementary Material 1**.

Search Strategy

PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Chinese Scientific Journals Full-Text Database (VIP) were confined to search to define eligible studies from the first data available in March 2022. No restrictions were chartered within the year and language of publication. The following key words are searched: "mind-body exercise," "tai chi," "yoga," "qigong," "aged," "middle-aged and old people," "old people," and "chronic pain." Complete search strategies are shown in **Supplementary Material 2**.

Eligibility Criteria

Inclusion Criteria

- Design of studies: parallel or crossover RCTs.
- Subjects: middle-aged and older patients (aged $\geq$ 45 years) with chronic pain (duration of pain $\geq$ 12 weeks).
- Types of intervention: interventions were the prescription of MBE training alone, including tai chi, yoga, and qigong, without additional treatments (e.g., pharmacotherapy, manipulation, or cognitive behavior therapy).
- Types of control group: control group of any form (e.g., waitlist, physical exercise, and education) other than MBE.
- Outcomes: main outcomes related to the intensity of pain were measured after intervention. Secondary outcomes include subjective physical function and QOL.
- Published form of article: journal articles, theses, and dissertations.
- Studies must contain raw data of interest outcomes or can be extracted from figures and tables.

Exclusion Criteria

- Studies unable to satisfy the inclusion criteria.
- Studies that were published in the form of conference abstracts, researcher protocol, and books.

Study Selection

Two assessors (i.e., YRW and JS) perform a preliminary screening of all retrieved articles based on title and abstract. If the topic of studies cannot be defined by the title and abstract, the full text of the article shall be evaluated. Any disaccords should be resolved through discussion to reach consensus. When the two assessors cannot agree, the corresponding author (YLW) will evaluate the study to determine whether it meets the inclusion criteria of the review.

Data Extraction

Tables' data extraction for each selected study was completed independently by two evaluators (YTL and ZYH) using a standard information extraction form, which was developed jointly by them. Two corresponding authors (YLW and XQW) reviewed the extracted data, including the publication information (e.g., author, year, and country of origin), subject characteristics (e.g., age, gender, sample size, and pain conditions), study design (e.g., parallel or crossover trail, two-arm or multiarm parallel trial), intervention and control groups (e.g., MBE modes, duration weeks, and follow-up weeks), and adverse events.

The mean and standard deviation (mean $\pm$ SD) of primary and secondary outcomes of preintervention and post intervention for the MBE groups and control groups were directly drawn from published data of the studies. When data were reported at more than one time point, we used only the data immediately at the end of the intervention. If the outcome was expressed only as a graph, the software Engauge Digitizer 10.8 (Mitchell et al., 2017) was used to extract the required data. When raw data cannot be sufficiently extracted, we contacted the authors of these studies to provide it; the RevMan 5.3 calculator was used to convert them to means and SDs when the standard errors (SEs), confidence intervals (Cls), or interquartile ranges (IQRs) were supplied rather than means and SDs.

Risk of Bias and GRADE

Two authors (YRW and JS) independently evaluated the quality of methods and the risk of bias of these studies by the Cochrane Risk of Bias Tool (Higgins et al., 2016), which divided the quality risk into three categories, namely, low, high, and unclear, which examined potential selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Given the exercise interventions involved in these studies, it is unclear whether blind subjects to treatment allocation are successful; therefore, patients blinding was considered as unclear risk of bias for each study. Furthermore, we assessed the quality of evidence outcomes using the recommendations assessment, development, and evaluation (GRADE) pathway (Atkins et al., 2004). GRADE may reduce the quality of evidence in the systematic evaluation of intervention: inconsistency, risk of bias, inaccuracy, indirectness, and publication bias. GRADEpro will be used to evaluate the five factors and classify the quality of evidence into four grades, namely, high quality, medium quality, low quality, and very low quality.

Data Synthesis and Analysis

Meta-analysis was generated by exploring the STATA/MP 16.0 software (StataCorp, Texas, USA) with the metan command. The standard mean difference (SMD) of the change score (end-point minus baseline score) and its 95% CI were used for assessing the effect size (ES) of MBE and control. We used *P*-value and I^2 to evaluate the heterogeneity. If $P \geq 0.05$ and $I^2 \leq 50\%$, the heterogeneity among studies was small, and the fixed effect model was adopted. If $P < 0.05$ and $I^2 > 50\%$, it shows that there is heterogeneity among studies, and the random effect model is adopted.

The size of heterogeneity was deciphered on the base of Cochrane Collaboration: I^2 values of low heterogeneity ($I^2 < 25\%$), moderate heterogeneity ($I^2 < 50\%$), and high heterogeneity ($I^2 > 75\%$) (Higgins et al., 2003). $P < 0.05$ was considered that the difference was statistically significant. Publication bias was evaluated by a funnel plot. The Egger test was used to assess whether the degree of asymmetry was significant. The funnel asymmetry due to publication bias will be adjusted using the trim and fill method.

Four subgroup analyses were conducted to explore factors impacting the result of MBE on chronic pain: chronic pain conditions (KOA vs. CLBP vs. other pain [neck pain and chronic multisite pain]), number of sessions (1–15 sessions vs. 15–30 sessions vs. 30–45 sessions vs. more than 45 sessions), MBE modes (TC vs. yoga vs. qigong), and type of control (active control and nonactive control).

RESULTS

Search Results

The process of study screening is shown in **Figure 1**. A total of 2,065 potential studies were identified by preliminary search for seven databases of which 1,325 duplicate studies were excluded. A total of 631 studies were excluded by title and abstract judgment,

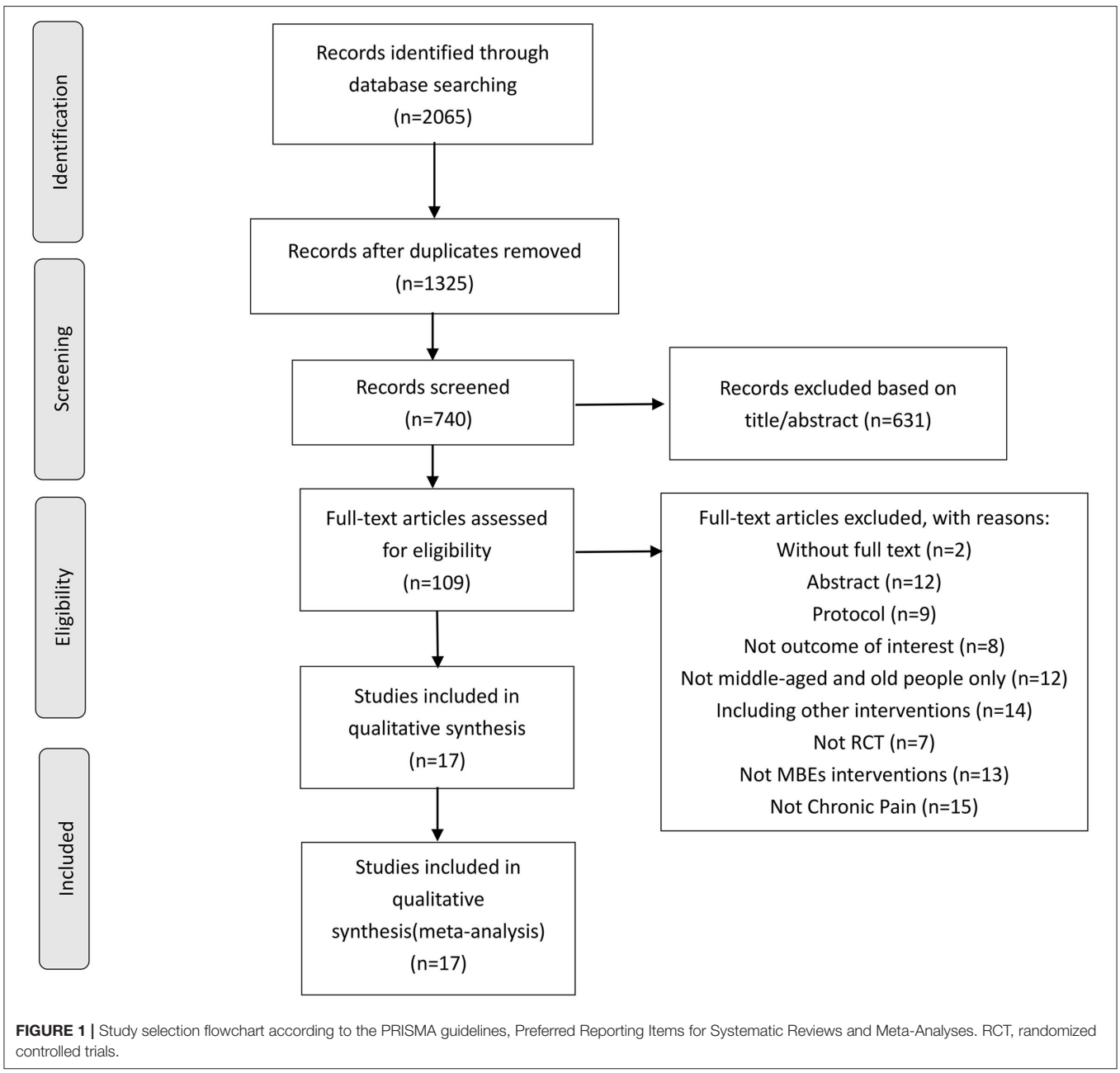


FIGURE 1 | Study selection flowchart according to the PRISMA guidelines, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. RCT, randomized controlled trials.

which are unable to fulfill the inclusion criteria of this systematic review. Then, we judged the full text of the remaining 109 studies, and 92 of them were excluded for several reasons including not RCTs ($n = 7$), not chronic pain ($n = 15$), abstract ($n = 12$), study protocol ($n = 9$), not middle-aged and elderly people only ($n = 12$), full-text not available ($n = 2$), not MBE interventions ($n = 13$), not outcome of interest ($n = 8$), including other interventions ($n = 14$). In this study, 17 eligible RCTs were included in this systematic review, and all of them were included in quantitative synthesis.

Characteristics of the Included Studies

Table 1 summarizes all 17 reviewed MBE RCTs ($n = 1,481$). The sample size of a single article ranged from 26 to 204 participants (the average age range is 55–76 years). Almost all studies included both women and men, except (Cheung et al., 2017) which did not report sex ratios and (Qiu, 2018) which included only women. A total of 11 studies (64.7%) (Raub, 2002; Cheung et al., 2014, 2017; Wang et al., 2016, 2021; Hu, 2017; Song et al., 2017; Cao, 2018; Qiu, 2018; Ye et al., 2019; Xiao et al., 2020) included patients who suffer chronic pain from KOA. Three studies (Teut et al., 2016; Cao, 2018; Liu et al., 2019) included patients with CLBP and three studies (Yang et al., 2005; von Trott et al., 2009; You et al., 2018) included other chronic pain patients.

The researchers implemented various mindful exercise interventions, which included yoga [two Hatha yoga (Cheung et al., 2014, 2017) and one Viniyoga (Teut et al., 2016)], TC [two Yang-style TC (Wang et al., 2016; Song et al., 2017); one Chen-style TC (Liu et al., 2019); one Sun-style TC (Raub, 2002); and three just demonstrated TC (Hu, 2017; Cao, 2018; You et al., 2018)], and qigong [five Baduanjin qigong (Ding, 2014; Hu, 2017; Qiu, 2018; Ye et al., 2019; Wang et al., 2021); one Wu Qin Xi Qigong (Xiao et al., 2020); one Korean qigong (Yang et al., 2005); and two just mentioned qigong (von Trott et al., 2009; Teut et al., 2016)]. There were five control comparators included nonphysical therapy [usual care (Cheung et al., 2014; Ding, 2014; Teut et al., 2016; Qiu, 2018; Ye et al., 2019); wait list (Raub, 2002; Yang et al., 2005; von Trott et al., 2009); education (Cheung et al., 2017; Hu, 2017); attention control group (Song et al., 2017)], physical therapy (Wang et al., 2016; You et al., 2018; Xiao et al., 2020), quadriceps strengthening exercises (QSEs) (Wang et al., 2021), core stabilization (Liu et al., 2019), and stretching (Cao, 2018). The intervention duration of all mindful exercises was between 4 and 24 weeks, and sessions ranged from 8 to 96 weeks. The frequency of the intervention group varied greatly, ranging from one to five times a week. The length of each exercise class also varied, ranging from 20 to 90 min a class. Eight studies were followed up after the intervention for 6–52 weeks.

Pain intensity as the main outcome can be obtained from 17 studies. The evaluation scales were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-pain (Raub, 2002; Cheung et al., 2014; Wang et al., 2016, 2021; Hu, 2017; Ye et al., 2019; Xiao et al., 2020) and Visual Analog Scale (VAS) (Yang et al., 2005; von Trott et al., 2009; Teut et al., 2016; Cheung et al., 2017; Song et al., 2017; Cao, 2018; Qiu, 2018; You et al., 2018; Liu et al., 2019). Twelve studies reported functional improvement outcomes using WOMAC-function (Cheung et al., 2014, 2017; Ding, 2014; Wang et al., 2016, 2021; Hu, 2017; Song et al., 2017; Qiu, 2018; Ye et al., 2019; Xiao et al., 2020), FFbHR (Teut et al., 2016), and Neck Pain and Disability (NPAD) (von Trott et al., 2009). QOL indicators were obtained from eight studies using the Health-related Short Form 12 (SF-12) (Raub, 2002; Cheung et al., 2014, 2017; Wang et al., 2021) and Health-related Short Form 36 (SF-36) scales (von Trott et al., 2009; Teut et al., 2016; Wang et al., 2016).

Effects of the Intervention

Primary Outcomes: Pain Intensity

All 17 articles included in this study ($n = 1,332$) measured pain intensity. Low-certainty evidence showed that MBE had a moderate effect on reducing pain compared with both the nonactive and active control group (SMD: −0.64, 95% CI: −0.86 to −0.42, $P < 0.001$; **Figure 2**), but the heterogeneity was relatively high ($I^2 = 73.0\%$, $P < 0.001$).

Subgrouping analysis by painful conditions significantly decreased heterogeneity in the KOA subgroup (SMD: −0.51, 95% CI: −0.73 to −0.28, $P < 0.001$, $I^2 = 59.1\%$, $P = 0.005$; **Supplementary Figure S1**), and increased the ES in CLBP subgroup (SMD: −0.95, 95% CI: −1.66 to −0.24, $P = 0.008$) with heterogeneity of 86.2% ($P < 0.001$). But in other chronic pain subgroups, it did not show the ES (SMD: −0.91, 95% CI: −1.85 to 0.03, $P = 0.06$) with heterogeneity of 86.7% ($P = 0.001$).

Categorizing studies by intervention methods of experimental group, the results show that three different MBE still had a good effect on reducing pain but did not cut heterogeneity observably. The overall data from 3 trials demonstrated that yoga had more analgesic effect compared with the control group (SMD: −0.80, 95% CI: −1.41 to −0.18, $P = 0.01$, $I^2 = 74.6\%$; **Supplementary Figure S2**). The TC subgroup revealed an effect (SMD: −0.69, 95% CI: −1.10 to −0.27, $P = 0.001$, $I^2 = 76.6\%$). In the qigong subgroup, the results synthesized from nine trials show ES (SMD: −0.57, 95% CI: −0.91 to −0.24, $P = 0.001$, $I^2 = 75.0\%$).

Categorizing studies by number of sessions (≤15 sessions vs. 15–30 sessions vs. 30–45 sessions vs. > 45 sessions). The ES of subgroup in ≤15 sessions (SMD: −1.12, 95% CI: −2.09 to −0.16, $P = 0.02$) and 30–45 sessions (SMD: −0.86, 95% CI: −1.39 to −0.32, $P = 0.002$) increased. While subgrouping analysis decreased the ES (SMD: −0.29, 95% CI: −0.46 to −0.12, $P = 0.001$) and decreased heterogeneity ($I^2 = 0.0\%$, $P = 0.81$) in fifteen to thirty sessions subgroup (**Supplementary Figure S3**).

Secondary Outcomes: Physical Function

Adequate information was available from 12 studies ($n = 1,082$) for functional improvement analysis. Low-certainty evidence has shown that the pooled SMD for the result was −0.75 (95% CI: −1.13 to −0.37, $P < 0.001$; **Figure 3**) with the heterogeneity of 88.5% ($P < 0.001$).

Subgrouping studies by type of painful condition, no evidence of an effect of MBE on CLBP was observed (SMD: 0.19, 95% CI: −0.07 to 0.44, $P = 0.16$), but its heterogeneity significantly diminished ($I^2 = 0\%$, $P = 0.79$; **Supplementary Figure S4**). The MBE demonstrated a noteworthy analgesic effect on KOA (SMD:

TABLE 1 | Principal characteristics of included studies.

Author, Year	Country	Sample size (F/M)	Age, Mean ± SD (years)	Pain conditions	Duration weeks	Follow-up weeks	Main pain outcome assessments	Experimental group intervention (T/session)	Control group intervention	Adverse events
Brismée et al. (2007)	USA	34/7	69.94±9.33	KOA	12	18	VAS/WOMAC	Yang-style Tai Chi (40 min/3 times a week/12 weeks/36 sessions)	Attention control	NO
Fransen et al. (2007)	Australia	112/40	70.06±6.18	HOA/KOA	12	NO	WOMAC/SF-12	Sun-style Tai Chi (60 min/2 times a week/12 weeks/24 sessions)	Waiting list	NO
von Trott et al. (2009)	Germany	111/6	75.82±7.43	NP	12	24	VAS/NPAD	Dantian Qigong (45 min/2 times a week/12 weeks/24 sessions)	Waiting list	Nausea/Aching muscles/Muscle tension
Yang et al. (2005)	Korea	32/8	72.62±6.5	Chronic pain	4	6	VAS	Korean Qigong (20 min/2 times a week/4 weeks/8 sessions)	Waiting list	NA
Cheung et al. (2014)	USA	36/0	71.9±6.04	KOA	8	12	WOMAC/SF-12	Hatha Yoga (60 min/once a week/8 weeks/8 sessions)	Waiting list	NO
Ding (2014)	China	20/20	61.25±4.73	LBP	12	NO	VAS	Baduanjin Qigong (40 min/5 times a week/12 weeks/60 sessions)	Pharmacological treatment	NA
Cheung et al. (2017)	USA	70/13	71.62±7.94	KOA	8	NO	VAS/WOMAC/SF-12	Hatha Yoga (45 min/once a week/8 weeks/8 sessions)	Education	NO
Teut et al. (2016)	Germany	156/20	72.65±5.63	LBP	12	24	VAS/FFbHR	Dantian Qigong (90 min/once a week/12 weeks/12 sessions) Vini Yoga (45 min/2 times a week/12 weeks/24 sessions)	Waiting list	NA
Wang et al. (2016)	USA	143/61	60.2±10.47	KOA	12	24/52	WOMAC/SF-36	Yang-style Tai Chi (60 min/2 times a week/12 weeks/24 sessions)	Physical therapy	NO
Cao (2018)	China	34/7	69.96±9.33	KOA	12	18	WOMAC	Tai Chi (60 min/3 times a week/12 weeks/36 sessions)	Education	NO

(Continued)

TABLE 1 | Continued

Author, Year	Country	Sample size (F/M)	Age, Mean ± SD (years)	Pain conditions	Duration weeks	Follow-up weeks	Main pain outcome assessments	Experimental group intervention (T/session)	Control group intervention	Adverse events
Hu (2017)	China	108/32	58.8±7.67	KOA	12	NO	VAS/WOMAC	Tai Chi (60min/5 times a week/12 weeks/60 sessions) Baduanjin Qigong (60 min/5 times a week/12 weeks/60 sessions)	Education	NO
Qiu (2018)	China	62/0	56.08±3.75	KOA	12	NO	VAS/WOMAC	Baduanjin Qigong (30min/3 times a week/12 weeks/36 sessions)	Pharmacological treatment	NA
You et al. (2018)	USA	35/10	74.53±8	Chronic multisite pain	12	NO	BPI	Yang-style Tai Chi (60 min/2 times a week/12 weeks/24 sessions)	Physical exercise	NO
Liu et al. (2019)	China	32/11	59.38±4.26	LBP	8	NO	VAS	Chen-style Tai Chi (60 min/3 times a week/12 weeks/36 sessions)	No treatment	NA
Xiao et al. (2020)	China	62/37	70.4±9.72	KOA	24	NO	WOMAC	Wuqinxi Qigong (60 min/4 times a week/24 weeks/96 sessions)	Physical therapy	NO
Ye et al. (2019)	China	30/20	63.78±6.07	KOA	12	NO	WOMAC	Baduanjin Qigong (40 min/3 times a week/12 weeks/36 sessions)	Waiting list	NO
Wang et al. (2021)	China	69/15	65.23±3.2	KOA	24	NO	WOMAC/SF-12	Baduanjin Qigong (40 min/3 times a week/24 weeks/72 sessions)	QSE	NO

M, male; F, female; LBP, low back pain; NP, neck pain; KOA, knee osteoarthritis; HOA, hip osteoarthritis; QSE, quadriceps strengthening exercises; CSE, core stabilization exercise; VAS, visual analog scale; BPI, Brief Pain Inventory; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; NPAD, Neck Pain and Disability; SF-36, Health-Related Short Form 36; SF-12, Health-Related Short Form 12; FFBH-R, Hanoverian Functional Questionnaire for Routine Diagnosis Of Dysfunction Due To Back Pain; NA, not available.

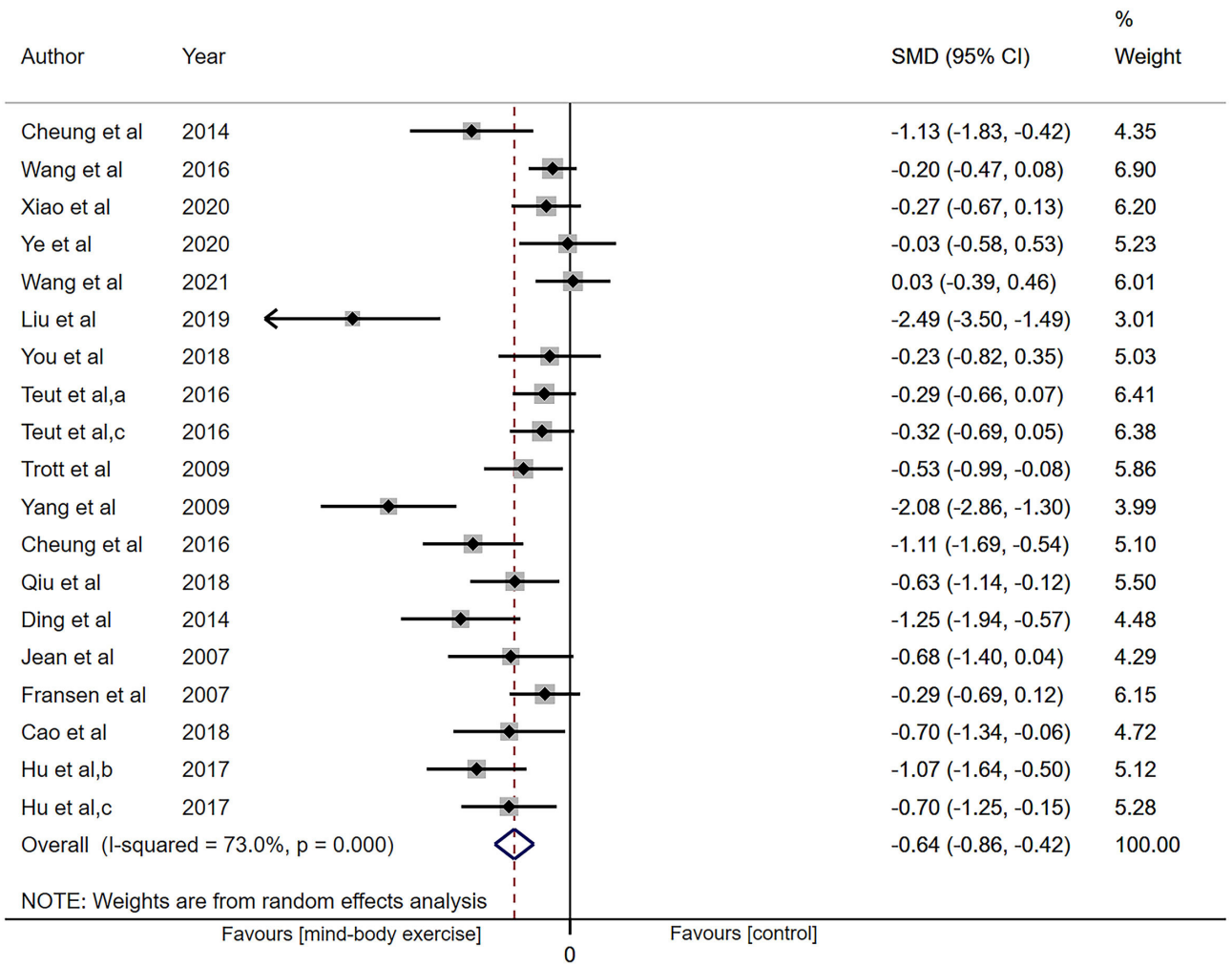


FIGURE 2 | Forest plot showing overall effect sizes (Hedges' g) of mind-body exercises on pain intensity within studies. These plots show the pooled standard mean difference (SMD) (large diamond shape) and I^2 resulting from the meta-analysis.

−0.83, 95% CI: −1.20 to −0.45, $P < 0.001$) with the heterogeneity of 83.1%. In other pain subgroup (neck pain), there was an increased effect (SMD: −1.83, 95% CI: −2.36 to −1.30, $P < 0.001$) with the heterogeneity of 0%.

Categorizing studies by intervention methods of experimental group, there was no indication of an effect of yoga treatment (SMD: −0.68, 95% CI: −1.64 to 0.28, $P = 0.17$; **Supplementary Figure S5**), while the TC group (SMD: −0.66, 95% CI: −1.17 to −0.15, $P = 0.01$) and qigong group (SMD: −0.83, 95% CI: −1.50 to −0.16, $P = 0.02$) displayed a significant analgesic effect.

Categorizing studies by number of sessions (≤15 sessions vs. 15–30 sessions vs. 30–45 sessions vs. > 45 sessions). Subgroup of 30–45 sessions showed an increased effect (SMD: −1.09, 95% CI: −1.61 to −0.58, $P < 0.001$) with decreased heterogeneity ($I^2 = 67.7\%$, $P = 0.02$), but there was no indication of an effect in other subgroups (**Supplementary Figure S6**).

Secondary Outcomes: QOL

Physical component summary (PCS) and mental component summary (MCS), as the two parts of QOL (i.e., SF-36 and SF-12), reflect various dimensions of QOL.

Physical Component Summary

Sufficient data were accessible from 8 studies ($n = 787$) for PCS analysis. The synthesized result showed heterogeneity ($I^2 = 85.4\%$, $P < 0.001$), and low-certainty evidence of the ES was not in favor of that MBE can improve PCS (SMD: 0.23, 95% CI: −0.16 to 0.62, $P = 0.24$; **Figure 4**).

Mental Component Summary

In terms of the MCS, eight investigations ($n = 787$) provided data for MCS analysis. There was high heterogeneity ($I^2 = 84.8\%$, $P < 0.001$), while low-certainty evidence presented there was no influence (SMD: −0.01, 95% CI −0.39 to 0.36, $P = 0.95$; **Figure 5**).

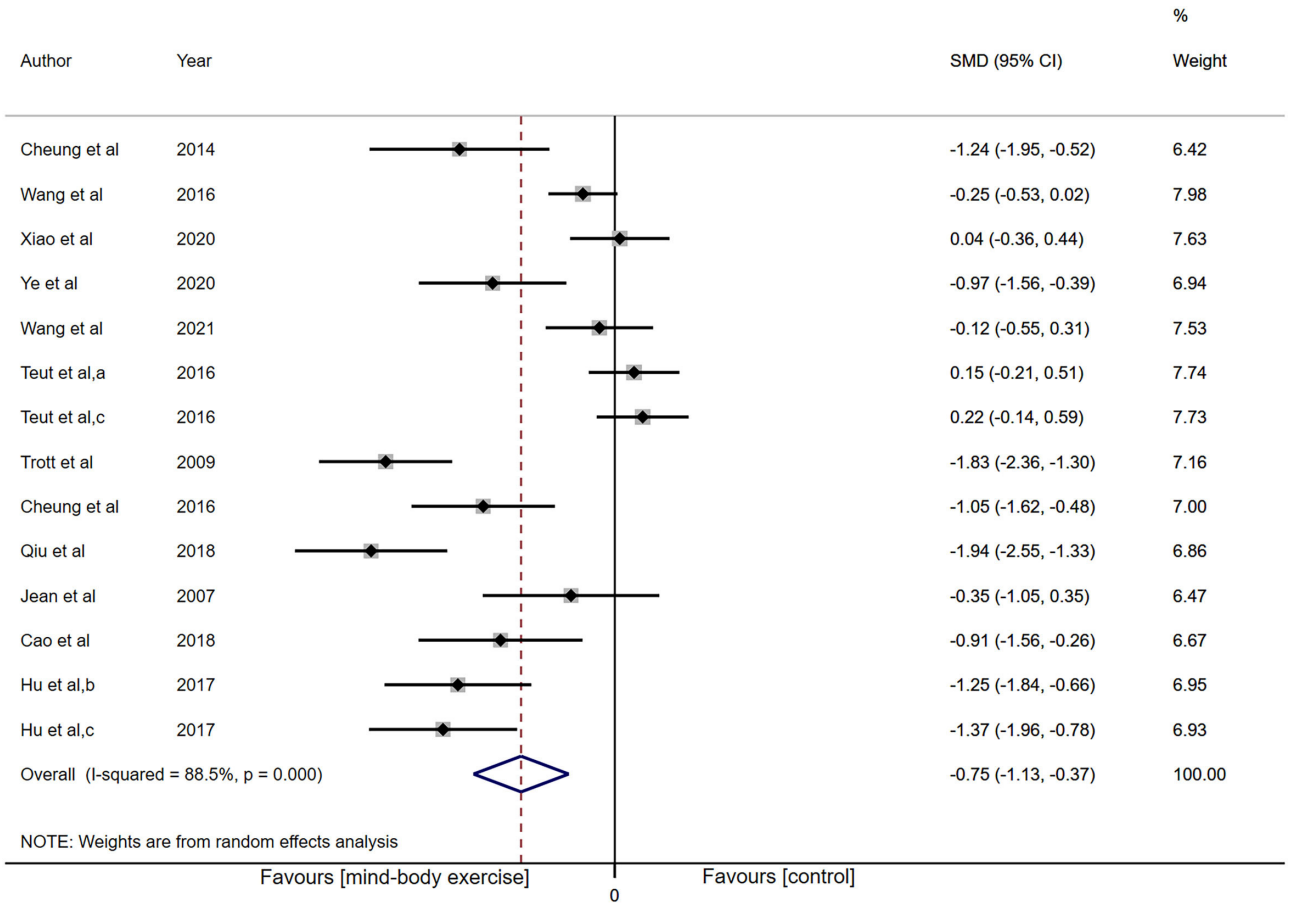


FIGURE 3 | Forest plot showing overall effect sizes (Hedges' g) of mind-body exercises on self-reported function within studies. These plots show the pooled SMD (large diamond shape) and I^2 resulting from the meta-analysis.

Risk of Bias and GRADE

The results of the bias risk graph included in the study are shown in **Figures 6**, **7**. Most articles showed low-risk random sequence generation (76%), allocation concealment (58%), incomplete outcome data (82%), selective reporting (100%), and other bias (100%). Due to the particularity of the experimental intervention protocol design, the low risk of blinding of participants and personnel ratio is 0%, and 58% of the studies showed low risk in the aspect of blinding of outcome assessment. The quality of evidence assessed by the GRADE approach is shown in **Supplementary Material 3**.

Sensitivity Analysis

Removing the literature comparisons one by one did not significantly change the heterogeneity of pain outcomes. This indicated that the outcomes achieved were strong and reliable. No outliers were found because the total ES of each investigation was within 2 SD of the total average impact size. Additionally, four high-risk biased trials were excluded to determine whether they could influence the outcome of the meta-analysis. The other 13 studies maintained statistically meaningful in an effect estimate of −0.51 (95% CI: −0.74 to −0.28) with heterogeneity of 69.7%. There was less difference between the results before and after analysis, and the heterogeneity was uninfluenced.

Publication Bias

The Egger's test results show physical function scores ($P = 0.004$, **Supplementary Figure S7**) and pain intensity scores ($P = 0.001$, **Figure 8**) observed significant publication bias, and we corrected the results by trim and fill analysis. The pooled estimate and 95% CI of pain intensity scores and physical function scores calculated by the fixed-effect model and random-effect model were −0.481 (−0.592, −0.37) and −0.639 (−0.862, −0.415), −0.49 (−0.615, −0.365) and −0.747 (−1.126, −0.368), respectively, after trim and fill analysis. Their results did not change before and after the trim and fill analysis, showing our results were robust.

Adverse Event of Intervention

Among the studies, 12 studies reported the safety of MBE. Adverse reactions data were not available from five trials (Yang et al., 2005; Teut et al., 2016; Cao, 2018; Qiu, 2018; Liu et al., 2019). Among the studied reporting adverse events, 10 reports (83%) mentioned that there were no adverse events related to MBE intervention. One study (von Trott et al., 2009) reported

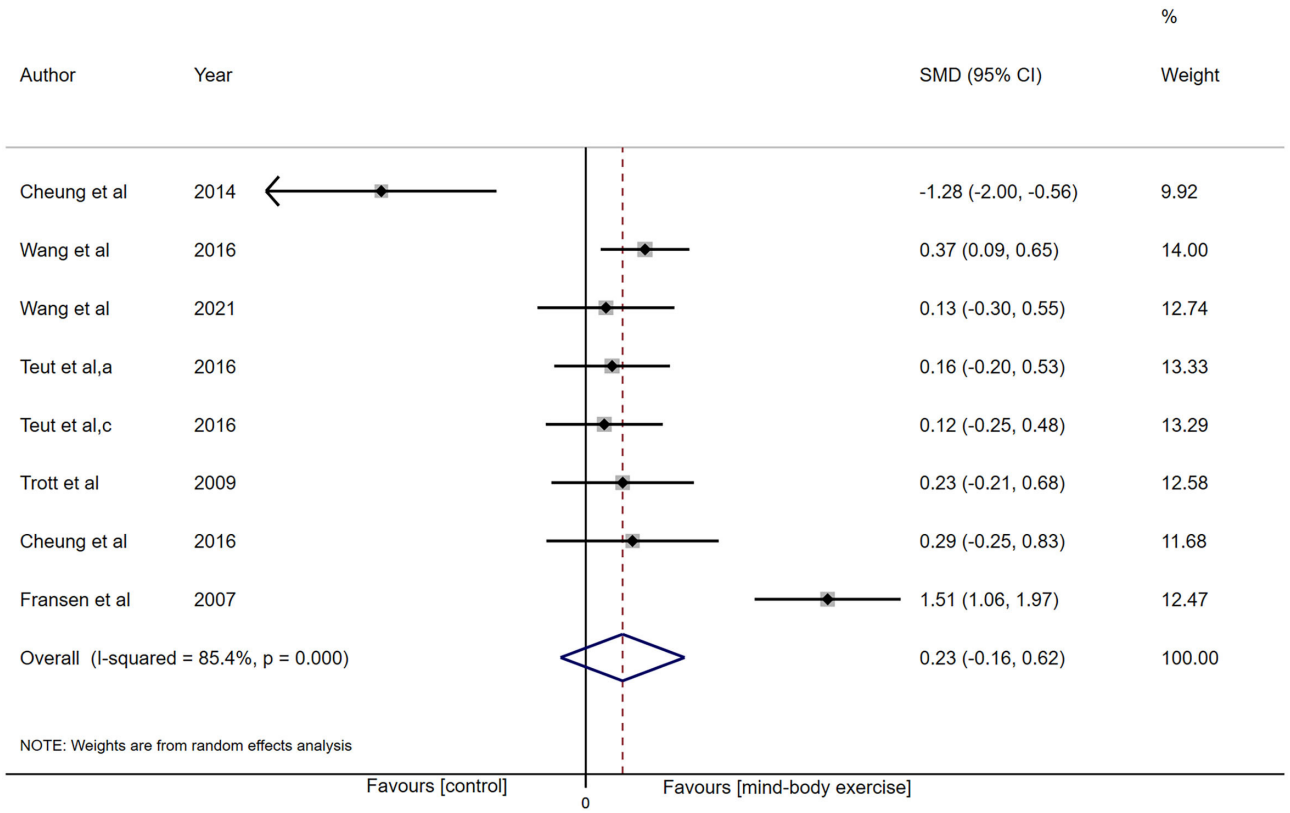


FIGURE 4 | Forest plot showing overall effect sizes (Hedges' g) of mind-body exercises on physical component summary within studies. These plots show the pooled SMD (large diamond shape) and I^2 resulting from the meta-analysis.

five minor side effects in qigong group (i.e., two nausea cases, two aching muscles, and one muscle tension). Another study (Raub, 2002) claimed that there was serious adverse event requiring hospitalization in 11 patients, but none of these events was related to the TC. Interventions such as TC, yoga, and qigong were highly safe and tolerable for the elderly who suffering from chronic pain.

DISCUSSION

Main Findings

This meta-analysis is the first to explore the effectiveness of three popular movement-based MBE modes systematically (i.e., TC, yoga, and qigong) regarding middle-aged and elderly people with chronic pain throughout comprehensive evaluate current evidence. The total effect amount showed that compared with both the nonactive and active control, MBE >8 sessions could significantly reduce the pain symptoms of middle-aged and elderly people, while the effect amount from large to small was yoga, TC, and qigong. MBE have shown good analgesic effects in the elderly with KOA and CLBP. Moreover, the recent meta-analysis (Morone and Greco, 2007; Chen et al., 2016; Zhang et al., 2017) results of separately summarizing KOA also demonstrated that TC and qigong have a good pain relief effect. However, due to the small sample size and high heterogeneity of CLBP, this effect needed to be carefully explained.

In terms of self-reported function, MBE had obvious benefits for KOA and neck pain, but the efficacy of CLBP was uncertain. TC and qigong improved the function significantly better than the control group, and the results revealed that MBE for at least 30–45 sessions had obvious benefits on the function. The meta of nonspecific LBP in the elderly published by Paulo R.C. found that there was weak and not clinically relevant evidence that yoga had an effect on pain and function (Nascimento et al., 2019). In another study (Wieland et al., 2017), yoga can improve the back-related function and reduce pain in adults with CLBP; however, the ES did not meet predefined levels of minimum clinical importance. The results of the subgroup analysis showed that yoga intervention may not improve the level of function for middle-aged and old patients with chronic pain, which may relate to its complexity compared with the other two MBE modes. Yoga usually requires professional guidance from a certified instructor, and self-practice at home may contribute to wrong movement patterns, which is an important factor affecting function (Sherman et al., 2011; Nambi et al., 2014; Saper et al., 2017). Only three of all included studies involved yoga intervention (Cheung et al., 2014, 2017; Teut et al., 2016), wherein the insufficient power of sample size may have affected the power of detecting significant differences in the level of function.

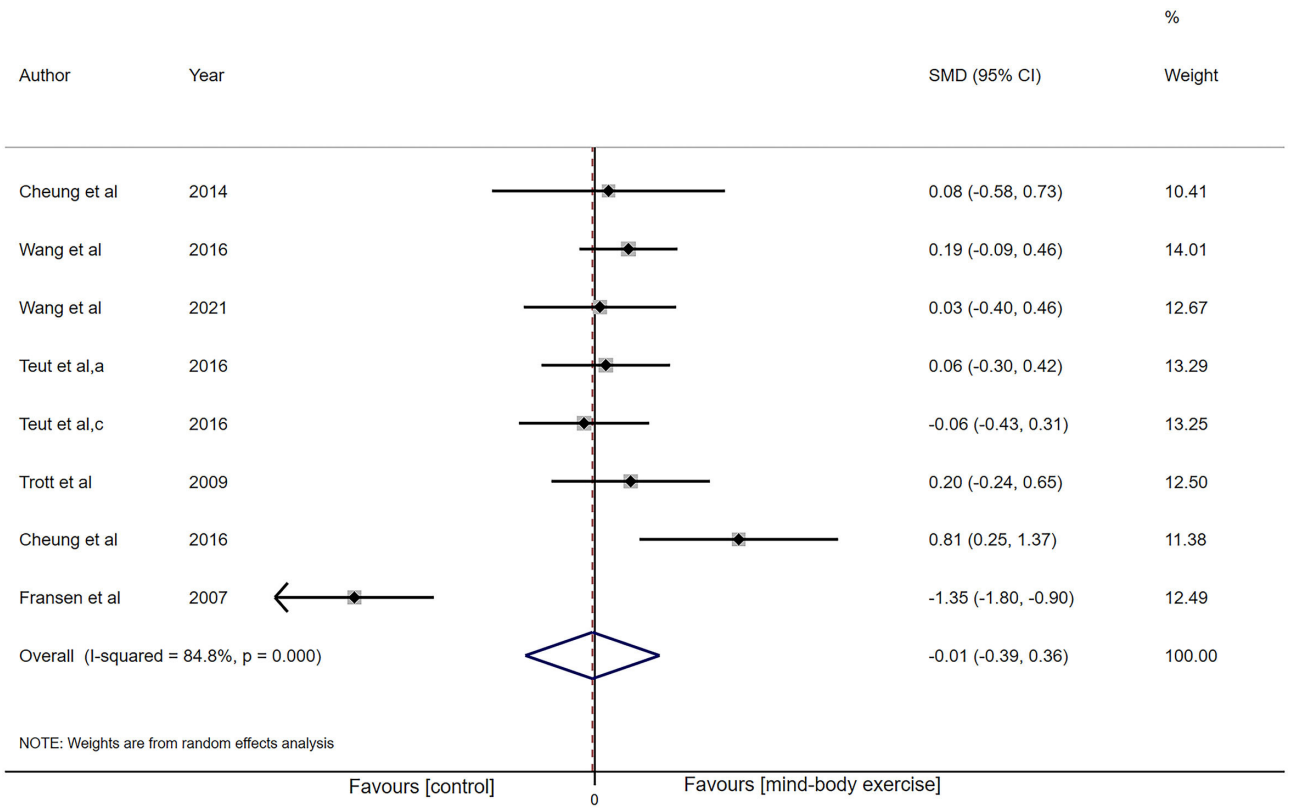


FIGURE 5 | Forest plot showing overall effect sizes (Hedges' g) of mind-body exercises on mental component summary within studies. These plots show the pooled SMD (large diamond shape) and I^2 resulting from the meta-analysis.

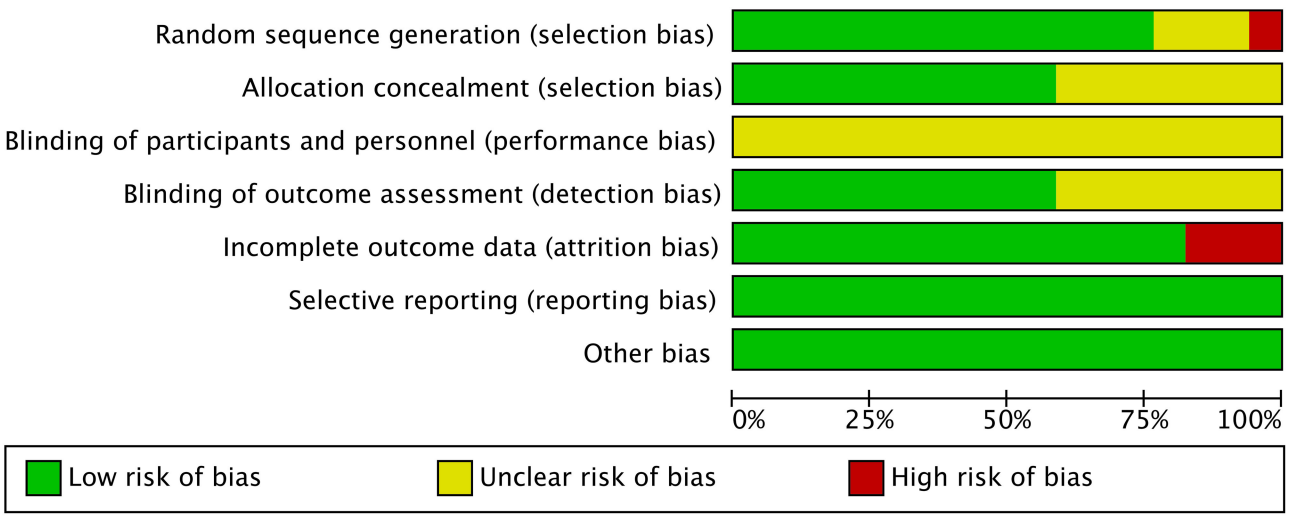


FIGURE 6 | Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

At present, there was no evidence that MBE has the advantage of improving the QOL. The effect of any type of MBE on MCS in elderly patients with chronic pain was not better than that in the control group. Similarly, MBE has no significant effect on PCS. The results of this study were also consistent with the previous results of MBE application in KOA (Zhang et al., 2017). In addition, Irwin et al. conducted TC intervention on older patients who had suffered chronic pain from the herpes zoster

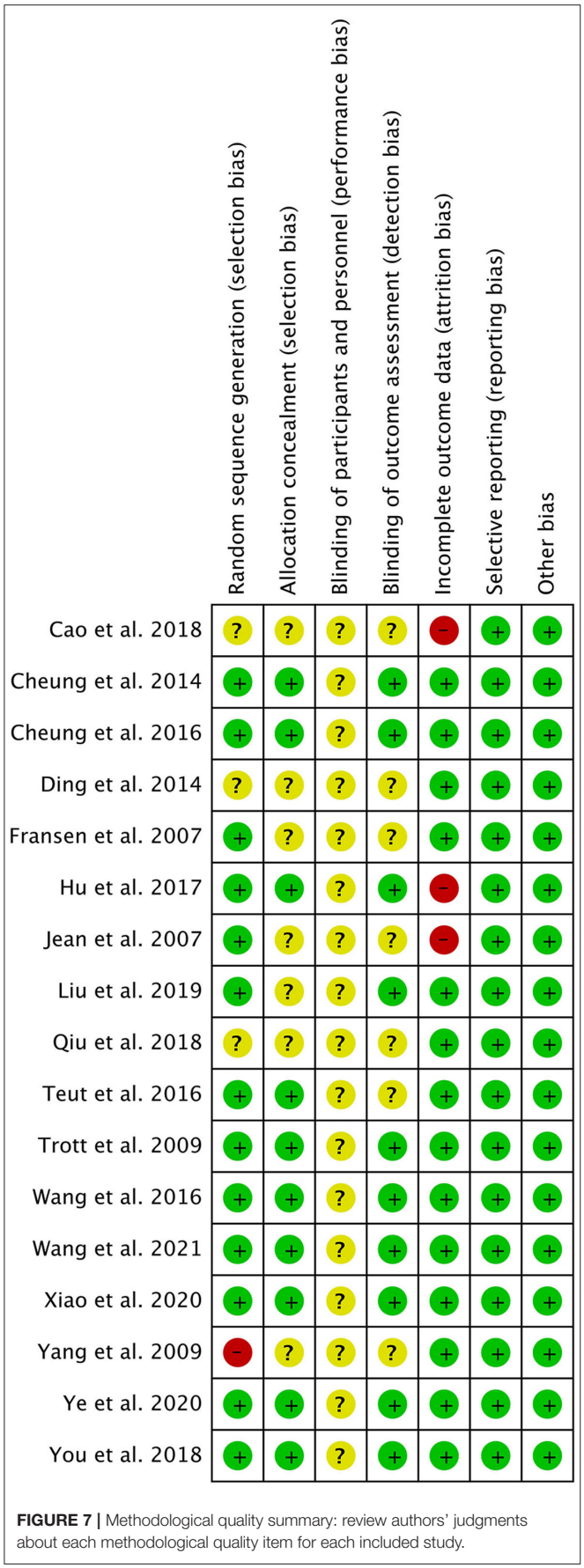


FIGURE 7 | Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

virus and found no significant increase in SF-36 scores (Irwin et al., 2003). One possible explanation for this result relates to the sessions of the MBE intervention and follow-up. MBE may indirectly improve QOL by regulating systemic function, the significant effect of which may take a long time to observe. Only data immediately after intervention were used as outcomes in this meta-analysis, which may lack evidence of QOL during long-term follow-up. It was worth emphasizing that no serious adverse events were found to be associated with MBE.

Potential Advantages of MBE for Elderly

In addition to reducing pain in elderly patients effectively, TC, as an effective alternative medical means, has been clinically proven to improve self-efficacy and physical function in elderly patients, reduce the risk of falls, and have a positive effect on blood pressure control. TC was also integrated into cognitive behavioral therapy to relieve the pressure of people with human immunodeficiency virus infection (McCain et al., 2008) and also incorporated into the health management of fibromyalgia patients (Wang et al., 2010b). Evidence of chronic pain population suggests that TC training is beneficial to chronic KOA pain and CLBP (Kong et al., 2016; Hall et al., 2017). Our study produced similar results and made up for the limitation of insufficient sample size of these meta-analyses.

A meta-study (Bai et al., 2015) involving 10 RCTs revealed that only internal qigong can improve chronic pain in adults, but external qigong had no significant difference. However, studies on traditional Chinese qigong, such as Wuqinxi and Baduanjin, have not been included in it. The scarcity of trials related to qigong in the English-language articles in contrast with the greater number of TC studies probably indicates the differing popularity of these interventions for the moment in the Western countries. These exercises combine low-effect control exercises, breathing, and meditative awareness and are worth studying in older adults with chronic pain. Although the mechanism is still unclear, qigong exercises can be used as a rehabilitation method to improve the symptoms of chronic pain patients and prevent further deterioration of the disease.

There have been few studies on yoga as an intervention for chronic pain in the elderly. The meta (Büssing et al., 2012) also showed short-term yoga interventions may be effective and could ameliorate several pain-associated disability. Studies on yoga for CLBP have shown that while yoga can reduce pain, there was no significant improvement in QOL or functioning (Teut et al., 2016). In addition, some other trials (Bellamy et al., 1988; Garfinkel et al., 1994; Kolasinski et al., 2005) have also shown that yoga can significantly improve the pain of knee, hip, and hand arthritis in older adults and also presented compelling evidence that yoga is safe.

Potential Analgesic Mechanism of MBE

The potential mechanisms by which MBE affects pain perception and function levels in older patients with chronic pain were not fully understood. The potential effect of it probably be ascribed these exercises to impact altered central elements such as central pain sensitization. Unlike regular aerobic exercise, MBE emphasizes slow, controlled body movements while regulating

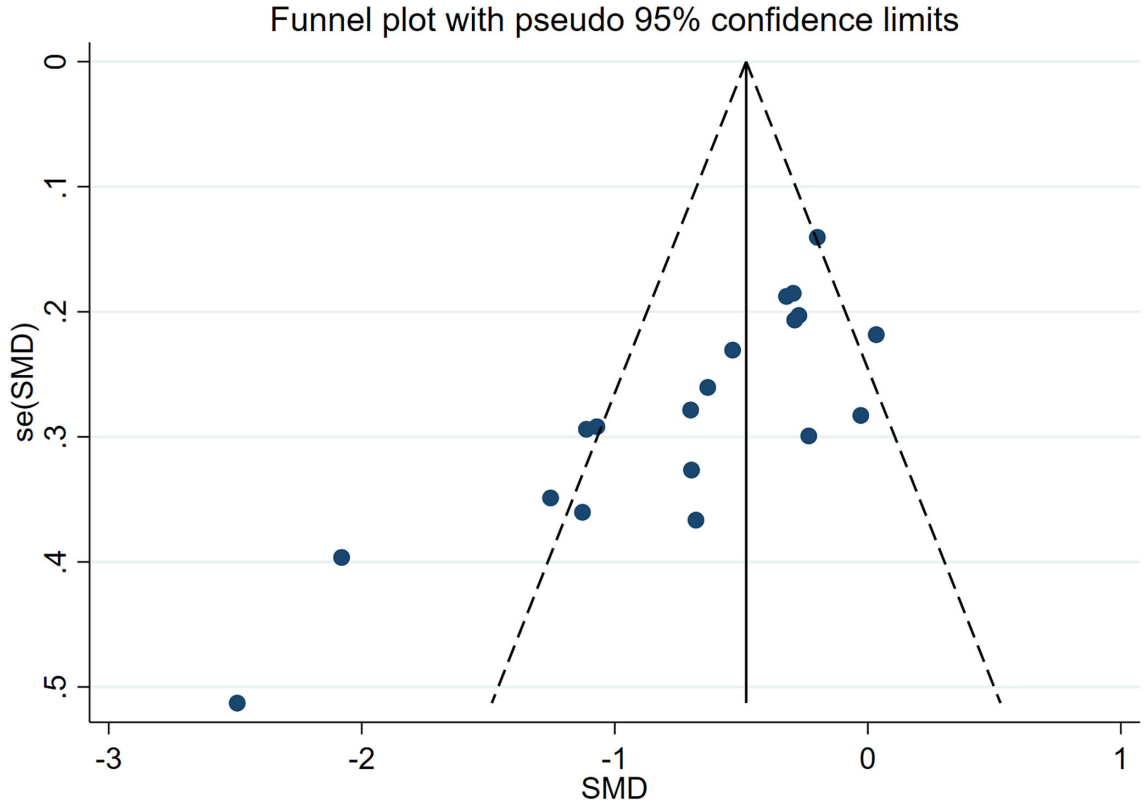


FIGURE 8 | Funnel plots with standard errors plotted against effect sizes for determining publication bias in chronic pain intensity.

focus and awareness through breathing and meditation. Studies have shown that long-term TC practice can induce regional structural changes in the precentral gyrus, insular sulcus, and middle frontal sulcus (Wei et al., 2013). Shen et al. investigated the association between neurobiological effects and pain/physical function among postmenopausal women with KOA after 8 weeks of TC interventions. Moderate-high correlations were observed between TC-associated pre-post changes in amygdala-medial prefrontal cortex functional group connectivity and pain and physical function improvement (Shen et al., 2021), indicating that MBE may directly affect the cerebral cortex to regulate pain and physical function through regular practice.

The effect of MBE may also involve the hypothalamic-pituitary-adrenal (HPA) axis, which dominates the endocrine regulatory system. Under normal conditions, activated HPA axis induced by stress releases cortisol, resulting in the downregulation of inflammatory cells. However, in patients with chronic pain, the existence of pain stress would lead to the disorder of endocrine system. Based on the Feng's view, slow and mild movements of MBE with deep breathing may alter the sympathetic-adrenal-medullary axis (SAM axis; sympathetic nervous system), reducing the HPA axis reactivity (Feng et al., 2020). The mechanism of chronic pain is full of complex factors (Edwards et al., 2006; Campbell and Edwards, 2009; Niederstrasser et al., 2014), which may involve proinflammatory immune responses, stress, indices of central sensitization, and central nociceptive processing system. The levels of stress-related pain and function may be consequently decreased through this HPA mechanism (Thayer and Lane, 2000).

Safety and Popularization

Extensive evidence not only proved the positive effects of MBE on pain, psychosocial health, stress, anxiety, and depression but also showed that MBE is a suitable and safe exercise pattern for middle-aged and elderly individuals and those who are less likely to engage in intense exercises (Chow and Tsang, 2007; Ross and Thomas, 2010; Wang et al., 2010a). MBE is usually conducted in group classes, which is a typical exercise group or classroom intervention. Therefore, although exercising in various modes, the results may be similar. In addition, there may be some specific scientific effects because a person's interest and enjoyment in a particular activity are often key factors in their adherence to regular practice (Terjestam et al., 2010). At the same time, our review also emphasized the importance of the frequency and duration of MBE interventions, some of which lasted up to 60 min/session. The authors of a study of frail elderly people in nursing homes noted the importance of keeping treatment short (Mcbee et al., 2004). The proposed changes seem reasonable and appropriate to maximize safety and cognitive understanding of therapy. In addition, many studies used the combination of group classes and homework for intervention. The low efficiency of

homework exercise may also be an important factor affecting the outcome and reducing the ability to detect the treatment effect.

Future Directions

The importance of high-quality designing clinical trials targeting older adults needs to be considered for future researchers. Future studies could examine the possible long-term outcomes modifiers present in this population, thus allowing the recommendation of more efficacious evidence-based interventions to this growing population. Additional information needs to be provided on the comparison of symptom improvement in chronic pain patients with various MBE modes and different age groups, such as focus only on elderly patients with chronic pain, which might be worth. More multiarm RCTs should be conducted in the future to determine the efficacy differences of different MBE modes in middle-aged and elderly patients with chronic pain.

Strengths and Limitations

This study has several strengths as follows:

- We conducted a robust systematic review and meta-analysis regarding the effect of MBE on chronic pain symptoms for middle-aged and elderly people.
- Three popular MBE modes (i.e., TC, yoga, and qigong) are included in the study;
- We included Chinese-language studies and gray literatures, which made the review more comprehensive;
- We used the rigorous meta-analytical ways and assessment, such as sensitivity analyses, additional models using fixed effects, assessment of publication bias, trim and fill analysis, and GRADE approach.

Several limitations should be considered as follows:

- It was difficult to blind subjects and coaches during MBE interventions, which may contribute to potential risks of performance bias. However, this is an inherent limitation of such studies and is usually reported in meta-analyses of exercise interventions (Kong et al., 2016; Goh et al., 2019; Owen et al., 2020). We expect future RCTs to identify appropriate blinding methods for participants and instructors to reduce the risk of performance bias;
- Several studies did not report "random sequence generation," "intention to treat analysis," and "allocation concealment," which probably overstate the pooled ES. However, subsequent sensitivity analysis showed that our results were robust;
- Potential publication bias and heterogeneity of the results were may be influenced by the styles of MBE and chronic pain conditions. This may require more sophisticated analytical methods and separate reporting.

CONCLUSION

Our results indicated that MBE (i.e., TC, yoga, and qigong) were effective treatments for reducing symptoms of middle-aged and elderly people with chronic pain compared with the nonactive and active control groups. TC and qigong had obvious benefits for KOA in self-reported function, but the efficacy of CLBP was uncertain. No significant benefit of MBE on QOL in older adults with chronic pain was found. The potential of yoga and TC as two common nonpharmacological treatments for chronic pain needs to be rigorously assessed in future studies. More high-quality RCTs should be conducted to explore the efficacy and mechanism of MBE on chronic pain in middle-aged and elderly people from various dimensions, such as affective and cognitive dimensions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Y-RW and JS wrote the manuscript and involved in the data analysis. Y-FW, Y-RW, X-QW, and Y-LW contributed to the conception. Z-YH and JS searched the literature. Y-YL, JS, Y-RW, Y-TL, and Y-LW contributed to the acquisition of data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.921069/full#supplementary-material

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Transcriptional Profiling Reveals Brain Region-Specific Gene Networks Regulated in Exercise in a Mouse Model of Parkinson's Disease

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Background: Exercise plays an essential role in improving motor symptoms in Parkinson's disease (PD), but the underlying mechanism in the central nervous system remains unclear.

Methods: Motor ability was observed after 12-week treadmill exercise on a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. RNA-sequencing on four brain regions (cerebellum, cortex, substantia nigra (SN), and striatum) from control animals, MPTP-induced PD, and MPTP-induced PD model treated with exercise for 12 weeks were performed. Transcriptional networks on the four regions were further identified by an integrative network biology approach.

Results: The 12-week treadmill exercise significantly improved the motor ability of an MPTP-induced mouse model of PD. RNA-seq analysis showed SN and striatum were remarkably different among individual region's response to exercise in the PD model. Especially, synaptic regulation pathways about axon guidance, synapse assembly, neurogenesis, synaptogenesis, transmitter transport-related pathway, and synaptic regulation genes, including Neurod2, Rtn4rl2, and Cd5, were upregulated in SN and striatum. Lastly, immunofluorescence staining revealed that exercise rescued the loss of TH^+ synapses in the striatal region in PD mice, which validates the key role of synaptic regulation pathways in exercise-induced protective effects *in vivo*.

Conclusion: SN and striatum are important brain regions in which critical transcriptional changes, such as in synaptic regulation pathways, occur after the exercise intervention on the PD model.

Keywords: exercise, Parkinson's disease (PD), RNA-Seq, brain region specific, synapses

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by degeneration of dopaminergic neurons in the substantia nigra (SN) (Samii et al., 2004). Clinical manifestations of patients with PD mainly consist of rest tremor, bradykinesia, rigidity, and loss of postural reflexes

(Jankovic, 2008). Levodopa remains the most common medication for alleviating some of the motor deficits in the early stages of the disease (Lane, 2019). However, chronic use of that drug probably induces side effects, such as levodopa-induced dyskinesia (LID) and impulse control disorders (Voon et al., 2017; Donzuso et al., 2020). Moreover, no specific medicine has been developed to reverse the progression of PD permanently. Therefore, clinicians and researchers have paid more attention on physical exercise.

Recent studies revealed that exercise on patients with PD improves their quality of life and physical function, including locomotion, balance, and gait performance (Goodwin et al., 2008; Shah et al., 2016; Mak and Wong-Yu, 2019; van der Kolk et al., 2019). The observed increments in gait speed and stride length after treadmill and robotic exercise for subjects with PD imply the repairment of nigrostriatal system and cerebellum controlling semi-autonomous stereotypic movements (Hirata et al., 2020; Surkont et al., 2021). In addition, the motor cortex was also found involved in the recovery of PD patients after exercise training (Rothwell, 1999; Fisher et al., 2008). Profound changes occurring in those brain regions during physical exercise may contribute to PD rehabilitation, and underlying molecular mechanisms need further studying.

Previous studies on animal models have demonstrated that exercise practice would modulate the function of striatum, probably by augmenting the dopamine content, improving the mitochondrial function and restricting the extracellular glutamate accumulation (Hendricks et al., 2012; Yue et al., 2012; Chen and Li, 2019). Lee et al. (2018) reported that treadmill running could improve motor balance and coordination in PD rats by suppressing the loss of purkinje cells in the cerebellar vermis.

Despite those clinical and animal studies, molecular mechanisms in the central nervous system (CNS) underlying exercise-induced effects have not been fully elucidated. Especially, most work focused on isolated brain regions (Kintz et al., 2017; Myers et al., 2018), and critical molecules in the cortex, cerebellum, SN or striatum were not overall screened. Systematic analysis of molecular pathways as well as interactions of target brains regions involved in exercise-induced PD rehabilitation is required. Here, we speculate physical exercise in patients with PD may improve motor symptoms by modulating critical molecular networks in those 4 brain region and by affecting the circuit function across them. Studies in the inter-connection of brain regions and corresponding molecular networks highly rely on bioinformatics. For instances, rank-rank hypergeometric overlap (RRHO) is a suitable approach that successfully revealed overlapping transcriptional patterns across brain regions (Bagot et al., 2016; Labonté et al., 2017; Peña et al., 2017). Weighted gene co-expression network analysis (WGCNA) is another widely used approach to explore gene networks involved in several CNS disorders, including Alzheimer's disease and schizophrenia (Rangaraju et al., 2018; Radulescu et al., 2020).

In the present study, we used an MPTP-induced mouse model of PD to evaluate the effect of treadmill exercise on motor ability. Our results demonstrated a better performance in movement and balance, for the "MPTP + Exercise" group compared to the "MPTP" group. Then, we utilized RNA-sequencing to generate transcriptional profiles in the SN, striatum, cortex, and cerebellum for control, MPTP, and exercised PD model. RRHO and WGCNA were further applied to identify brain region-specific patterns and networks of co-regulated genes associated with exercise. Our data suggested an overlapping transcriptional pattern in the SN and striatum, and an opposite regulation in the SN and striatum after exercise. Pathways analysis revealed synaptic-related processes, especially synaptogenesis in the striatum was upregulated. Finally, we performed immunofluorescence experiments and validated that MPTP treatment reduces the number of striatal TH^+ synapses while treadmill exercise restores it. Overall, this work provides a novel understanding in the molecular basis of PD exercise by leveraging a systematic and unbiased approach on transcriptional regulation, and may further promote the development of anti-PD strategy.

MATERIALS AND METHODS

Animals

C57BL/6J mice (8-week-old, female) were purchased from Charles River, Beijing. Mice were maintained at 22 ± 1°C on a 12-h light/dark cycle. All experiments were conducted following international standards on animal welfare.

Chronic Mouse Model of Parkinson's Disease

After 1-week adaptation, mice were injected with MPTP (25 mg/kg, 10 doses, s.c.) in combination with probenecid (Dauer and Przedborski, 2003). During the chemical preparation and animal injections, safety precautions for MPTP use were observed (Jackson-Lewis and Przedborski, 2007).

Treadmill Exercise Protocol

After the entire course of MPTP, the PD mice in the exercise groups (PD + EX) were forced to run on a treadmill (Duanshi, China) for 5 days/week, 40 min/day with a speed up to 15 m/min (5 min at 6 m/min, 5 min at 9 m/min, 20 min at 12 m/min, 5 min at 15 m/min, and 5 min at 12 m/min) for 12 consecutive weeks (Lau et al., 2011).

Motor Behavior Analysis

After the entire course of MPTP and exercise, the mice were evaluated for their motor dysfunction by open field, rotarod, and pole test. In the open field, the mice were placed in a 100 _ 100 cm field individually for 15 min between 9 and 12 am (Huang et al., 2015). Then, we used the image processing system Xeye Aba 3.2 to analyze average velocity. In the rotarod test, mice were placed on a rotarod over 300 s at an accelerating speed (from 5 rpm to 50 rpm) (Petroske et al., 2001; Meredith and Kang, 2006). In the pole test, the time when mice were taken from the top of the pole for 3 times was recorded, then the average time was calculated (Ogawa et al., 1985; Matsuura et al., 1997).

Brain Tissue Preparation

Following the final behavioral test, all the animals (Saline: $n = 4$, MPTP: $n = 4$, MPTP + EX: $n = 4$) were euthanized *via* cervical dislocation. the SN, striatum, cortex, and cerebellum samples were micro-dissected from the brain. Then, they were frozen at −80°C until the RNA extraction was performed. The cohort of animals (Saline: $n = 5$, MPTP: $n = 5$, MPTP + EX: $n = 5$) were anesthetized and then perfused transcranially with 4% paraformaldehyde and 0.1 M PBS. Then the brain was kept in 4% paraformaldehyde for at least 8 h, then cryoprotected in 20 and 30% sucrose for 48 h. Finally, brains were sliced into 15 μm sections for staining.

RNA Isolation

Ice cold TRIzol Reagent (Life Technologies) was added to frozen tissue on ice. The total RNA was extracted following the manufacturer protocol by TRIzol Reagent. RNA concentrations were assessed by Nanodrop 2000/2000C, and RNA quality was checked by the Agilent 2100 Bioanalyzer.

Transcriptome Analysis

After RNA-seq library preparation, all reads were mapped to *Mus musculus* as the reference genome by Tophat2 (v2.01). Then, we normalized FPKM (Fragments Per Kilobase of transcript per Million fragments mapped) of genes were estimated by Cuffquant (Cufflinks v2.21). Then, we calculated the number of FPKM by RSEM (V1.2.4) software. We used DESeq (V1.14.0) software to identify DEGs which FPKM > 1 and $p < 0.05$. We used the RRHO test to identify the degree of overlap in gene signatures among the brain regions in PD and exercised PD mice. WGCNA was used for the co-expressed gene modules. Pearson correlation coefficient analysis was performed for various groups and brain regions. Enrichment analysis, including GO analysis and KEGG pathway analysis, were performed by DAVID.

Immunofluorescence

Six slices that extended through the regions of interest, including the cortex, cerebellum, SN, and striatum, were collected for TH^+ immunofluorescence. All slices in the striatum were incubated in chicken anti-Tyrosine Hydroxylase (1:250, abcam, Cambridge, United Kingdom), rabbit anti-PSD95 (1:1,000; Synaptic Systems, Göttingen, Germany), and mouse anti-synapsin antibodies (1:1,000; Synaptic Systems, Göttingen, Germany) overnight at 4°C. After washing in PBS three times, sections simultaneously treated with 488-conjugated donkey anti-chicken IgG (1:1,000 dilution; Vector Laboratories Newark, CA, United States), 568-conjugated donkey anti-rabbit IgG (1:1,000 dilution; Vector Laboratories Newark, CA, United States), and 647-conjugated goat anti-mouse IgG (1:1,000 dilution; Vector Laboratories Newark, CA, United States) for another 1 h at room temperature. Then, the slices were observed under a confocal laser scanning microscope. Images were processed with software Imaris (Bitplane, Schlieren, Switzerland).

Statistical Analysis

All data were expressed as mean ± SEM. Normal distributions and equal variances were determined for all data sets. A one-way or mixed-model ANOVA was performed as required. Tukey's test and LSD were followed to conduct multiple comparisons, respectively. For all data, $p < 0.05$ was considered to be statistically significant. Data analysis was performed by SPSS 19.0, and graphs were plotted by GraphPad Prism 7.

RESULTS

Treadmill Exercise Improves Motor Dysfunction in Parkinson's Disease Model

After the 5-week MPTP treatment, we assessed the animals' motor function by the rotarod test, the open field test, and the pole test (**Figure 1A**). Animals in the saline group exhibited significant different performance in behavior tests, compared to mice when MPTP treatment was just completed (**Figures 1B–D**). The two groups (MPTP and MPTP + EX) exhibited lower retention times on the rotarod test as compared to the saline group (**Figure 1C**). The pole test showed that both the MPTP and MPTP + EX group descend to the floor more slowly (**Figure 1B**) and exhibited a slower average velocity as compared to the saline group (**Figure 1D**).

After 12 weeks of exercise (treadmill training), we investigated whether that would alleviate motor deficits. Notably, the time to descend to the floor increased in the MPTP vs. Saline group ($p < 0.001$) and exercise drove a significant decrease compared to the MPTP group (**Figure 1B**, $p < 0.05$). The results unveiled a reduction in rotarod test time for the MPTP group compared to the saline group (**Figure 1C**, $p < 0.001$), and exercise reversed that tendency (**Figure 1C**, $p < 0.01$). In the open field test, average velocity was slowed in the MPTP vs. saline group (**Figure 1D**, $p < 0.001$), and exercise reversed that tendency (**Figure 1D**, $p < 0.05$).

DEG Analysis Reveals Brain-Region-and Exercise-Specific Response Transcriptional Profiles in Parkinson's Disease Mice

To determine whether transcriptional profiles response to PD in a brain-region- and exercise-specific, we examined transcriptional profiles in 4 brain regions: cortex, cerebellum, SN, and striatum. For each condition and brain region, unbiased RRHO analysis was applied to reveal the transcriptional changes in 4 brain regions in MPTP mice. Results of RRHO analysis disclosed opposing up- and down-regulation of transcriptional signatures in the SN and striatum (**Figure 2A**), and a similar but weaker change for gene regulation in striatum and cerebellum (**Figure 2A**). Overlapping patterns were found across the cerebellum region. Our analysis revealed a coordinated up- and down-regulation of genes between the SN and striatum in MPTP + EX (**Figure 2B**). While the overlapping region between the cerebellum and SN was weaker in MPTP + EX (**Figure 2B**).

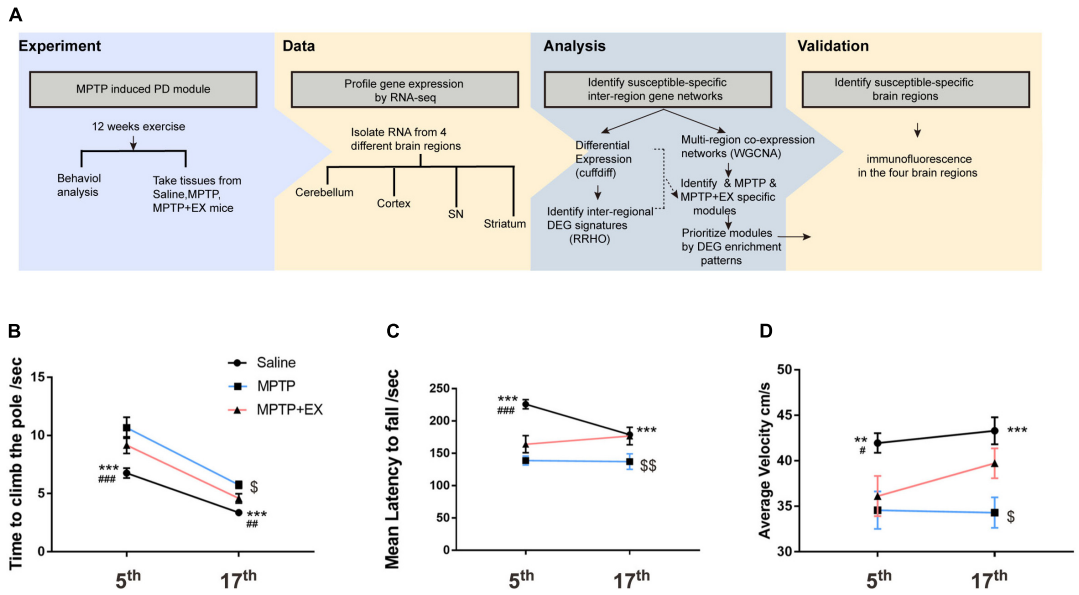


FIGURE 1 | Motor function recovery in mice treated with MPTP after the 12-week treadmill exercise. **(A)** Scheme of the experimental design. **(B)** Time spent in descending to the floor for the saline (n = 24), MPTP (n = 12), and MPTP + EX (n = 12) groups. **(C)** Time spent in the rotarod for the saline (n = 24), MPTP (n = 12), and MPTP + EX (n = 12) groups. **(D)** Average speed in the open field for the saline (n = 24), MPTP (n = 13), and MPTP + EX (n = 13) groups. Data are mean ± s.e.m. Statistical analysis is performed using mixed-model ANOVA followed by the LSD *post hoc* test. $^{**}p < 0.01$, saline vs. MPTP; $^{***}P < 0.001$, saline vs. MPTP; # $p < 0.05$, saline vs. MPTP + EX; ### $p < 0.001$, saline vs. MPTP + EX; \$ $p < 0.05$, MPTP vs. MPTP + EX; \$\$ $p < 0.01$, MPTP vs. MPTP + EX.

Additionally, we detected minor overlap genes between MPTP and MPTP + EX transcriptional patterns in the cortex region, but stronger overlapping patterns in SN, especially in the striatum (**Figure 2C**). A comparison of DEGs in the MPTP vs. saline group and MPTP + EX vs. MPTP revealed overlapping across all 4 brain regions (**Figure 2D**). Moreover, the change directionality observed in the PD model and exercised PD model were different (**Figure 2E**). These analyses indicated that SN and striatum might have different responses to exercise in patients with PD.

Remarkable Different Genes in SN and Striatum Regions Affected by Exercise for Parkinson's Disease Mice

To further investigate the role of SN and striatum in PD and the exercise group for PD, genes with opposite expression patterns after modeling and locomotion were filtered. Genes selected in the SN are shown in **Figure 3A**. After exercise, 155 genes were down-regulated and 66 genes were up-regulated. Pathway analysis revealed several pathways enriched in PD model or exercised MPTP-induced PD model in SN. After exercise, the down-regulation of pathways were striking, including oxidative stress and apoptotic pathways. Meanwhile, we saw the up-regulation of memory, axon guidance, and synapse assembly pathways (**Figure 3B**). Furthermore, transcription factor analysis revealed that Pax6, Dbx2, Pou3f2, Zkscan6, Vsx1 were the top 5 remarkable transcription factors in SN. Their downstream genes were growth, development, and inflammation-related genes like Neurod2, Rtn4rl2, and Cd5, etc., (**Figure 3C** and **Supplementary Table 2**). In the striatum, 49 genes were down-regulated and 185 genes were up-regulated after exercise (**Figure 3D**). More pathways were enriched in up-regulated pattern after exercise. The enriched pathways were found to be related to neurogenesis, synaptogenesis, and transmitter transport like connective tissue development, head development, neuronal system regulation of neuron differentiation synapse organization, neurotransmitter receptor transport to the postsynaptic membrane (**Figure 3E**). Further analysis revealed that Ep300, Tmem33, T, Zfp280d, and Elk1 were the top 5 remarkable transcription factor binding sites in the striatum. Their downstream genes focus on development-related genes like Bmp5, Nr4a2, and Ntn5, etc., (**Figure 3F** and **Supplementary Table 3**). These results indicated that the microenvironment of DA neurons in SN might be improved, and synaptogenesis was promoted in the striatum after exercise in the PD model.

WGCNA Identify Specific Transcriptional Signatures Associated With Exercise Rehabilitation in Parkinson's Disease Model

To further investigate transcriptional signatures in SN and striatum and gain more insights into the molecular mechanisms involved in PD's exercise, we conducted WGCNA to detect gene co-expression network modules of saline, MPTP and MPTP + EX groups from multi-brain-region which combined SN and striatum. Our analysis identified gene co-expression modules, each name labeled by random color. As shown in **Figure 4A**, our analysis showed that the black module was positively correlated with exercise rehabilitation in SN,

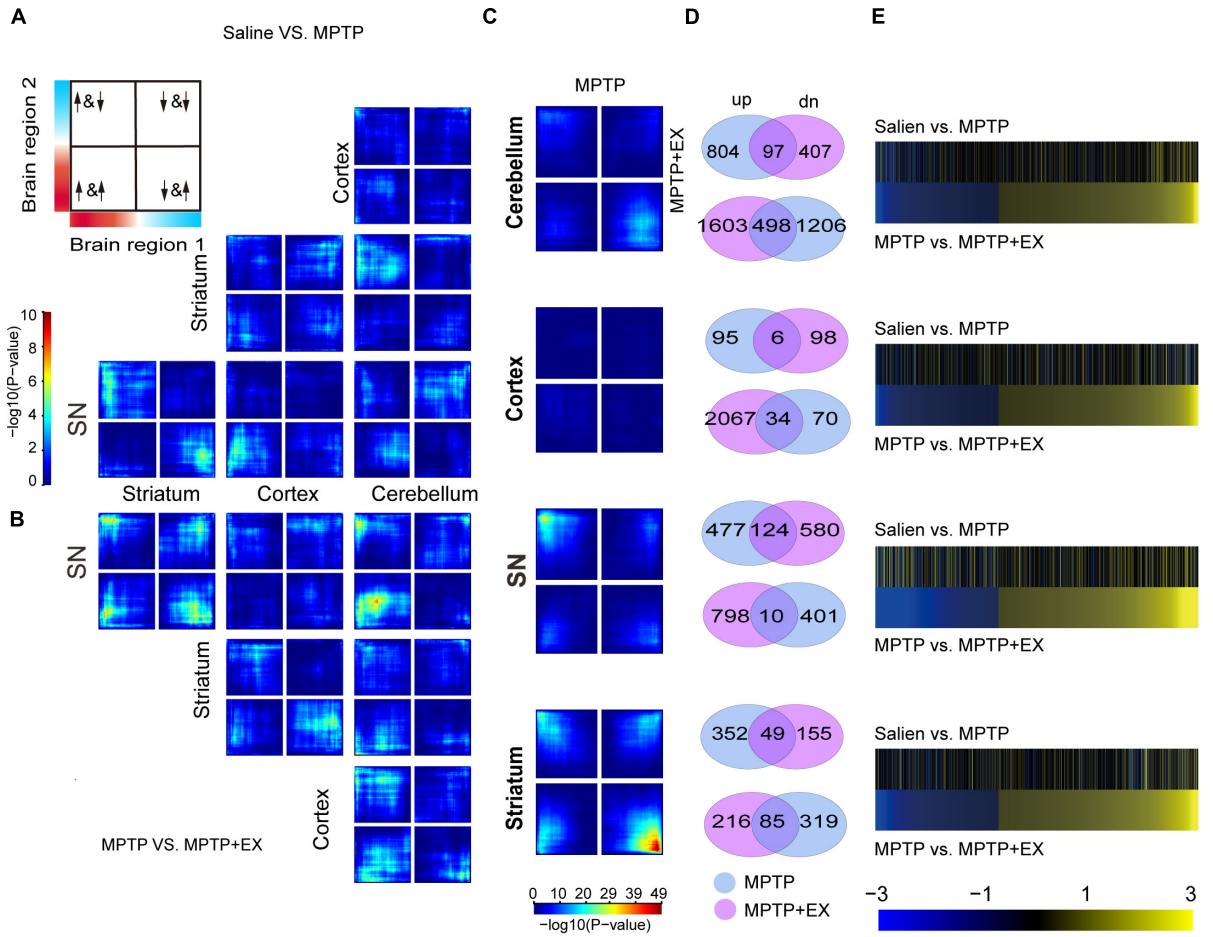


FIGURE 2 | Inter-regional expression patterns reveals PD- and exercise-specific co-upregulation signatures. **(A,B)** RRHO maps comparing differential expression between 2 brain regions in PD mice [saline vs. MPTP, **(A)**] and exercised PD mice [MPTP vs. MPTP + EX, **(B)**]. The upper left in Panel A displays the overlap relationship across brain regions, and signals in the bottom left quarter show the genes overlap in common. The color bar spanning in Panel A represents *p*-values. **(C)** RRHO maps comparing differential expression between PD (saline vs. MPTP) and exercised PD mice (MPTP vs. MPTP + EX). **(D)** Venn diagrams display the overlap genes in MPTP and MPTP + EX in 4 brain regions. **(E)** Heat maps compare transcriptional changes [log(FC)] in PD to exercised PD mice across brain regions. For each brain region, the top pair of heat maps represents directionality of changes in PD mice for genes expressed in PD mice, while the bottom pair of heat maps represents directionality of changes for genes expressed in exercised PD mice.

and MEred showed a positive correlation with exercise rehabilitation in the striatum (**Figure 4A**). Furthermore, our hub gene analysis exhibited the top 10 hub genes in the black model comprised of Fat, Skor2, Ltbp2, Crtam, Nrep, Lltifb, Krt25, Mybpc3, Pkp3, and Slc5a1. Most of these hub genes in this module encode cell adhesion and cell proliferation factors (**Figure 4B**). The Fat gene-encoded protein most likely functions, such as cell adhesion molecule, controlling cell proliferation, and playing an essential role in cerebellum development. The top 10 highly connected hub genes for the red model included K1, F5, Aqp1, Folr1, Tmprss11a, Krt8, Kcne2, Olfr1507 Slc4a5, and Wdr86, which were associated with synaptic vesicle transport (**Figure 4C**). These analyses further indicated improved synaptogenesis in the striatum after exercise in the PD model, which is deeply associated with behavior improvement.

Exercise Increased TH$^+$ Fibers and Synapses Obviously in the Striatal Region but Failed to Increase DA Neurons in the SN of Parkinson's Disease Model

The previous results demonstrated an improvement in locomotor performance after exercise intervention in the PD model. Our results showed up-regulation of synapse-related genes and pathways in the striatal region after the motor intervention and an improvement in the microenvironment in SN. These suggested an improved state of DA neurons and increased number of related synapses. To further test our hypothesis, we performed TH staining in four brain regions. As seen in **Figures 5A,B**, immunofluorescence processing of SN sections showed a 70% decrease of TH positive neurons after MPTP

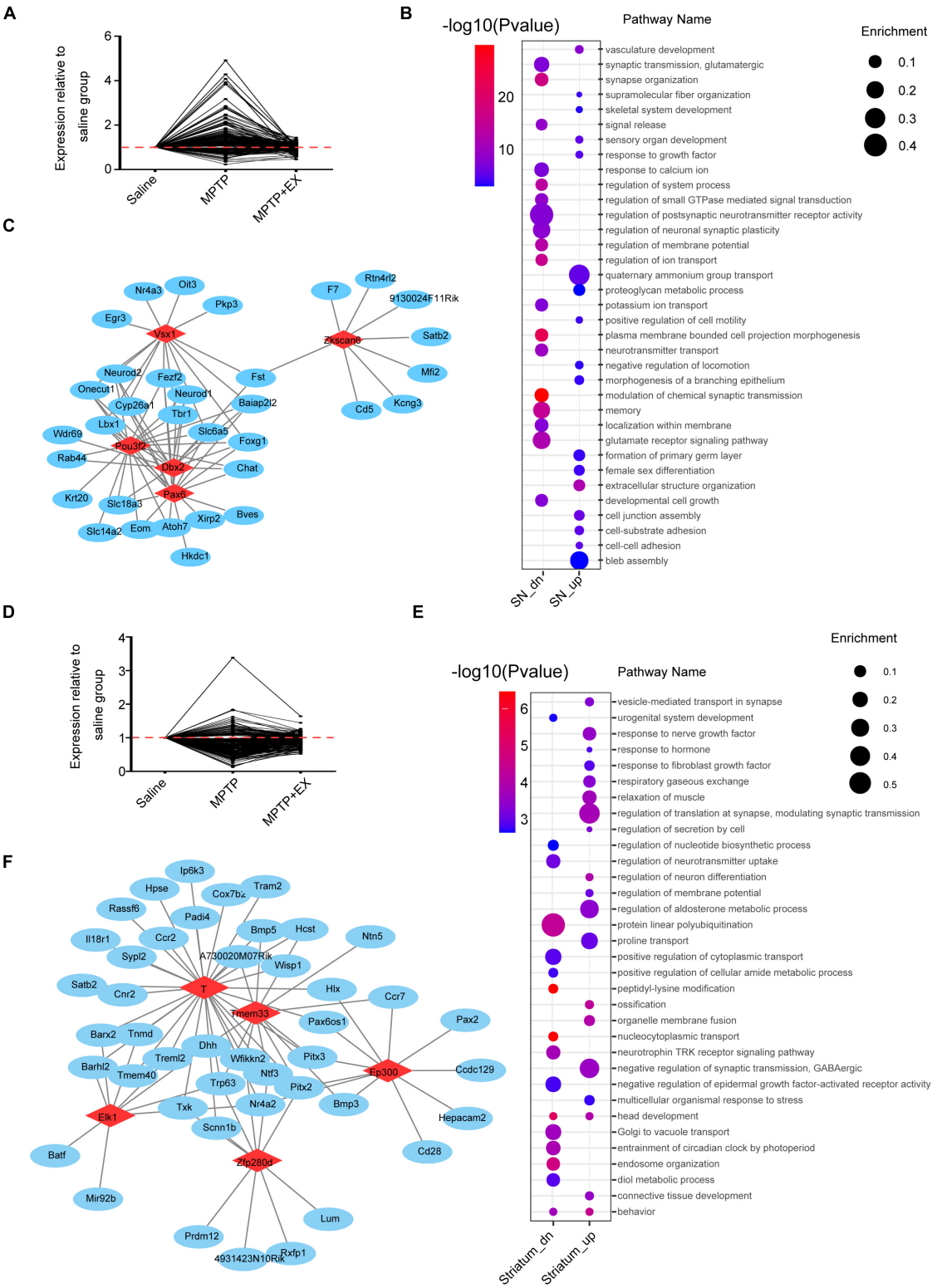


FIGURE 3 | Remarkably different genes among the individual region. **(A)** Genes upregulated in the MPTP group (MPTP vs. saline) and downregulated in the MPTP + EX group (MPTP + EX vs. MPTP) in SN (FPKM > 1, $P < 0.05$). **(B)** Representative pathways enriched in SN (Enrichment: the ratio of observed gene numbers to expected gene numbers). **(C)** Transcription factor analysis in SN. Red nodes resemble transcriptional factors (TFs) and blue nodes are corresponding promoters, demonstrating a transcriptional regulation between TFs and genes. **(D)** Genes upregulated in the MPTP group (MPTP vs. saline) and downregulated in the MPTP + EX group (MPTP + EX vs. MPTP) in striatum (FPKM > 1, $P < 0.05$). **(E)** Representative pathways enriched in striatum. **(F)** Transcription factor analysis in striatum. Red nodes resemble TFs and blue nodes are corresponding promoters, demonstrating a transcriptional regulation between TFs and genes.

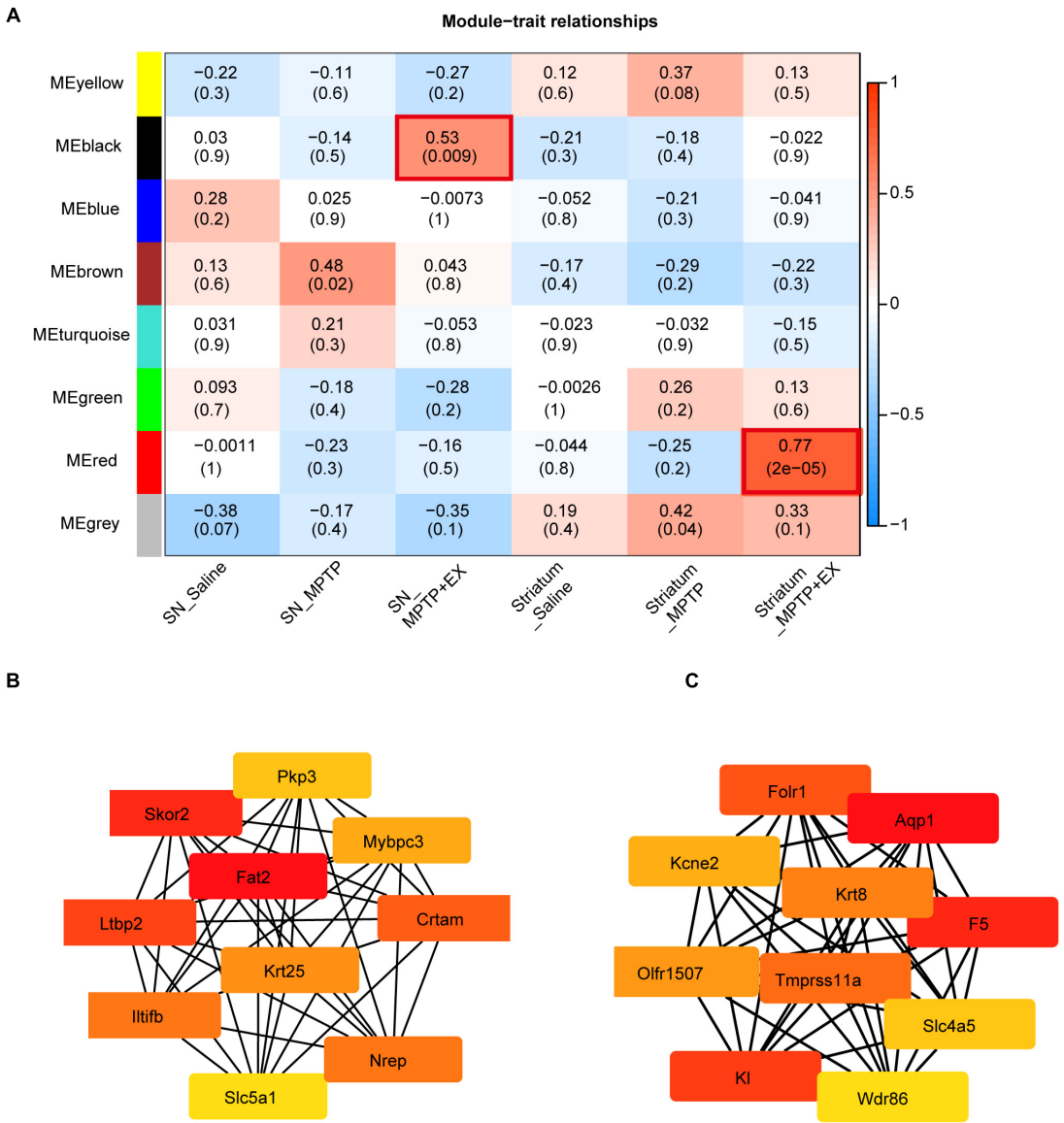


FIGURE 4 | Identification of modules associated with the exercise treatment for PD mice in SN and striatum. **(A)** Heatmap of the correlation between the module eigen genes and exercise treatment of PD. We selected the MEblack-grade block and MEred-grade block for subsequent analysis according to the *p*-value and Pearson's coefficient. **(B,C)** Hub genes analysis in the MEblack-grade block and MEred-grade block (ME: Module Eigen genes).

administration in sedentary and exercise animals compared to the saline group ($P < 0.001$). Results of immunofluorescence also showed that while there was a hint of recovery of TH^+ cells in the SN after exercise, it was not statistically significant (**Figure 5B**). Fluorescence intensity in striatal areas showed an enhancement after the exercise intervention, but no corresponding change was detected in the motor cortex or cerebellum (**Figure 5A**). To further test our hypothesis that the increased fluorescence intensity in the striatal region resulted from the improved synaptic condition of DA nerve fibers, we performed TH^+ fiber (green) and synaptic marker staining in the dorsolateral striatal. The staining and statistical results showed that the synapses recovered to half of the control group after the exercise intervention (**Figures 5C,D**).

DISCUSSION

In this study, molecular network models were developed to extend the understanding of transcriptional mechanisms of exercise for PD. The whole transcriptome in 4 interconnected brain regions related to PD and locomotor activity was detected by performing a co-expression network analysis. Initial results suggested the crucial role of SN and striatum in exercise for PD mice, rather than cortex

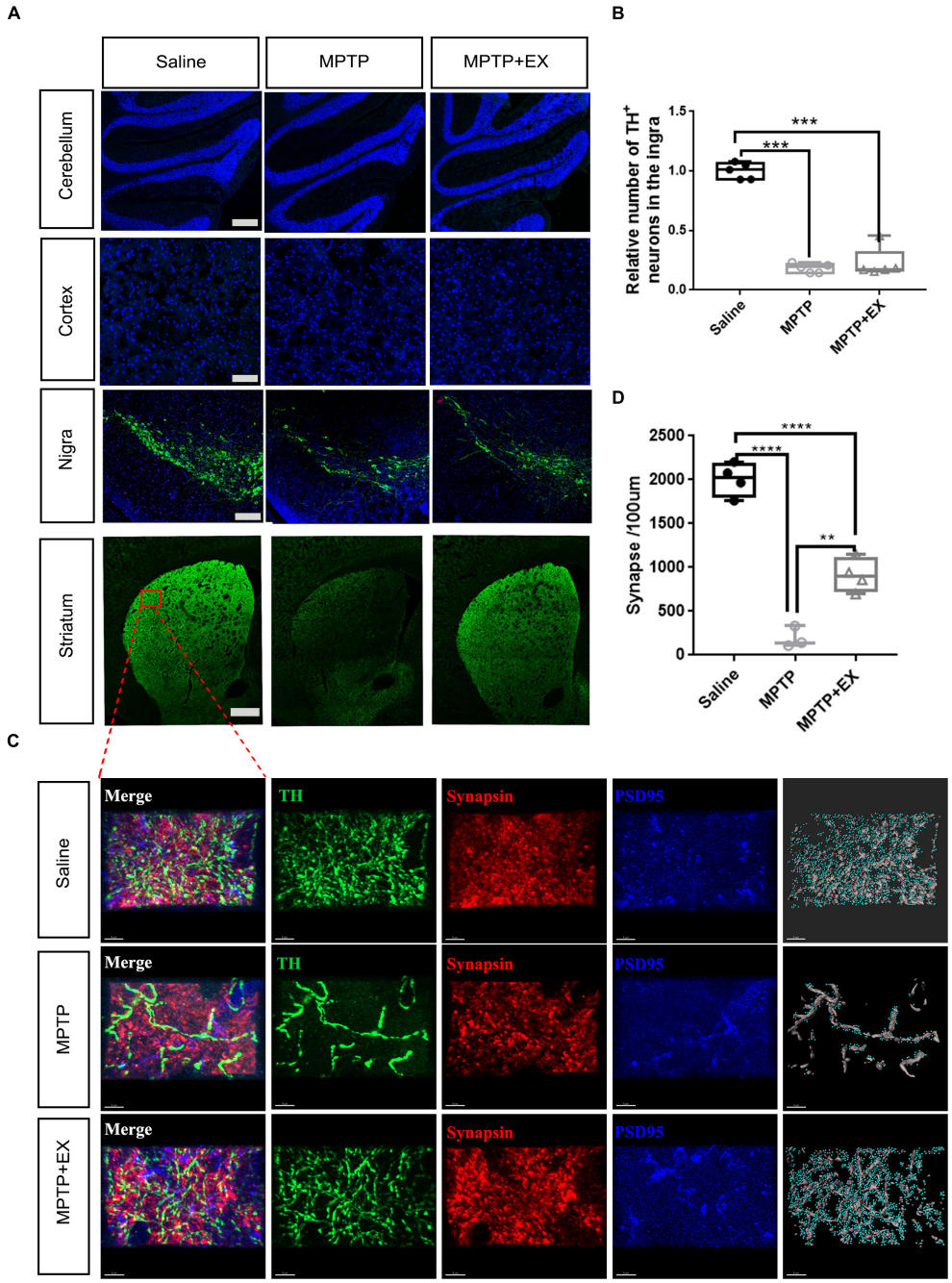


FIGURE 5 | Immunohistochemical staining experiments validate synaptogenesis involved in exercise-induced PD recovery. **(A)** TH^+ staining in the cerebellum (scale bar, 200 μm), cortex (scale bar, 200 μm), SN (scale bar, 200 μm), and striatum (scale bar, 500 μm). **(B)** Relative number of TH^+ cells in the SN for Saline, MPTP, and MPTP + EX groups (n = 5 per group). **(C)** Immunohistochemical staining of TH^+ fibers (green) stained with synaptic markers in striatum (scale bar, 5 μm). Presynaptic terminals and postsynaptic structures were stained by synapsin (Syn, red) and postsynaptic density protein 95 (PSD95, blue), respectively. Synapses were identified by the close proximity of pre- and postsynaptic elements (< 1 μm). A 3D construction of PSD-95 and presynaptic synapsin was performed with "create spots" algorithm in Imaris (scale bar, 5 μm). **(D)** Quantitation of synapses in the striatum for saline, MPTP, and MPTP + EX groups (n = 3–5 per group). Data are mean ± s.e.m. Statistical analysis was performed using one-way ANOVA followed by Tukey's *post hoc* test; $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

and cerebellum. Pathways analysis reveals up-regulation in synapse-related pathways in SN and up-regulation of synaptogenesis in the striatum, which was further confirmed by immunofluorescence in striatum.

Previous clinical and animal studies of mechanisms in PD and exercised PD mice have focused on individual candidate genes, or one single brain region in isolation. For example, MRI observed that the caudate nucleus and putamen in the striatum

were significantly atrophic and PD (Barbagallo et al., 2016). Impaired higher cortical function was found in patients with PD and FMRI showed enhanced connectivity in the M1 region of the motor cortex after an 8-week exercise treatment in patients (Messa et al., 2019). Moreover, decreased dopamine receptors D1 and D3 in the cerebellum was found in patients with PD (Yang et al., 2021). RRHO and WGCNA have been previously applied to generate insight into other diseases. Although those observations disclosed some key molecules involved in the PD pathophysiology, they did not exhibit enough evidence in circuitry dysfunction, which was also considered a critical characteristic for subjects with PD (Petersson et al., 2019, 2020). Here, we successfully identify novel transcriptional networks associated with exercised PD mice by RRHO and WGCNA. We found a similarity of transcriptional regulation between SN and striatum in PD with the exercise group. The interaction between those two brain regions probably arose from the nigrostriatal pathway, in which the loss of dopaminergic neurons was considered as the hallmark of PD. For example, acute α-synuclein preformed fibrils (PFFs) spreading along nigrostriatal path impaired neurotransmission and microglial reactivity in adult mice (Sun et al., 2022). Lahiri and Bevan presented direct evidence that stimulating nigrostriatal dopamine axons persistently enhances the intrinsic excitability of direct pathway striatal neurons (Lahiri and Bevan, 2020). Moreover, several studies implied that physical exercises reduce motor deficits in Parkinson's disease through rescuing lesions in nigrostriatal dopamine (DA) system (Toy et al., 2014; Hou et al., 2017; Shi et al., 2017). Our results are consistent with those observations, which suggest a fundamental role of nigrostriatal pathway in regulating motor symptoms in PD.

Results from pathway analysis showed that, in the SN, exercise suppress oxidative stress and apoptotic pathways, whereas it upregulates memory, axon guidance, and synapse assembly pathways, which promote neuronal growth, development, and inhibit inflammation (Hirsch and Hunot, 2009). In the striatum, neurotrophic factor response pathways, neurogenesis, synaptogenesis, and transmitter transport-related pathway were up-regulated after exercise. The enrichment of those molecules would improve the microenvironment of the SN and facilitate the synapse formation in the striatum, according to previously published literature (Petzinger et al., 2013; Mak et al., 2017). WGCNA analysis further conformed to the association between exercised phenotype and pathways, and further screened for critical modules and hub genes. Some of hub genes shown in **Figures 4B,C** have been reported in previous studies of PD: Krt25 is implicated in motor coordination (Zhang et al., 2018); Aqp1, encoding astrocytic water channel proteins aquaporin 1 (AQP1) might profoundly affect α-syn deposition in the neocortex of patients with PD (Hoshi et al., 2017); FolR1 is selectively expressed in the surface of midbrain DA progenitors and its level may represent the condition of TH positive neurons (Gennet et al., 2016). Comprehensively considering their functions, we proposed that the hub genes manipulate behavioral susceptibility by driving synaptogenesis, neuronal network formation, and improving microenvironment in the nigrostriatal system after exercise. From the results, we suspected that the generation of compensatory neuron adaptations is most likely to occur by exercise for PD mice.

In immunofluorescence assay, we found exercise restored the synaptic density in the striatum of MPTP-treated animals, although the loss of TH positive neurons was not affected (**Figure 5**). This observation not only validated the key molecular pathways obtained from WGCNA, but also demonstrated a reconstruction of neural circuits in striatum during the physical exercise. Recent studies have identified axonal dysfunction in the SN as a typical feature for PD (Sanchez-Catasus et al., 2021; Wang et al., 2022). The synapse regeneration in striatum after exercise in the present study also represents the recovery of nigrostriatal pathway. Nevertheless, the underlying mechanism of reconstructing nigrostriatal neural circuits after exercise has not been known yet. Although inhibition of SN microglia activation has been proposed to play a role (Wang et al., 2022), further investigations are still needed to achieve comprehensive conclusions and to develop effective anti-PD strategy.

In the present study, mice were treated with high-intensity aerobic training; thus the outcome of exercise intervention in patients with PD may also be deeply associated with practice intensity. In addition, changes in those four brain regions would not cover all exercise-induced effects for PD. Other regions, such as pedunculopontine nucleus (PPN), controlling the gait initiation, modulation, and other stereotyped movements might be also involved. Previous animal studies have shown the degeneration of PPN neurons may trigger the impairment of locomotor and postural disturbances in PD (Gai et al., 1991; Masini and Kiehn, 2022), and "bursting" glutamatergic PPNd neurons are related to the initiation of programmed movements while non-bursting cholinergic PPNc neurons are related to the maintenance of steady-state locomotion (French and Muthusamy, 2018). As gait performance and mobility of PD patients can be improved after physical training (Mak et al., 2017). Therefore, PPN may act as another target region of the brain for exercise-induced rehabilitation in PD, and studies upon molecular mechanisms in PPN are promising. Last but not least, cell-type-specific alterations in transcriptome profile should also play a role in PD progress or rehabilitation (Smajiæ et al., 2021), but those were not investigated in this research. Further studies utilizing single cell RNA sequencing in brains can be performed to further elucidate the mechanism in PD rehabilitation after physical exercise.

CONCLUSION

This study provides a powerful example of four brain regions in PD and exercised PD mice by integrating large-scale transcriptomic data. We provided evidence that exercise contributes to the recovery of motor deficits in PD, probably *via* modulating connections between the SN and striatum. Pathways in neurogenesis, synaptogenesis, transmitter transport, axon guidance, and synapse assembly are critical for exercise-induced benefits.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in Gene Expression Omnibus (GEO), GSE205907.

ETHICS STATEMENT

The animal study was reviewed and approved by Tongji Hospital, School of Medicine, Tongji University, Shanghai, China.

AUTHOR CONTRIBUTIONS

WT and HY made the PD mouse model. WT, YH, and QG trained the mice. WT and KZ analyzed the RNA-sequence data. WT and LL performed behavioral tests. WT, JZ, and YS conducted immunofluorescence. YES, SL, and LJ designed the experiments and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.891644/full#supplementary-material

Supplementary Figure 1 | Heatmaps of differentially expressed genes (DEGs) in cerebellum **(A)**, cortex **(B)**, SN **(C)**, and striatum **(D)**. The color bar represents $\log_2$ (FPKM).

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Traditional Chinese Exercise for Neurodegenerative Diseases: A Bibliometric and Visualized Analysis With Future Directions

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Jiang B, Feng C, Hu H, George D, Huang T and Li Z (2022) Traditional Chinese Exercise for Neurodegenerative Diseases: A Bibliometric and Visualized Analysis With Future Directions. Front. Aging Neurosci. 14:932924. doi: 10.3389/fnagi.2022.932924

Background: Traditional Chinese Exercise (TCE) has expanded out of China into the world and is frequently used in the prevention and treatment of many diseases. Although many studies have explored the ability of TCE as an intervention for neurodegenerative diseases, there are limited articles summarizing the research. The aim of this study was to investigate current research trends around TCE for neurodegenerative diseases and predict future directions for such research.

Materials and Methods: Data was collected from the Web of Science Core Collection (WoSCC). All articles and reviews on TCE in relation to neurodegenerative diseases were retrieved. The data analysis was performed using the CiteSpace (5.8R3) software, and the results were displayed in network maps.

Results: The search identified 220 publications between 1999 and 2021. The United States was the most productive country (n = 89), followed by China (n = 68). The United States had the greatest centrality, indicating its tremendous global influence and close collaborations with other countries. Fuzhong Li from the Oregon Research Institute, United States, was not only the most prolific author (n = 5), but also the most co-cited author (n = 120). The Shanghai University of Sport contributed to the most publications (n = 12). *PLOS ONE* was the most published journal, while *Movement Disorders* was the most cited journal. Tai Chi, Parkinson's disease, quality of life, balance, and older adult were the most high-frequency keywords, while Alzheimer's disease had the highest centrality.

Conclusion: The number of publications on TCE related to neurodegenerative diseases has shown major growth in the past decade. However, there is a need for research institutions to strengthen cooperation between countries and institutions. Tai Chi,

Parkinson's disease (PD), Alzheimer's disease, older adults and falls reduction have been the recent research focus. It is anticipated that in the future, PD will continue to be a central focus with the effects of Baduanjin, Wuqinxi, and Yijinjing requiring further research.

Keywords: Traditional Chinese Exercises, neurodegenerative diseases, bibliometric analysis, visualization, scientometric analysis, Tai Chi, Parkinson's disease

INTRODUCTION

Neurodegenerative disorders are characterized by the progressive degeneration or loss of neuronal structure and function in the central nervous system. Common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and motor neurone disease. As the world's aging population is on the rise, the incidence of neurodegenerative diseases is also growing, with about 50 million individuals affected worldwide (Ehrenberg et al., 2020). Many neurodegenerative diseases still lack effective treatments today, which can ultimately result in the physical and functional disabilities of the patients (Fari et al., 2021). It is of great value to explore potential treatments for neurodegenerative diseases, including complementary and alternative therapies such as traditional Chinese medicine and exercise intervention.

Traditional Chinese Exercise (TCE), which originated in China about 3,000 years ago, is increasingly recognized as an integral part of non-pharmacological intervention (Wang et al., 2015; Li et al., 2020). TCEs, including Tai Chi, Qigong, Baduanjin, Yijinjing, and Wuqinxi, are low-medium-intensity exercises that have a strong theoretical basis of traditional Chinese medicine. Characterized by the inter-coordination of body movement, breathing, and meditation, TCEs are mainly in the form of self-cultivation, sometimes with simple tools such as swords and sticks (Song et al., 2020). Therefore, it has very low requirements for equipment and is not limited by location or facility. Growing evidence has demonstrated that TCE is beneficial for improving both physical and mental health (Wang et al., 2015; Guo et al., 2018; Li W. et al., 2021). Under the idea that exercise is medicine (EIM), TCE has been frequently used in medical treatment and prevention of various diseases in Eastern and Western countries (Song et al., 2020). There is also an increasing number of studies reporting that TCE has been used for treating neurodegenerative disease with positive results. For example, a recent randomized controlled experiment reported that Qigong could improve cognitive function in patients with neurodegenerative diseases (Jin et al., 2020). A recent literature review of complementary therapies in PD suggested that TCEs are equally effective at improving motor symptoms of PD compared to other exercise regimens (Deuel and Seeberger, 2020). However, few studies have comprehensively collected global data related to the application of TCEs for neurodegenerative diseases.

Since the work of Garfield in 1987, bibliometric analysis has become a popular quantitative method to analyze the quality and scholarly impact of publications within a certain research field (Garfield, 1987; Rahaman et al., 2021). CiteSpace, which is a java-based information visualization software, was developed by Dr. Chaomei Chen (School of Information Science and Technology, Drexel University, Philadelphia, PA, United States) (Chen, 2004). This software has been widely used for bibliometric analysis and knowledge visualization of scientific literature data. This software allows knowledge network maps, such as cooperation network maps, co-citation network maps, and co-occurrence network maps, to be built. Using these maps, information is readily accessible for readers to intuitively understand the research hotspots and development processes of various knowledge domains (Zhou et al., 2022). In medical research, CiteSpace-based bibliometric analysis has been extensively conducted to allow scientists to explore the structures and dynamics of a certain field during a given period (Maggio et al., 2022), so as to establish its general outline and discovering future research directions (Janmaijaya et al., 2018).

Hitherto, to the best of our knowledge, there has been no published bibliometric analysis work in the field of TCE regarding neurodegenerative diseases. Therefore, in this study, we conducted a bibliometric analysis based on CiteSpace to systematically analyze research themes, hotspots, and new frontiers of the application of TCE in neurodegenerative diseases, offering a valuable approach besides traditional systematic reviews to understand the current research and emerging trends in this field.

MATERIALS AND METHODS

Data Collection and Search Strategy

All data were collected from the Web of Science Core Collection (WoSCC). The three indexes, namely, the Science Citation Index Expanded (SCI-Expanded), the Social Sciences Citation Index (SSCI), and the Emerging Sources Citation Index (ESCI), were selected from the WoSCC as the data source. The search was performed on 17 March 2022. All original research articles and reviews in English were retrieved. The time span was from inception to 31 December 2021. To ensure the breadth of the search scope, we included as many search terms related to Traditional Chinese Exercises or neurodegenerative diseases as possible (**Table 1**). A total of 220 papers were collected and exported in plain text format with full records and references.

TABLE 1 | Summary of literature selection in this study.

Content			
Data source	Web of Science Core Collection		
Time span	Inception-2021		
Languages	English		
Literature types	Article or review		
Search strategy	#1	4099	[TS = (tai-ji OR "Tai Chi" OR "Chi, Tai" OR "Tai Ji Quan" OR "Ji Quan, Tai" OR "Quan, Tai Ji" OR "Taiji" OR "Taijiquan" OR "T'ai Chi" OR "Tai Chi Chuan" OR qigong OR "qi gong" OR "chi gong" OR "ch'i Kung" OR "baduanjin" OR "ba duan jin" OR "wuqinxi" OR "yijinjing" OR "yi jinjing" OR "liuzijue" OR "traditional exercise" OR "Chinese traditional exercise" OR "traditional Chinese exercise" OR "Chinese exercise" OR "mind-body exercise")]
	#2	473263	[TS = ("multiple sclerosis" OR "amyotrophic lateral sclerosis" OR "Parkinson's" OR "Parkinson disease" OR "Alzheimer's" OR "Alzheimer disease" OR "Huntington's" OR "Huntington disease" OR Neurodegenerative)]
	#3	220	#1 AND #2 AND [DT = ("ARTICLE" OR "REVIEW") AND LA = ("ENGLISH")]

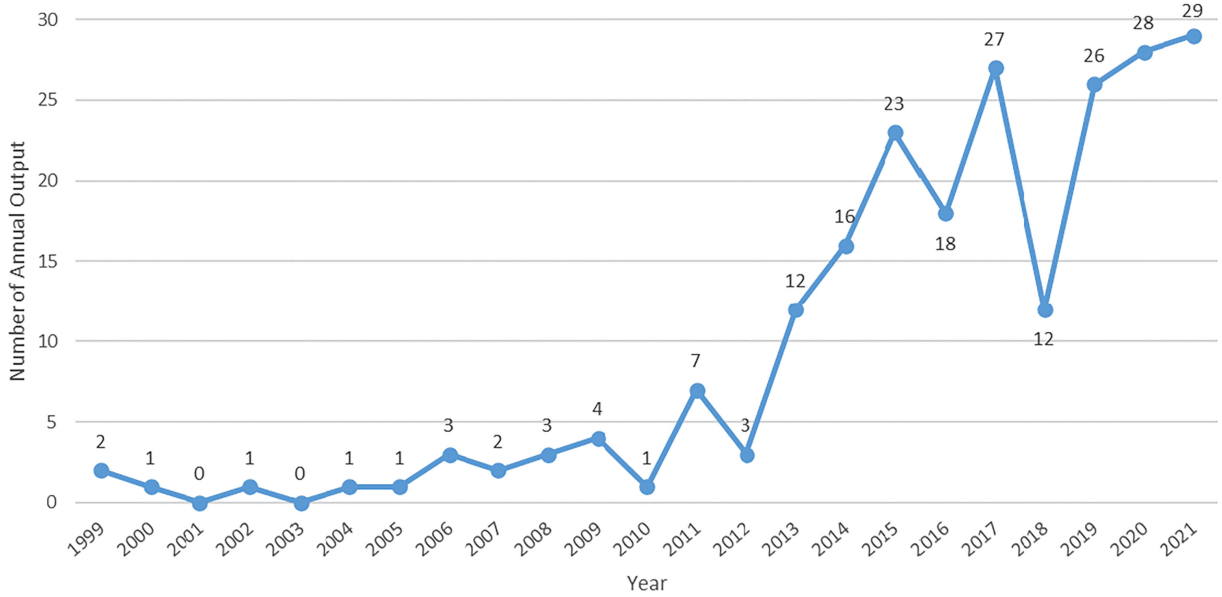


FIGURE 1 | The annual number of publications on TCE for neurodegenerative diseases between 1999 and 2021.

Analysis Tool

All valid data were imported to Microsoft Excel 2019 and CiteSpace (5.8R3) for performing visual analysis. Microsoft Office Excel 2019 was utilized to analyze the trend of the number of articles published by year. CiteSpace was used to visually analyze countries/regions, institutions, authors, journals, cited references, keywords, as well as keywords with strong citation bursts over time. Related CiteSpace visualization knowledge maps, which consist of nodes and links, were drawn. The links represent the cooperation, co-occurrence, and co-citation relationships between two nodes. The nodes represent countries, institutions, authors, journals, and cited references. Nodes with a larger size indicate higher occurrence or citation frequency (Chen et al., 2014). The color of nodes indicates the occurrence or citation years. Centrality is an index for quantitatively evaluating the importance of a node in a network, and a centrality greater than 0.1 is considered significant. The outer purple trim of a node indicates high centrality, and nodes with high centrality are regarded as pivotal points or key points in a specific field (Liang et al., 2018).

RESULTS

Publication Years

A total of 220 papers, including 119 articles and 101 reviews, were obtained, excluding duplicates. As shown in **Figure 1**, the number trend of annual publications related to TCE combined with neurodegenerative diseases showed less growth before 2011, with less than 5 papers published per year on the topic. But this has shown a rapid growth from 2012 to 2015, a fluctuating growth from 2015 to 2021, and was steady at 26 or more papers per year in the last 3 years. These results indicate that this topic has received much more attention in the past decade than previously.

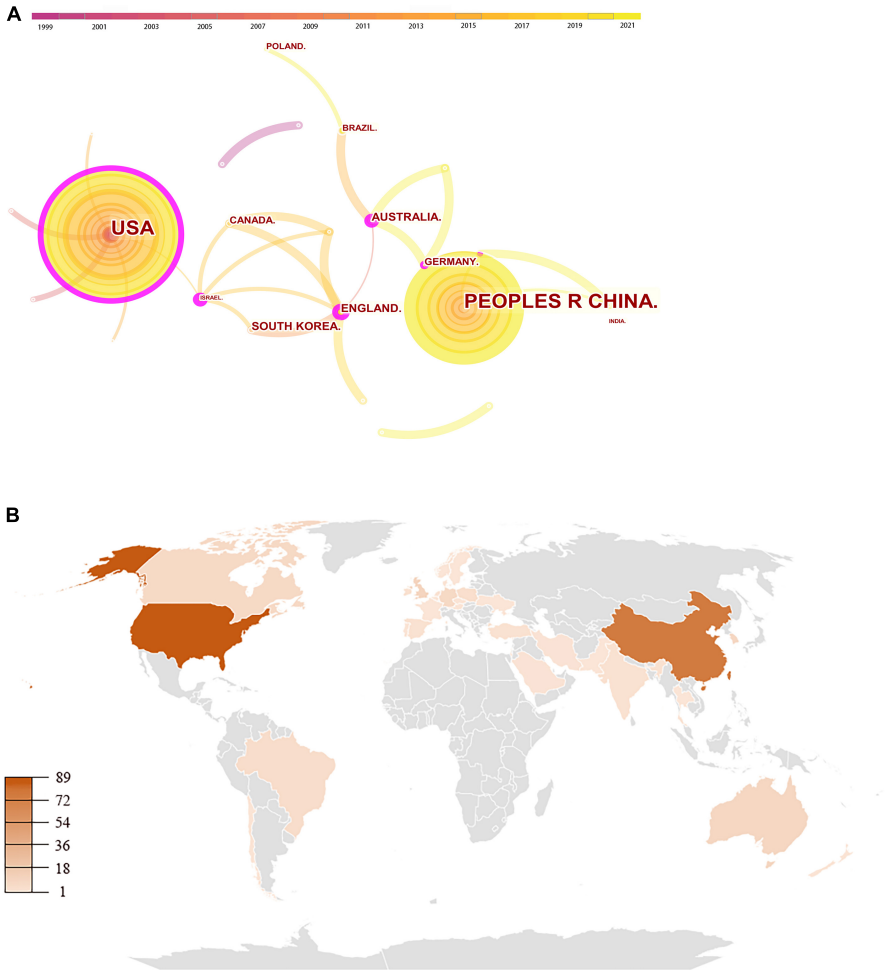


FIGURE 2 | Visualization of countries/regions. **(A)** Collaboration network of countries/regions. The nodes in the map represent countries. The lines between the nodes represent cooperation relationships. The size of the node area shows the number of co-citations. The colors in the nodes represent the years. The purple ring represents centrality. **(B)** World map of publications distributed in various countries/regions.

TABLE 2 | Top 10 countries/regions in terms of publications and centrality.

Rank	Country/Region	Count (%)	Rank	Country/Region	Centrality
1	United States	89 (40.5%)	1	United States	0.33
2	China	68 (30.9%)	2	England	0.25
3	England	11 (5.0%)	3	Israel	0.25
4	Australia	10 (4.5%)	4	Australia	0.19
5	South Korea	9 (4.1%)	5	China	0.08
6	India	9 (4.1%)	6	Brazil	0.06
7	Germany	8 (3.6%)	7	Germany	0.02
8	Canada	8 (3.6%)	8	Netherlands	0.02
9	Brazil	6 (2.7%)	9	South Korea	0
10	Poland	5 (2.3%)	10	India	0

Analysis of Countries/Regions and Institutions

As shown in **Figure 2A**, the country distribution map consists of 37 nodes and 28 links. The top 5 countries/regions with the highest number of papers were the United States, China, England, Australia, and South Korea, while the United States, England, Israel, and Australia were the only four countries/regions with a centrality value higher than 0.10 (**Table 2**). A detailed overview is presented as a world map (**Figure 2B**). The United States was the most dominant country in terms of both publication volume and centrality, holding 89 publications and a centrality value of 0.33. Although China came in second in the publication volume with 68 papers, its centrality was merely 0.08, indicating that the global influence of these papers was not proportional to their quantity. The co-institution network map is shown in **Figure 3**, with 262 nodes and 314 links. The top 3 prolific institutions were the Shanghai University of Sport, the Hong Kong Polytechnic University, and the Chinese University of Hong Kong, all of which are in China (**Table 3**). In terms of centrality, the Shanghai University of Sport had the highest centrality value of 0.09. These results illustrate that the United States was the most active and influential research country, while China had the most productive and influential institutes.

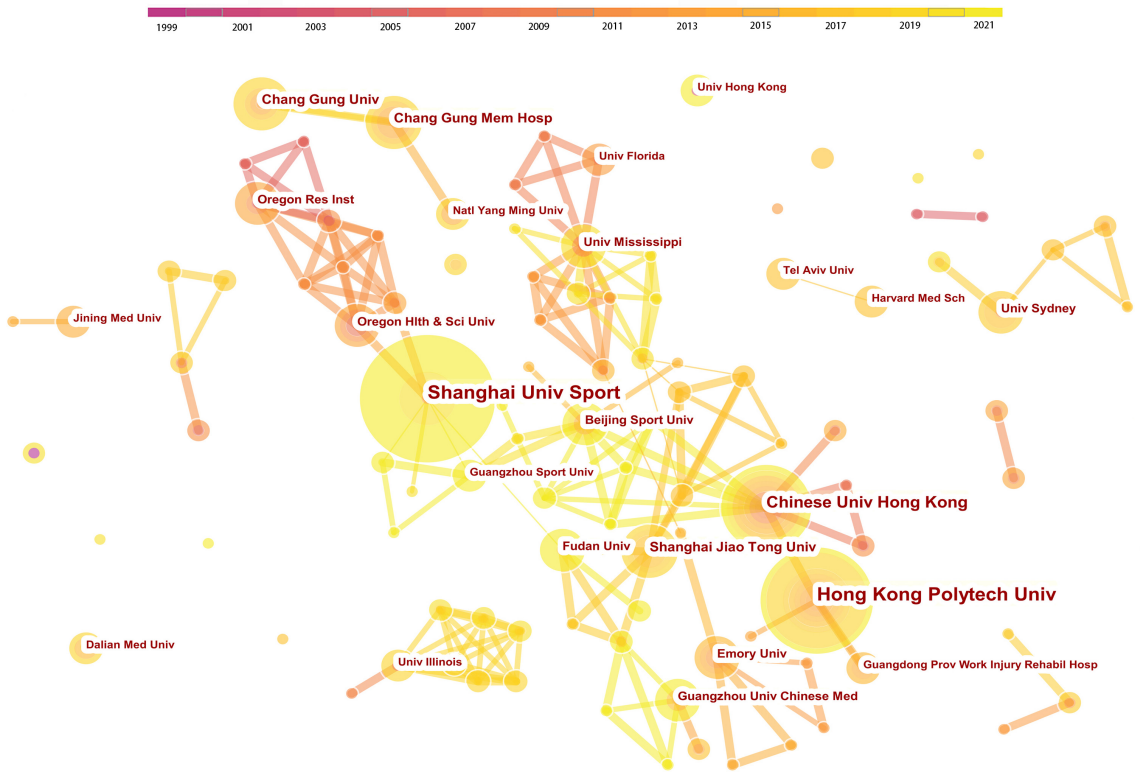


FIGURE 3 | Collaboration network of institutions. The nodes in the map represent institutions, and lines between the nodes represent collaborative relationships. The size of the node area shows the number of co-citations. The colors in the nodes represent the years. The purple ring represents centrality.

TABLE 3 | Top 10 institutions in terms of publications and centrality.

Rank	Institution	Count (%)	Rank	Institution	Centrality
1	Shanghai univ sport	12 (5.5%)	1	Shanghai univ sport	0.09
2	Hong kong polytech univ	10 (4.5%)	2	Fudan univ	0.07
3	Chinese univ hong kong	8 (3.6%)	3	Shanghai jiao tong univ	0.06
4	Shanghai jiao tong univ	5 (2.3%)	4	Indiana univ	0.05
5	Chang gung univ	5 (2.3%)	5	Univ mississippi	0.04
6	Chang gung mem hosp	5 (2.3%)	6	Beijing sport univ	0.04
7	Univ mississippi	4 (1.8%)	7	Guangzhou sport univ	0.04
8	Oregon res inst	4 (1.8%)	8	Chinese univ hong kong	0.02
9	Emory univ	4 (1.8%)	9	Georgia inst technol	0.02
10	Fudan univ	4 (1.8%)	10	Delaware state univ	0.02

Analysis of Authors

The co-authorship and cited authors were analyzed to identify potential partnerships. The co-authorship network (**Figure 4A**) was composed of 350 nodes and 563 links. Among the authors, Fuzhong Li from the United States was the author who had the highest number of papers (n = 5), and this was followed by Zhen Wang (n = 4) from China (**Table 4**). All the other authors had only three or fewer papers each. It is worth noting that none of the authors had a significant centrality, indicating the lack of cooperation among these authors. **Figure 4B** displays the network of cited authors, with 622 nodes and 1,787 links. Fuzhong Li from the United States had the highest citation counts (n = 120), followed by Madeleine E Hackney (n = 85) from the United States and Natalie E Allen (n = 46) from Australia (**Table 4**).

Analysis of Journals

The 220 papers were published in 136 journals. The 10 most productive journals published 59 papers, accounting for 26.8% of the total number of papers identified (**Table 5**). *PLOS ONE* was the most productive journal with 10 papers published, which was followed by *Evidence-Based Complementary and Alternative Medicine* with 8 publications. Among the 10 journals, *Movement Disorders* was the journal with the highest impact factor (IF),

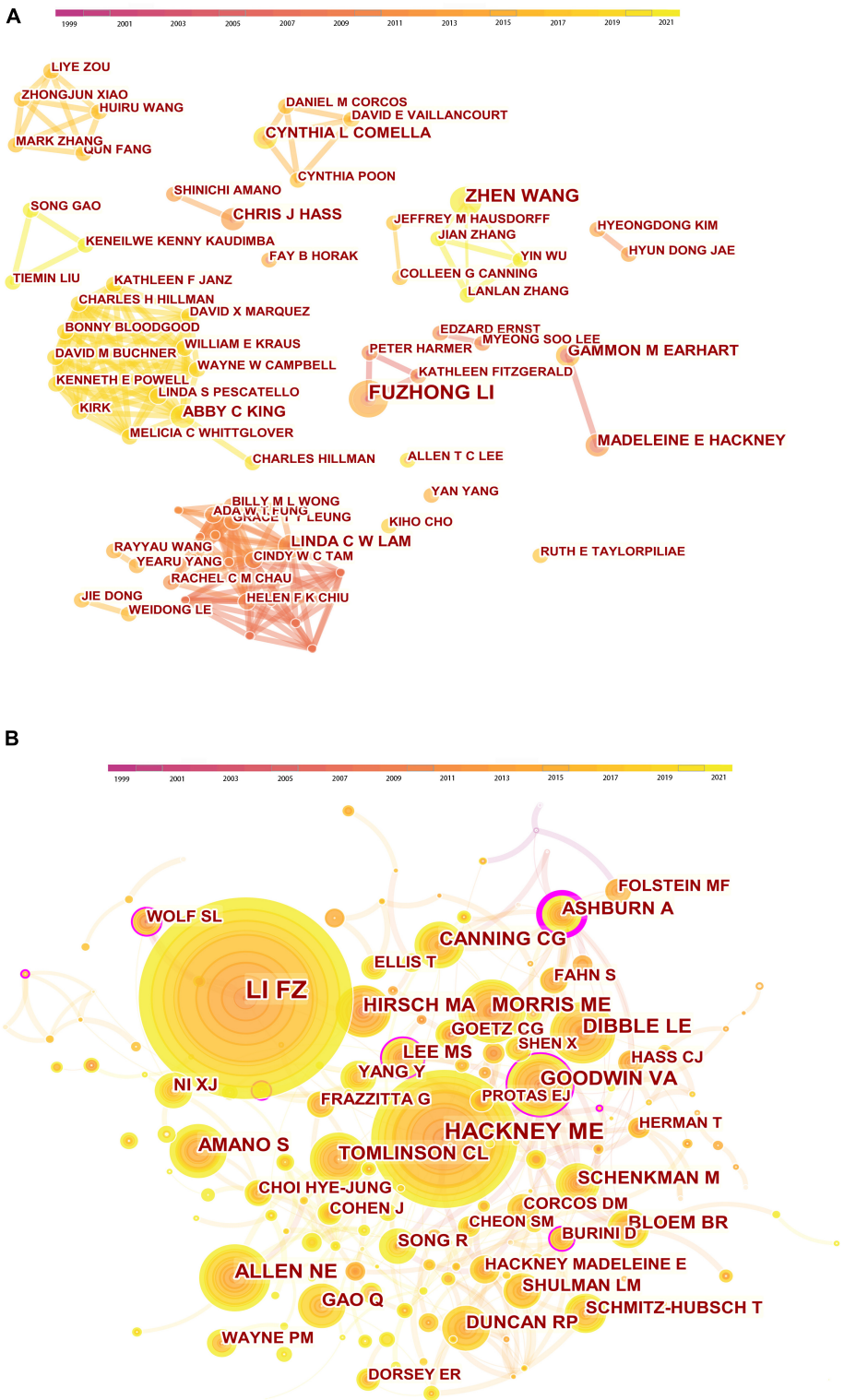


FIGURE 4 | Visual analysis of authors. **(A)** Collaboration network of co-authors. The nodes in the map represent authors, and lines between the nodes represent the collaborative relationships. The colors in the nodes represent the years. **(B)** Network visualization map of cited authors. The nodes in the map represent co-cited authors, and lines between the nodes represent co-citation relationships. The colors in the nodes represent the years. The purple ring represents centrality.

with an IF of 10.338. Besides, the analysis of journal co-citation was also performed to uncover the interdependence and cross-relationship between journals. The top-ranked journal by citation counts was *Movement Disorders* with 140 citations, followed by *Archives of Physical Medicine and Rehabilitation* (138 citations) and *Neurology* (129 citations). Among the 10 top-cited journals, *New England Journal of Medicine* had the highest IF of 91.253.

Analysis of References

Table 6 demonstrates the top 5 most co-cited references. These references could be considered as the most popular papers in this field. The top co-cited reference was published in *New England Journal of Medicine*, which is the leading journal in clinical medicine, and was authored by Fuzhong Li et al. This study revealed that Tai Chi improved balance impairments and reduced falls in patients with PD. The second co-cited reference was published by Qiang Gao et al., which also found that Tai Chi exercise could improve the balance and decrease the fall risks in patients with PD. The third co-cited reference was published by Shinichi Amano et al., which suggested the use of short-term Tai Chi exercise for persons with PD should not be considered an effective means to improve dynamic postural control during gait initiation and gait performance.

Analysis of Keywords

The keywords with a high frequency represent hot topics, while the keywords with a high centrality reflect the influence of corresponding research content in a research field. The keywords co-occurrence is illustrated in **Figure 5**, which consists of 366 nodes and 1,086 links. **Table 7** demonstrates that the top 10 high-frequency keywords on this topic were Tai Chi, Parkinson's disease, quality of life, balance, older adult, randomized controlled trial, gait, physical activity, individual, and fall. The top 10 high-centrality keywords were Alzheimer's disease, balance, dementia, risk factor, aerobic exercise, gait, Tai Chi, cognitive function, basal ganglia, and older adult.

A citation burst refers to the increasing frequency in citation within a certain time interval, which can reflect the development of cutting-edge research topics (Chen et al., 2012). The burst detection in CiteSpace is based on Kleinberg's algorithm (Kleinberg, 2003). **Figure 6** shows the top 25 keywords with the strongest citation burst from 1999 to 2021. The red line indicates the time period of the keyword burst, while the blue line represents the time interval. The keyword "non-motor symptom," which appeared in 2020, was the keyword with the strongest citation bursts. There were seven burst keywords (i.e., validity, non-motor symptom, motor, yoga, validation, scale, and Parkinson's disease), which continued to 2021.

DISCUSSION

General Information

In this study, a total of 220 publications were acquired from the Web of Science Core Collection, from inception to 31 December 2021, most of which were published after 2012. The relatively small number of studies before 2010 suggests that the research was still in its infancy. The significant overall growth in the year of 2010 indicated the increasing attention in the international arena on TCE for treating neurodegenerative diseases. Another bibliometric study of TCE regarding improving cognitive function (Li W. et al., 2021) also found a significant growth trend in annual publications since 2012, indicating that TCE has indeed experienced a period of rapid development in the last decade. The major growth in publications regarding TCE provided strong support for TCE to expand out of China and go international. From 2019 to 2021, the annual number of papers increased steadily and slightly. It can be inferred that there will still be a relatively large number of publications in this field published in the coming years.

Analyzing the literature sources, 37 countries/regions published 220 papers. Many Western developed countries, such as the United States, England, Australia, and Germany, ranked high in the number of papers. This reflects the popularity and wide interest of TCE in the management of neurodegenerative diseases in the Western world. The United States was the most influential country in this field, which ranked first in terms of the publication volume and centrality. This is likely due to the fact that the United States is the world's largest economy. Moreover, some outstanding experts in this field, such as Fuzhong Li, were based in the United States. Although TCE originated and flourished in China, in this study, China held a non-significant centrality with fewer papers than the United States. This may be related to the fact that many Chinese scholars like to publish non-English articles. Besides, there were 37 countries/regions and 28 links in the cooperation network of countries/regions (**Figure 2A**), indicating the lack of international communication. Therefore, more attention should be paid to the cooperation between countries to improve the development of this field. The analysis of institutions showed that some institutions in China, led by Shanghai University of Sport, had taken the lead in global research on this topic. These sterling research institutions are the key in improving the academic influence of China in this field.

From the perspective of authors, Fuzhong Li from the Oregon Research Institute in the United States was both the most prolific author and the most cited author. Li has been engaged in examining the effects of exercise, including Tai Chi, on balance, physical functioning, and the risks of falls for over two decades. The top 5 prolific authors and the top 5 cited authors are mainly from the United States, indicating the strong academic influence and great contributions of American researchers in this field. Through a network of co-authors, the cooperative relationships between scholars are distributed in a decentralized manner, suggesting that most authors prefer to cooperate with authors in a certain circle, especially from the same institution. This may partly explain why the topmost prolific authors had a non-significant centrality. Therefore, strengthening cooperation among authors from different institutions or countries should be encouraged.

In the analysis of journals, the most prolific journal was *PLOS ONE*, while the most cited journal was *Movement Disorders*. Among the top 10 published journals, only the journal *Movement Disorders* held an impact factor (IF) greater than 10.000, while the others had an IF between 2.446 and 4.891. This shows the

TABLE 4 | The top 5 prolific authors and cited authors.

Rank	Author	Country	Count	Centrality	Rank	Cited Author	Country	Count	Centrality
1	Li FZ	United states	5	0.06	1	Li FZ	United states	120	0.06
2	Wang Z	China	4	0.01	2	Hackney ME	United states	85	0.07
3	Earhart GM	United states	3	0.02	3	Allen NE	Australia	46	0.06
4	Hackney ME	United states	3	0.01	4	Morris ME	Australia	45	0.06
5	Lam L	China	3	0.01	5	Dibble LE	United states	43	0.02

TABLE 5 | The top 10 prolific journals and cited journals.

Rank	Journal	Count (%)	IF (2020)	Cited journal	Frequency	IF (2020)
1	PLOS ONE	10 (4.5%)	3.24	Movement disorders	140	10.338
2	Evidence-based complementary and alternative medicine	8 (3.6%)	2.63	Archives of physical medicine and rehabilitation	138	3.966
3	Neurorehabilitation and neural repair	7 (3.2%)	3.919	Neurology	129	9.91
4	Complementary therapies in medicine	5 (2.3%)	2.446	Parkinsonism and related disorders	125	4.891
5	Disability and rehabilitation	5 (2.3%)	3.033	New england journal of medicine	110	91.253
6	International journal of environmental research and public health	5 (2.3%)	3.39	Physical therapy	103	3.021
7	Journal of alternative and complementary medicine	5 (2.3%)	2.582	Journal of neurology neurosurgery and psychiatry	98	10.283
8	Movement disorders	5 (2.3%)	10.338	Journal of the american geriatrics society	97	5.562
9	Parkinsonism and related disorders	5 (2.3%)	4.891	Clinical rehabilitation	95	3.477
10	Archives of physical medicine and rehabilitation	4 (1.9%)	3.966	PLOS ONE	95	3.24

TABLE 6 | The top 5 cited references.

Rank	Title	Cited Frequency	Year	First Author	Journal	IF (2020)
1	Tai chi and postural stability in patients with parkinson's disease	57	2012	Fuzhong Li	New england journal of medicine	91.253
2	Effects of tai chi on balance and fall prevention in parkinson's disease: a randomized controlled trial	25	2014	Qiang Gao	Clinical rehabilitation	3.477
3	The effect of tai chi exercise on gait initiation and gait performance in persons with parkinson's disease	23	2013	Shinichi Amano	Parkinsonism and related disorders	4.891
4	The impact of tai chi and qigong mind-body exercises on motor and non-motor function and quality of life in parkinson's disease: a systematic review and meta-analysis	19	2017	Rhayun Song	Parkinsonism and related disorders	4.891
5	A randomized controlled trial of patient-reported outcomes with tai chi exercise in parkinson's disease	18	2014	Fuzhong Li	Movement disorders	10.338

difficulty in publishing high-impact papers in this field. The top 10 cited journals, however, generally had a greater IF, with the highest IF being 91.253 for *New England Journal of Medicine*. These top cited journals, to a certain extent, reflect the best source in the research field of TCE for neurodegenerative diseases.

According to the analysis of references, the top 5 cited references were all published between 2012 and 2017. All of these five papers had explored Tai Chi or Qigong as an intervention for PD, and four of them were clinical studies while the remaining one was a meta-based systematic review. Their widespread

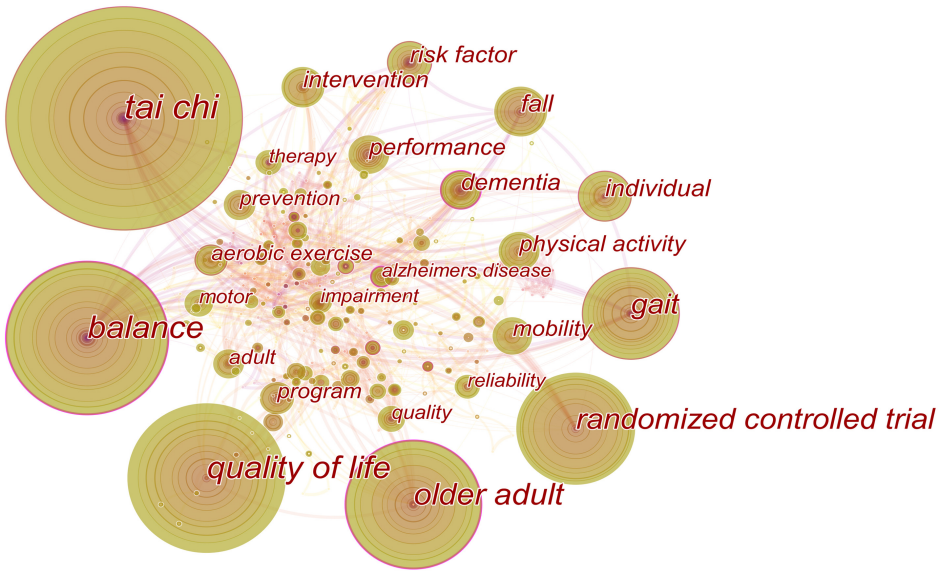


FIGURE 5 | Co-occurring keywords map. The nodes in the map represent keywords. The lines between the nodes represent co-occurrence relationships. The purple ring represents centrality.

TABLE 7 | The top 10 keywords in terms of frequency and centrality.

Rank	Count	Keywords	Rank	Centrality	Keywords
1	132	Tai Chi	1	0.36	Alzheimer's disease
2	91	Parkinson's disease	2	0.32	Balance
3	87	Quality of life	3	0.28	Dementia
4	66	Balance	4	0.22	Risk factor
5	59	Older adult	5	0.21	Aerobic exercise
6	51	Randomized controlled trial	6	0.18	Gait
7	26	Gait	7	0.16	Tai Chi
8	25	Physical activity	8	0.14	Cognitive function
9	21	Individual	9	0.13	Basal ganglia
10	20	Fall	10	0.12	Older adult

citation indicates that they are influences in this field. It is noteworthy that Fuzhong Li, who was also the most prolific and most cited author, held two of the top 5 cited papers. This reflects his high academic influence and significant contributions in this research field.

Hotspots in Traditional Chinese Exercises for Neurodegenerative Diseases

In this study, we used keyword frequency, keyword centrality, and keyword bursts as indicators to reveal the research hotspots of the field. We summarized these research hotspots as (a) Tai Chi, (b) PD, (c) AD, (d) older adults, and (e) falls reduction.

Tai Chi

As a representative type of TCEs, Tai Chi is a form of mind-body exercise with mild-to-moderate intensity, which is already recommended as a regimen of life promotion in China and other countries (Lan et al., 2013). Tai Chi is characterized by slow, smooth, and graceful movements such as body rotation, weight shift, slow strides, and single-leg standing, which challenge postural stability and balance and could improve neuromuscular function (Kuramoto, 2006; Lan et al., 2013). Beneficial effects of Tai Chi on balance control, cognitive function, cognitive-motor coordination, and limb muscle strength in patients affected by neurodegenerative diseases have been well reported, and Tai Chi intervention is more effective when combined with medications (Hong et al., 2000; Lam et al., 2012; Wu et al., 2013; Song et al., 2014). However, controversy still exists on the "dose" of Tai Chi intervention, which includes training methods, frequencies, and durations. The clinical studies in the field largely had small sample sizes, short observation time, and diversity regarding study design and styles of Tai Chi, which made them fail to fully reflect the therapeutic effects of Tai Chi (Gow et al., 2017; Yu et al., 2021). Hence, further randomized controlled clinical trials with a larger sample size and adequate intervention time are still needed to confirm the effects of Tai Chi for neurodegenerative diseases.

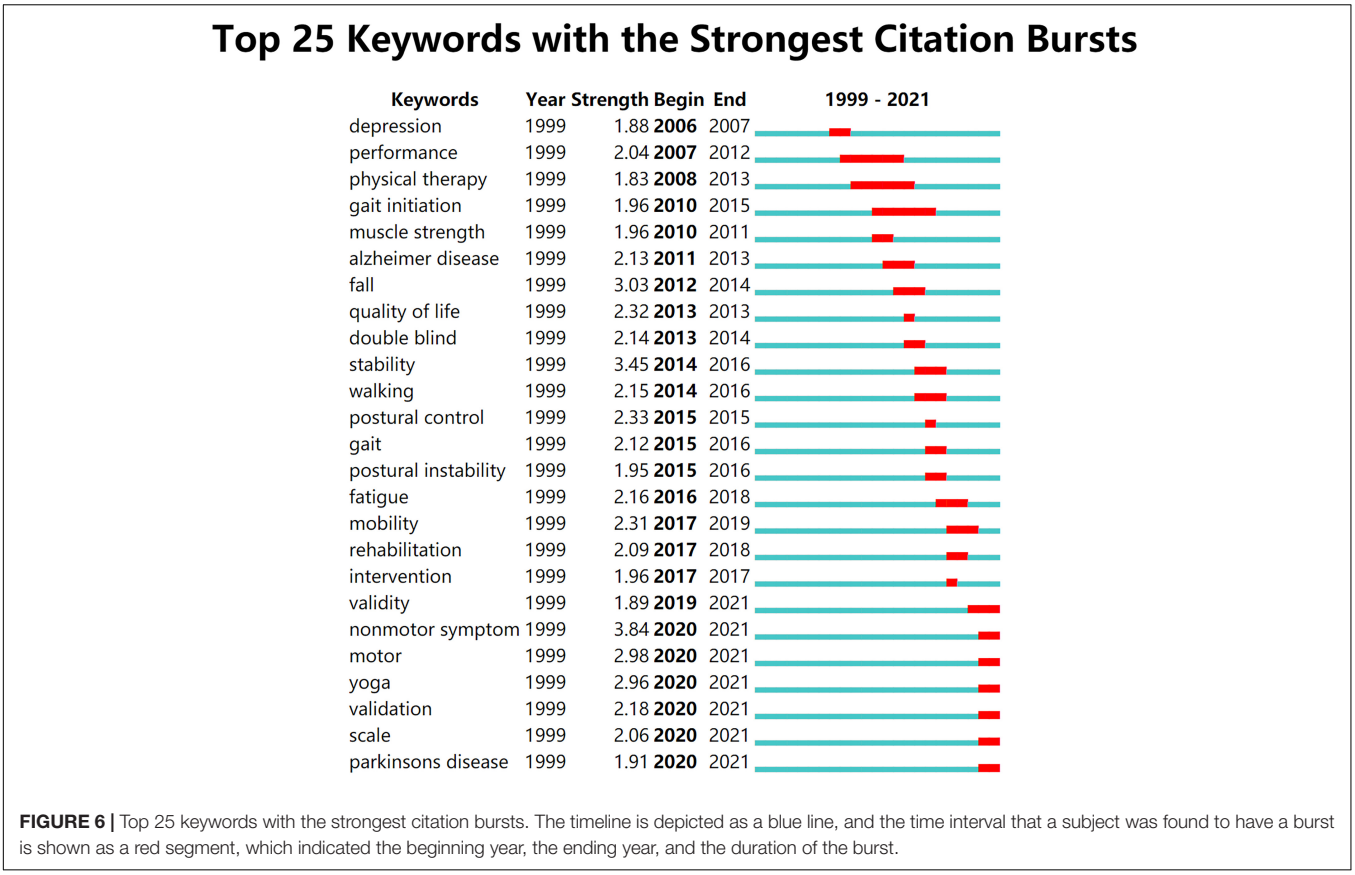


FIGURE 6 | Top 25 keywords with the strongest citation bursts. The timeline is depicted as a blue line, and the time interval that a subject was found to have a burst is shown as a red segment, which indicated the beginning year, the ending year, and the duration of the burst.

Parkinson's Disease

As a kind of movement disorder characterized by basal ganglia degeneration, PD mainly affects middle-aged and elderly adults. Exercise has been considered as a key component in the management of PD and might significantly improve the self-care ability and quality of life in patients with PD (Kedzior and Kaplan, 2019; Klein et al., 2019; Chen et al., 2020). Research has demonstrated that TCE, as complementary and alternative medicine (CAM) therapies, are able to improve motor and non-motor functions in patients with early to middle stage PD (Carvalho et al., 2021; Fogaca et al., 2021; Shen et al., 2021; Wan et al., 2021). For patients with later-stage PD, however, physical exercise intervention might be hard to complete due to the severe rigidity and poor condition of patients.

Alzheimer's Disease

Alzheimer's disease is the predominant form of dementia that mainly occurs in the aged population (Anderson, 2019). The common symptoms of AD include progressive cognitive dysfunction, memory loss, and amnesia. Patients with AD often lose the ability to take care themselves, which imposes a great burden on families, communities, and society. Although no effective treatments can stop or reverse the progression of AD currently, early detection, accurate diagnosis, and early intervention, including TCE are attractive strategies to slow the progression and reduce the burden on public health.

Older Adults

In clinical research on TCE for neurodegenerative disease, study participants were mostly aged 60 years or older. This can be explained by the high prevalence of neurodegenerative diseases among the middle-aged and elderly population and the fact that retired people have more free time to focus on their health than younger ones. As the elderly population continues to grow in developed countries and China, the research on the intervention of age-related chronic diseases has become a hot topic of scientific and technological innovation.

Falls Reduction

Falls are common and even life threatening for patients with neurodegenerative disease. Since most neurodegenerative diseases are progressive and currently have no cure, as the disease worsens and the patients get older, they are prone to have decreased body coordination, slower postural responses, and cognitive decline, which are associated with increased falls risk (Segev-Jacubovski et al., 2011). A previous meta-analysis-based study found that exercise interventions which target balance, gait, and muscle strength increase, such as Tai Chi, can effectively reduce fall rates in older adults (Sherrington et al., 2020).

Future Research Directions

The most popular keywords varied over the years changing from depression, performance, physical therapy to fall, stability,

and finally to validity, non-motor symptom (**Figure 6**). Most of the burst keywords are related to PD, indicating that the research on TCE for PD has been a major trend in the past two decades. Besides, there has been much focus on clinical studies and systematic reviews, but less on basic studies or mechanism research. Based on the high-frequency and high-centrality keywords and the evolution of burst keywords, future research directions in this field could be concluded as follows:

(1) Parkinson's disease is one of the most common neurodegenerative diseases, and patients with PD often manifest "motor" abnormalities like tremors, rigidity, "postural instability," bradykinesia, and freezing, while non-motor symptoms including "fatigue" and "depression" are also prevalent among them. Many clinical trials and meta-analysis reporting TCE used to treat PD have been published in recent years (Cheon et al., 2013; Ni et al., 2014; Li Y. et al., 2021). PD will continue to be a focus of future research.
(2) To date, in the field, an overwhelming majority of research has focused on Tai Chi. Also, only a few neurodegenerative diseases have been researched, especially PD and AD. Future research is likely to explore other TCE, like Baduanjin, Wuqinxi, and Yijinjing. In addition, the effects of TCE in the management of other neurodegenerative diseases such as Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis should also be further studied.

This study still has some limitations. First, dual-map overlay and cluster analysis were not involved in this study. Second, we took the keywords as the topic of a paper to analyze, but some authors might not put important words that were present in the title as "keywords." Thus, it might have the keyword analysis. Third, limitations of the CiteSpace software resulted in only the WoSCC database being searched for articles. Fourth, only articles and reviews were included excluding meeting records, letters, and books. Finally, only publications published in the English language were included; however, TCE likely receives research attention in non-English-speaking East Asian countries. Therefore, a more comprehensive bibliometric study which includes non-English papers and more databases such as China National Knowledge Infrastructure (CNKI) could be conducted in the future to present a broader overview of this field.

CONCLUSION

This bibliometric analysis provides information on the most influential papers, hot spots of previous research, and future directions of the research on Traditional Chinese Exercise (TCE) for neurodegenerative diseases. The number of the publications in this field has shown major growth over the past decade. However, there is a great need for research institutions and authors to strengthen cooperation with researchers in other countries and institutions. Tai Chi, PD, Alzheimer's dementia, older adults, and falls reduction are current research hotspots. Since the concentration of research is only in certain areas such as Tai Chi and PD, it is expected that other kinds of TCE, such as Baduanjin, Wuqinxi, and Yijinjing, may be studied in the future. In addition, the effects of TCE in the management of Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis have also yet to be studied. The findings from this bibliometric study may help researchers identify hot topics and discover new directions for future research in this field.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BJ drafted and revised the manuscript. CF drew all of the pictures. HH drafted the manuscript. DG reviewed and revised the manuscript. TH and ZL contributed to the conception and design of the study. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Efficacy of Traditional Chinese Exercise in Improving Gait and Balance in Cases of Parkinson's Disease: A Systematic Review and Meta-analysis

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Background: The efficacy of traditional Chinese exercise (TCE)-based intervention in the improvement of motor function in patients with Parkinson's disease (PD) is controversial. The present study aimed to assess the effects of TCE on balance and gait outcomes, as well as motor symptoms in individuals with PD, and evaluate potential discrete moderators such as TCE dosage-related variables.

Method: PubMed, Embase, Cochrane's Library, Web of Science, Medline, and Scopus were systematically searched from their dates of inception to February 2022. All studies were randomized controlled trials (RCTs) of TCE-based interventions for PD. The treatment effects were estimated using a random-effect meta-analysis model with standardized mean differences (Hedges' g). The Physiotherapy Evidence Database was used to evaluate the methodological quality of the study.

Result: Fifteen studies involving a total of 873 participants were included in the final analysis. The meta-analytic findings revealed significant improvements in balance outcomes [Berg Balance Scales (BBS) ($g = 0.83$, 95% CI = 0.37–1.29, $p = 0.000$, $I^2 = 84\%$), time up and go (TUG) ($g = -0.80$, 95% CI = −1.13– −0.47, $p = 0.000$, $I^2 = 81\%$), and the one legged blind balance test ($g = 0.49$, 95% CI = 0.13–0.86, $p = 0.01$, $I^2 = 10\%$)], as well as gait outcomes [gait velocity ($g = 0.28$, 95% CI = 0.02–0.54, $p = 0.04$, $I^2 = 64\%$), 6-min walking test (6MWT) ($g = 0.32$, 95% CI 0.01–0.62, $p = 0.04$, $I^2 = 15\%$), stride length ($g = 0.25$, 95% CI = 0.08–0.41, $p = 0.003$, $I^2 = 42\%$)], and motor symptoms [Unified Parkinson's Disease Rating Scale part III (UPDRS-III) ($g = -0.77$, 95% CI = −1.06– −0.48, $p = 0.000$, $I^2 = 76\%$)]. However, cadence ($g = -0.03$) and step length ($g = 0.02$) did not differ significantly. The moderator shows that the effects of TCE on BBS and gait velocity were moderated by Pedro score, exercise type, control group type, and number of sessions. Meta-regression found that TCE (exercise duration, number of sessions, and session duration) was significantly associated with improved UPDRS-III and BBS scores.

Conclusion: These findings provide evidence for the therapeutic benefits of TCE as an adjunct therapy for patients with PD. TEC dosage (high-intensity long sessions) may moderate some favorable effects.

Systematic Review Registration: PROSPERO, identifier CRD42022314686.

Keywords: traditional Chinese exercise, gait, balance, Parkinson's disease, meta-analysis

INTRODUCTION

Parkinson's disease (PD) is characterized by bradykinesia, balance disruption, rigidity, and gait impairment, and is the second most common neurodegenerative disease after Alzheimer's disease (Kalia and Lang, 2015; Abbruzzese et al., 2016). Recent research has revealed that the disease impacted ∼6.1 million people worldwide in 2016, among whom more than 1% of people over 65 years of age were affected. It is expected to affect 13 million people by 2040 (Dorsey et al., 2018; Gomez-Inhiesto et al., 2020). The degradation of the nigrostriatal dopaminergic system is an extremely significant pathogenic alteration in PD (Kordower et al., 2013; Biondetti et al., 2021). There are no disease-modifying treatments for PD, and only dopaminergic replacement therapy combined with medication therapy and deep brain stimulation can improve symptoms (Connolly and Lang, 2014; Curtze et al., 2015). However, gait and balance problems persist in people with PD despite optimum medication, and commonly result in falls with potentially serious repercussions (van der Marck et al., 2014; Swanson and Robinson, 2020; Longhurst et al., 2022).

Experts recommend exercise and physical therapy as effective adjuvants to levodopa therapy since pharmaceutical and surgical management of PD remains inadequate (Fox et al., 2011). Physical activity slows the decline of motor capabilities and extends functional independence in people with PD (Earhart and Falvo, 2013; van der Kolk and King, 2013). The health advantages of alternative traditional Chinese exercise (TCE) such as Tai Chi and Qigong (Baduanjin) are becoming increasingly popular. Tai Chi and Qigong (Baduanjin) currently have the most substantial evidence of efficacy available, particularly in the improvement of muscle strength, aerobic capacity, and postural stability (Field, 2011; Carcelén-Fraile et al., 2021; Yuen et al., 2021). These are low-cost, mild-to-moderate-intensity workouts that emphasize physical–mental link training with slow, gentle, and symmetrical motions, a meditative state, and breathing control that must be linked with gradual body activity (Wang et al., 2015; Song et al., 2017; Zou et al., 2018a,b; Fidan et al., 2019).

According to a large body of research, TCE improves balance and gait function in patients with PD. Zhu et al., for example, found that 3-month Tai Chi training improves motor symptoms, balance, and cognitive function in patients with PD in randomized controlled research (Zhu et al., 2020). Dong et al. discovered that Baduanjin exercise helped to improve balance, gait, and daily activities in patients with PD (Dong et al., 2021). However, several systemic reviews have yielded inconsistent findings on the health advantages of TCE in individuals with PD. For example, a systemic review of five studies found that Tai Chi practice can reduce fall rates and enhance balance and functional mobility in patients with PD compared with no intervention or alternative physical training (Liu et al., 2019). Conversely, a systematic review conducted by Yang et al. revealed that Tai Chi exercise did not significantly affect gait velocity, step length, or gait endurance in patients with PD (Yang et al., 2014).

Furthermore, previous systematic reviews habitually focus on single exercises, which may not reflect TCE's overall health effects accurately. To date, no meta-analyses have been conducted to assess whether various types of TCE (Tai Chi and Qigong) and dosage variables (frequency, exercise duration, and number and duration of sessions) affect TCE-induced balance, gait, and motor symptoms. The effect of variables on the effect size of trials was not assessed using meta-regression analysis. Although some previous systematic reviews had small sample sizes, none of them used Hedges' g statistic to calculate the effect size. These disparate research findings suggest that additional, comprehensive studies are warranted to confirm the effects of TCE on gait and balance outcomes in people with PD.

Therefore, the present study was conducted with the first goal of determining the effects of TCE balance and gait outcomes, along with motor symptoms, in individuals with PD. The second goal was to determine whether any potential moderators (e.g., high and low methodological quality, active and non-active control groups) and a continuous meta-regressor for TCE dosage-related variables (e.g., frequency, exercise duration, and number and duration of sessions) that influenced the intervention effects were present.

METHODS

The meta-analysis adhered to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' criteria (PRISMA) (Moher et al., 2009).

Search Strategy

A two-stage literature search was conducted to locate relevant articles. To start, electronic databases (PubMed, Embase, Cochrane's Library, Web of Science, Medline, and Scopus) were searched from the date of their establishment to February 2022. Second, reference lists of published publications were combed for research not indexed in electronic databases. The following keywords were used: (1) "Tai Chi" OR "Qigong" OR "Baduanqin"

Abbreviations: PD, Parkinson's disease; TCE, traditional Chinese exercise; RCTs, randomized controlled trials; PEDro, Physiotherapy Evidence Database; CI, confidence interval; ES, effect size; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; BBS, Berg Balance Scales; TUG, time up and go; 6MWT, 6-minute walking test.

OR "Wuqinxi" OR "Yijinjing" OR "traditional Chinese exercise; AND (2) "PD"; AND (3) "randomized controlled trials" OR "clinical trial." The **Supplementary Material** contains a complete description of the search approach.

Eligibility Criteria

Studies were included if the following criteria were met: (1) the study was a randomized controlled trial (RCT); (2) the target population was individuals with PD; (3) type of intervention: an experimental group included in the form of TCE [Tai Chi, Qigong (Baduanjin)]; (4) TCE was compared with a control group exposed to any- (active) or no intervention (non-active); (5) balance function, gait parameters, and motor symptoms were evaluated as the outcomes and all included outcome indicators were assessed at the beginning and the end of the intervention; (6) studies written in English. The exclusion criteria were as follows: (1) non-RCT studies; (2) animal studies, case reports, conference abstracts, and letters to the editor; (3) insufficient data or irrelated outcomes; (4) non-English reviews.

Study Selection

Two reviewers (MW and MZ) independently assessed the article's eligibility based on the title and abstract retrieved. The full text was reviewed if the abstract was considered relevant or ambiguous. Any unclear information was obtained *via* an e-mail to the corresponding author. If there was disagreement, an agreement was reached after a third reviewer evaluated the article.

Data Extraction and Quality Assessment

Two reviewers (MW and MZ) assessed the articles and extracted data separately and independently. Details of the retrieved articles are summarized in **Table 1**. Data regarding the study characteristics (first author; year of publication; country; trial design; mean age; sample size; drug regimen during the experimental period; intervention characteristics, including the type of intervention, frequency, and duration; outcome measures and adverse events) of each article were extracted. The passive intervention was defined as the blank control in the control group, whereas the exact total training time in the experimental group was defined as the active intervention. Any conflicts or ambiguities in the reporting methods or results during data extraction were discussed with a third reviewer (WS) and resolved by consensus.

We assessed the methodological quality of each included trial using the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003), which consists of 11 items to evaluate the quality of studies. It scores trials ranging from 0 (low quality) to 10 (high quality), yet, the first item (eligibility criterion) is excluded from the total score as it is required to prove external validity. A score of 6 is considered the cut-off for high-quality trials (Moher et al., 2009). The Cochrane Collaboration's tool (Higgins et al., 2011) was used to assess the risk of bias in each study. This tool covers sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. We divided objects into three categories: "low risk," "high risks," and "unclear risk." Two authors (MW and WS) completed the scoring process, and any differences that arose throughout the evaluation were reviewed by a third reviewer (LT) and resolved by consensus. Each study's scores were unanimously agreed upon and summarized in **Table 2**.

Statistical Analysis

All analyses were conducted using Comprehensive Meta-analysis Version 2.2 software (Biostat Inc., Englewood, NJ, USA). We used an inter-group, pre- to post-intervention, meta-analysis design based on standardized mean differences (Hedges' g). In the total estimated effect sizes (ESs), the random effects model was utilized with a 95% confidence interval (CI) to avoid the high likelihood of false-positive results (Heung-Sang Wong et al., 2017). Hedges' g, a variant of Cohen's d that corrects for sample size biases, was used to calculate the ESs. The ES was categorized as follows in accordance with the Cochrane's handbook: small (0.2–0.49), moderate (0.5–0.79), or large (0.8 or more) (Higgins et al., 2003). A positive ES indicated a more favorable outcome for the experimental group. The I^2 statistic estimated heterogeneity among studies and classified as 25% (low heterogeneity), 50% (moderate heterogeneity), or 75% (high heterogeneity) (Higgins et al., 2003). If the data was unsuitable for our analysis, the previous statistical formula was used to convert the data into mean and SD format (Hozo et al., 2005). The funnel plot and Egger's regression test were used to identify publication bias. The impact of publication bias on the pooled results was further investigated using a 'trim and fill' strategy in the event of publication bias. A sensitivity analysis was also performed to detect the presence of highly influential studies that could skew the results. Studies were deemed influential if their removal significantly modified the summary effect (i.e., from significant to non-significant). The significance level was set at $p \leq 0.05$.

Finally, all moderators (methodological quality, type of control group, exercise type, exercise duration, exercise frequency, and number of sessions) were implemented as categorical variables. The meta-regressors were continuous variables related to TCE dosage [exercise frequency (sessions per week), exercise duration (weeks), number of sessions (n), and session duration (min)].

RESULTS

Search Results

The flowchart in **Figure 1** summarizes the PRISMA-compliant literature search and selection process. Our comprehensive review of the literature uncovered 556 studies, of which 378 remained after duplicates were deleted. We then examined the names and abstracts of the remaining papers, of which 342 were excluded. The remaining 36 studies were read in their entirety. Among these 36 articles, three were excluded because they were not RCTs, one presented duplicated data from a previous RCT, eight were excluded because participants did not meet the inclusion criteria, four did not use TCE intervention, and five did not have data access. Eventually, 15 RCTs (Schmitz-Hübsch et al., 2006; Hackney and Earhart, 2008; Li et al., 2012,

TABLE 1 | Characteristics of randomized controlled trials included in the meta-analysis.

			Participant characteristics				Intervention protocol			
References	**Country**	**Study design**	**Age, mean (SD)**	**N (EG/CG)**	**H&Y**	**Med**	**Intervention**	**Control**	**Outcome**	**Adverse effects**
Schmitz-Hübsch et al. (2006)	Germany	RCT	EG:64(8) CG:63(8)	56 (32/24)	NA	ON	Qigong 1 × 90 min/week 16 weeks	No intervention	UPDRS-III	NR
Hackney and Earhart (2008)	USA	RCT	EG:64.9(8.3) CG:62.6(10.2)	23 (17/16)	1.5–3	ON	Tai Chi 2 × 60 min/week 13 weeks	No intervention	UPDRS-III; BBS; TUG; gait velocity; 6 MWT; stride length; OLBB	NR
Li et al. (2012)	USA	RCT	EG:68(9) CG1:69(8) CG2:69(9)	195 (65/65/65)	1–4	ON	Tai Chi 2 × 60 min/week 24 weeks	Stretching; resistance	UPDRS-III; TUG; gait velocity; stride length;	Fall ($n = 11$) Muscle pain ($n = 6$) Dizziness ($n = 5$) Hypotension ($n = 4$)
Amano et al. (2013)	USA	RCT	EG:66(11) CG:66(7)	24(15/9)	2–3	ON	Tai Chi 3 × 60 min/week 16 weeks	No intervention	UPDRS-III; gait velocity gait cadence; step length	NR
Choi et al. (2013)	Korea	RCT	EG:60.81(7.6) CG:65.54(6.8)	20 (11/9)	1–2	ON	Tai Chi 3 × 60 min/week 12 weeks	No intervention	UPDRS-III; TUG; 6 MWT; OLBB	NR
Gao et al. (2014)	China	RCT	EG:69.54(7.32) CG:68.28(8.53)	76 (37/39)	1–4	ON	Tai Chi 3 × 60 min/week 12 weeks	No intervention	UPDRS-III; BBS; TUG	NR
Zhang et al. (2015)	China	RCT	EG:66(11.8) CG:64.35(10.53)	40 (20/20)	1–3	ON	Tai Chi 2 × 60 min/week 12 weeks	Multimodal exercise training	UPDRS-III; BBS; TUG; gait velocity; stride length	NR
Xiao and Zhuang (2016)	China	RCT	EG:66.52(2.13) CG:68.17(2.27)	89 (45/44)	1–3	ON	Qigong (Baduanjin) 4 × 75 min/week 24 weeks	Walking	UPDRS-III; BBS; TUG; Gait velocity; 6 MWT; stride length	NR
Xiao et al. (2016)	China	RCT	EG/CG:67.8(9.4)	68(35/33)	NA	ON	Qigong (Baduanjin) 4 × 60 min/week 24 weeks	Conventional training	UPDRS-III; BBS; TUG; Gait velocity; 6 MWT	NR
Liu et al. (2016)	China	RCT	EG:65.84(5.45) CG:62.5(3.13)	41(23/18)	NA	ON	Qigong 5 × 60 min/week 10 weeks	Daily activities	One legged blind balance; TUG	NR
Lee et al. (2018)	Korea	RCT	EG:65.8(7.2) CG:65.7(6.4)	41(25/16)	1–3	ON	Qigong (QI Dance) 2 × 60 min/week 8 weeks	No intervention	UPDRS-III; BBS	NR
Kurt et al. (2018)	Turkey	RCT	EG:62.41 (6.76) CG:63.61(7.18)	40(20/20)	2–3	ON	Tai Chi (Ai Chi) 5 × 60 min/week 5 weeks	Land-based exercise	UPDRS-III; berg; TUG	NR
Vergara-Diaz et al. (2018)	USA	RCT	EG:65.7(3.86) CG:62.0(7.77)	25(12/13)	2–2.5	OFF	Tai Chi 2 × 60 min/week 24 weeks	Usual healthcare	UPDRS-III; TUG; gait velocity;	NR
Wan et al. (2021)	China	RCT	EG:64.95(7.83) CG:67.03(7.47)	40(20/20)	1–4	ON	Qigong 4 × 60 min/week 12 weeks	No intervention	TUG; gait velocity; stride length; gait cadence; OLBB	NR
Li et al. (2022)	China	RCT	EG:62.7(5.51) CG1:61.9(5.64) CG2:61.9(6.76)	95(32/31/32)	1–2.5	ON	Tai Chi 2 × 60 min/week 48 weeks	Brisk walking; no intervention	UPDRS-III; BBS; TUG; gait velocity; gait cadence; stride length; step length	NR

UPDRS-III, Unified Parkinson's Disease Rating Scale part III; BBS, Berg Balance Scales; 6 MWT, 6 min walking test; TUG, time up and go test; OLBB, one legged blind balance; H&Y, Hoehn and Yahr stage; NA, not available; Med, anti-Parkinson medication ("OFF" refers to medication off during measurement); NR, no report; EG, experimental group; CG, control group.

TABLE 2 | Physiotherapy Evidence Database (PEDro) scores of the 15 included studies.

References	Scores	Methodological quality	PEDro item number										
			1	2	3	4	5	6	7	8	9	10	11
Schmitz-Hübsch et al. (2006)	8	Good	1	1	1	1	0	0	1	1	1	1	1
Hackney and Earhart (2008)	6	Good	1	1	0	1	0	0	1	0	0	1	1
Li et al. (2012)	8	Good	1	1	1	1	0	0	1	1	1	1	1
Amano et al. (2013)	6	Good	1	1	0	1	0	0	1	1	0	1	1
Choi et al. (2013)	6	Good	1	1	0	1	0	0	1	1	0	1	1
Gao et al. (2014)	7	Good	1	1	1	1	0	0	1	1	0	1	1
Zhang et al. (2015)	8	Good	1	1	1	1	0	0	1	1	1	1	1
Xiao and Zhuang (2016)	7	Good	1	1	0	1	0	0	1	1	1	1	1
Xiao et al. (2016)	5	Fair	1	1	0	1	0	0	0	1	0	1	1
Liu et al. (2016)	4	Fair	1	1	0	1	0	0	0	0	0	1	1
Lee et al. (2018)	7	Good	1	1	1	1	0	0	1	0	1	1	1
Kurt et al. (2018)	6	Good	1	1	1	1	0	0	0	1	0	1	1
Vergara-Diaz et al. (2018)	6	Good	1	1	1	1	0	0	0	1	0	1	1
Wan et al. (2021)	5	Fair	1	1	1	1	0	0	0	0	0	1	1
Li et al. (2022)	7	Good	1	1	1	1	0	0	1	0	1	1	1

Studies were classified as having excellent (9–10), good (6–8), fair (4–5), or poor (< 4). 0: does not meet the criteria; 1: meets the criteria. Criteria (without eligibility criteria) were used to calculate the total PEDro score; Item 1 = Eligibility criteria; Item 2 = Random sequence; Item 3 = Allocation concealment; Item 4 = Similar at baseline; Item 5 = Subjects blinded; Item 6 = Therapists blinded; Item 7 = Assessors blinded; Item 8 = <15% dropouts; Item 9 = Intention-to-treat analysis; Item 10 = Between-group comparisons; Item 11 = Point measures and variability data.

2022; Amano et al., 2013; Choi et al., 2013; Gao et al., 2014; Zhang et al., 2015; Liu et al., 2016; Xiao and Zhuang, 2016; Xiao et al., 2016; Kurt et al., 2018; Lee et al., 2018; Vergara-Diaz et al., 2018; Wan et al., 2021) were deemed eligible for inclusion in the meta-analysis. The two researchers have the same rate of research selection and data extraction as 4 and 82%, respectively.

Study Characteristics

Table 1 lists the characteristics of each of the included studies, which were published between 2006 and 2022. Seven studies were conducted in China (Gao et al., 2014; Zhang et al., 2015; Liu et al., 2016; Xiao and Zhuang, 2016; Xiao et al., 2016; Wan et al., 2021; Li et al., 2022), four in the USA (Hackney and Earhart, 2008; Li et al., 2012; Amano et al., 2013; Vergara-Diaz et al., 2018), two in Korea (Choi et al., 2013; Lee et al., 2018), one in Germany (Schmitz-Hübsch et al., 2006), and one in Turkey (Kurt et al., 2018). The TCE program was used to treat PD in all experimental groups, with nine studies using Tai Chi and six studies using Qigong. Active (e.g., brisk walking, stretching, resistance, or usual healthcare) or passive interventions (i.e., no intervention, wait-list) were employed in the control group. These participants were prescribed 75–90 min of exercise in each session one to five times per week for 5–48 weeks. The outcomes of these 15 studies were as follows: Unified Parkinson's Disease Rating Scale part III (UPDRS-III), Berg Balance Scales (BBS), time up and go (TUG), one-legged blind balance test, gait velocity, 6-min walking test (6 MWT), stride length, cadence, and step length. One study (Li et al., 2012) reported on suspected side effects such as dizziness ($n = 5$), muscle pain ($n = 6$), and symptoms of hypotension ($n = 4$). The remaining studies reported no TCE-related side effects.

Study Quality

Table 2 presents the methodology quality of the included studies. The quality of the studies ranged between fair and good (score range: 5–9 points), with 80% of studies being classified as good quality and 12% as fair quality. Nine studies used a concealed allocation procedure (Schmitz-Hübsch et al., 2006; Li et al., 2012, 2022; Gao et al., 2014; Zhang et al., 2015; Kurt et al., 2018; Lee et al., 2018; Vergara-Diaz et al., 2018; Wan et al., 2021), and all reported random assignment. We could not blind patients and therapists because this was an interventional movement study. However, 10 trials blinded the outcome assessors (Schmitz-Hübsch et al., 2006; Hackney and Earhart, 2008; Li et al., 2012, 2022; Amano et al., 2013; Choi et al., 2013; Gao et al., 2014; Zhang et al., 2015; Xiao and Zhuang, 2016; Lee et al., 2018). Five studies had a dropout rate of >85% (Hackney and Earhart, 2008; Liu et al., 2016; Lee et al., 2018; Wan et al., 2021; Li et al., 2022). Nine studies in particular did not analyze missing data using intent-to-treat analyses (Hackney and Earhart, 2008; Amano et al., 2013; Choi et al., 2013; Gao et al., 2014; Liu et al., 2016; Xiao et al., 2016; Kurt et al., 2018; Vergara-Diaz et al., 2018; Wan et al., 2021). The risk of bias assessment of all included studies is shown in **Figure 2**.

Synthetic Results

Regarding balance outcomes (**Figure 3** and **Table 3**), the pooled data demonstrated that TCE resulted produced large and

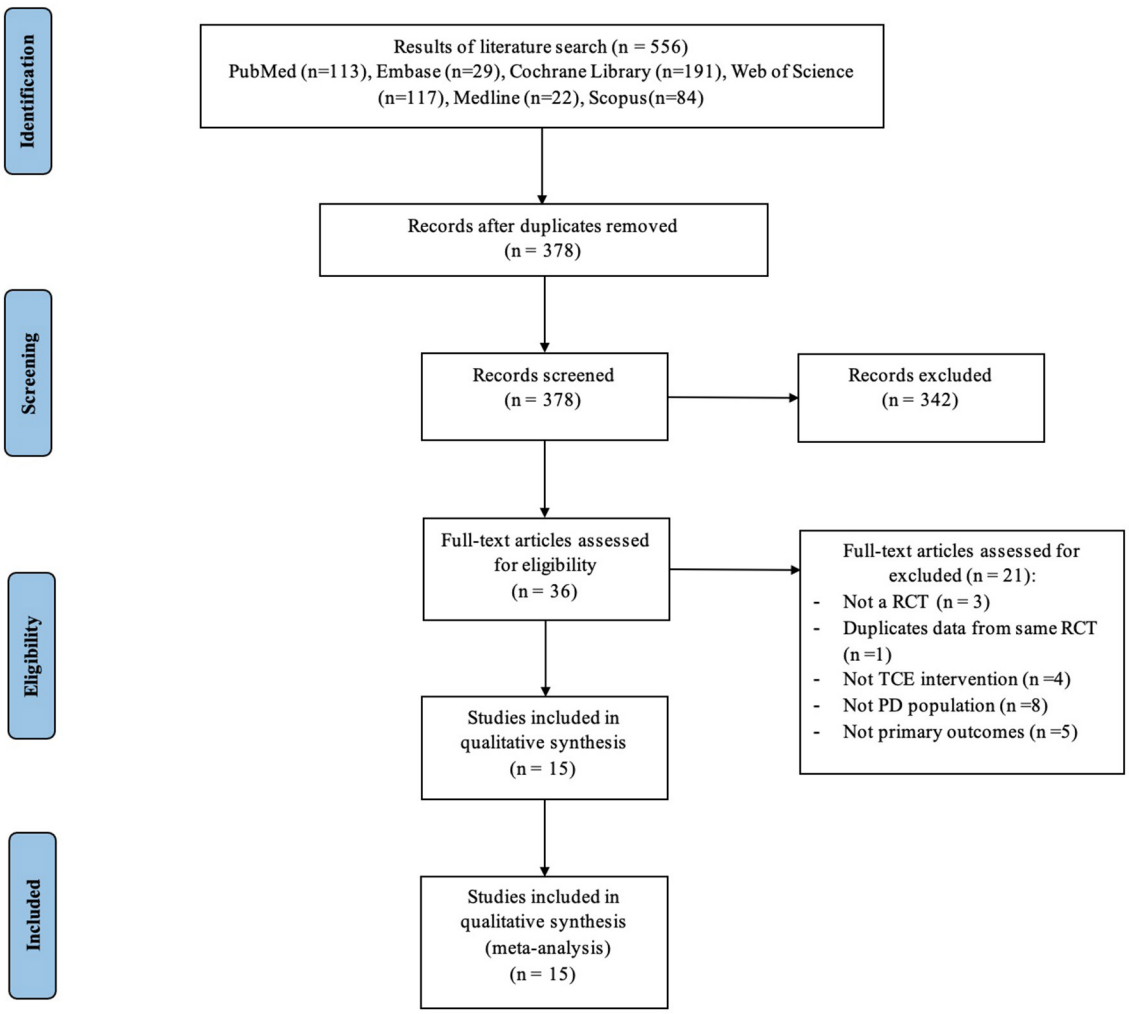


FIGURE 1 | Process of study selection following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

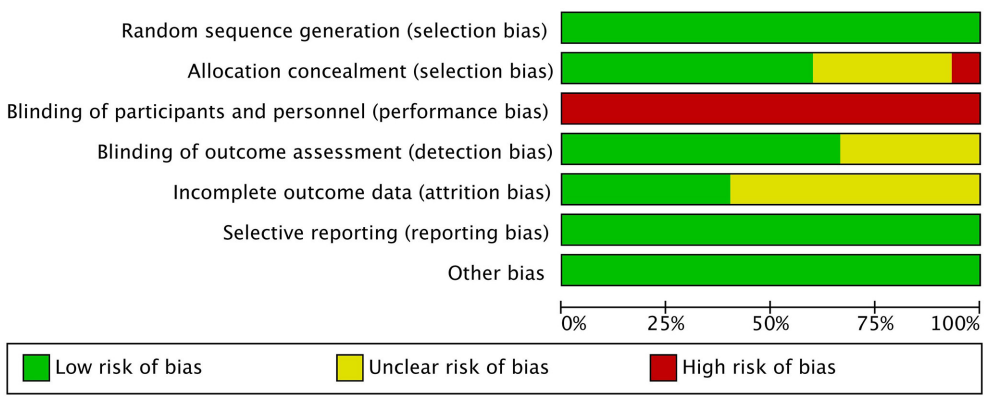
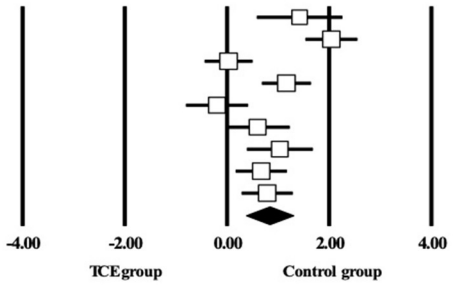


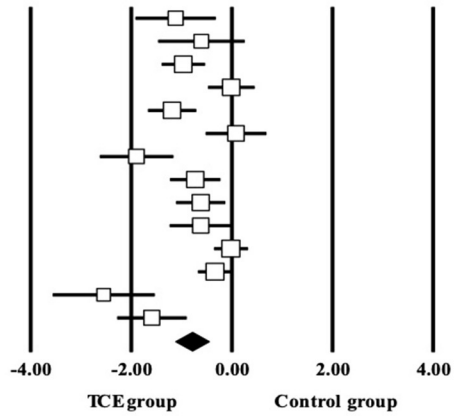
FIGURE 2 | Assessment of risk of bias with selected studies.

significant improvements in BBS when compared to the control group (g = 0.83, 95% CI = 0.37–1.29, p = 0.000, I^2 = 84%) and TUG (g = −0.80, 95% CI = −1.13– −0.47, p = 0.000, I^2 = 81%). Moreover, pooled analyses from four parallel trials revealed that the one-legged blind balance test exerted a small and significant increase in effect size (g = 0.49, 95%

Study name	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hackney 2008	BBS	1.421	0.428	0.183	0.582	2.260	3.321	0.001
Xiao 2016 W	BBS	2.043	0.260	0.068	1.534	2.553	7.857	0.000
Xiao 2016 C	BBS	0.031	0.240	0.058	-0.439	0.501	0.130	0.897
Gao 2014	BBS	1.163	0.246	0.061	0.681	1.645	4.729	0.000
Zhang 2015	BBS	-0.195	0.311	0.097	-0.804	0.414	-0.628	0.530
Lee 2018	BBS	0.600	0.321	0.103	-0.029	1.229	1.871	0.061
Kurt 2018	BBS	1.034	0.331	0.109	0.385	1.682	3.125	0.002
Li 2022 1 B	BBS	0.670	0.256	0.066	0.168	1.172	2.618	0.009
Li 2022 2 N	BBS	0.786	0.257	0.066	0.283	1.289	3.065	0.002
		0.832	0.235	0.055	0.372	1.291	3.545	0.000



Study name	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hackney 2008	TUG	-1.116	0.410	0.168	-1.920	-0.312	-2.721	0.007
Choi 2013	TUG	-0.607	0.441	0.195	-1.471	0.257	-1.376	0.169
Xiao 2016 W	TUG	-0.965	0.222	0.049	-1.401	-0.529	-4.342	0.000
Xiao 2016 C	TUG	-0.011	0.240	0.058	-0.481	0.459	-0.046	0.964
Gao 2014	TUG	-1.188	0.247	0.061	-1.672	-0.705	-4.815	0.000
Zhang 2015	TUG	0.082	0.310	0.096	-0.525	0.690	0.265	0.791
Kurt 2018	TUG	-1.895	0.375	0.141	-2.631	-1.159	-5.047	0.000
Li 2022 1 B	TUG	-0.728	0.257	0.066	-1.232	-0.224	-2.830	0.005
Li 2022 2 N	TUG	-0.618	0.253	0.064	-1.114	-0.122	-2.444	0.015
Wan 2021	TUG	-0.618	0.318	0.101	-1.240	0.004	-1.946	0.052
Li 2012 1r	TUG	-0.018	0.174	0.030	-0.360	0.324	-0.104	0.917
Li 2012 2s	TUG	-0.333	0.176	0.031	-0.678	0.011	-1.899	0.058
Vergara-Diaz 2018	TUG	-2.547	0.520	0.270	-3.565	-1.529	-4.903	0.000
Liu 2016	TUG	-1.589	0.355	0.126	-2.285	-0.893	-4.476	0.000
		-0.797	0.169	0.029	-1.129	-0.466	-4.714	0.000



Study name	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hackney 2008	One-legged blind balance	0.023	0.380	0.144	-0.722	0.767	0.060	0.952
Choi 2013	One-legged blind balance	1.113	0.465	0.216	0.202	2.025	2.394	0.017
Wan 2021	One-legged blind balance	0.482	0.315	0.099	-0.134	1.099	1.533	0.125
Liu 2016	One-legged blind balance	0.538	0.314	0.099	-0.078	1.154	1.711	0.087
		0.494	0.188	0.035	0.125	0.862	2.628	0.009

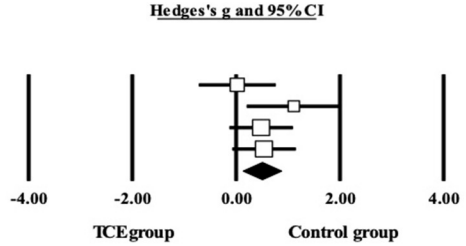


FIGURE 3 | Forest plot showing the effects of TCE vs. control group on BBS outcomes: BBS, TUG, one-legged blind balance.

CI = 0.13–0.86, $p = 0.01$, $I^2 = 10\%$) compared with the control group.

Regarding gait outcomes (**Figure 4** and **Table 3**), the pooled results showed that TCE caused small and significant improvements in gait velocity ($g = 0.28$, 95% CI = 0.02–0.54, $p = 0.04$, $I^2 = 64\%$), 6MWT ($g = 0.32$, 95% CI 0.01–0.62, $p = 0.04$, $I^2 = 15\%$) and stride length ($g = 0.25$, 95% CI = 0.08–0.41, $p = 0.003$, $I^2 = 42\%$) compared with the control group. However, no significant results were found for TCE intervention on cadence ($g = -0.03$, 95%CI = −0.31–0.25, $p = 0.82$, $I^2 = 0\%$) and step length ($g = 0.02$, 95%CI = −0.30–0.34, $p = 0.92$, $I^2 = 41\%$) compared with the control group.

Regarding motor symptoms (**Figure 5** and **Table 3**), 13 studies reported UPDRS-III scores, including 15 parallel comparisons between the TCE and control groups (as two studies included

TABLE 3 | Synthesized results for the effects of TCE vs. control group intervention.

Variables	k	g	95% CI	I^2 %	Between-group homogeneity			Publication bias Egger's test (*p*)
					Q-value	df (Q)	*p*-value	
Balance outcomes								
BBS	9	0.83	0.64–1.00	84	48.78	8	0.000	0.43
TUG	14	−0.80	−1.13– −0.47	81	68.22	13	0.000	0.01
OLBB	4	0.49	0.13–0386	10	3.33	3	0.34	0.30
Gait outcomes								
Gait velocity	11	0.28	0.02–0.54	64	27.77	10	0.002	0.46
6 MWT	4	0.32	0.01–0.62	15	3.55	3	0.32	0.35
Stride length	8	0.25	0.08–0.41	42	12.09	7	0.10	0.17
Cadence	4	−0.03	−0.31–0.25	0	3.02	3	0.82	0.37
Step length	3	0.02	−0.41–0.45	41	3.39	2	0.18	0.50
Motor symptoms								
UPDRS-III	15	−0.77	−1.06– −048	76	58.39	14	0.000	0.45

UPDRS-III, Unified Parkinson's Disease Rating Scale part III; BBS, Berg Balance Scales; OLBB, one legged blind balance; 6 MWT, 6 min walking test; TUG, time up and go test.

two paired trials each). Data from fifteen trials demonstrated a significant improvement in UPDRS-III compared with the control group ($g = -0.77$, 95% CI = −1.06– −0.48, $p = 0.000$, $I^2 = 76\%$).

According to the sensitivity analysis, no study significantly impacted the outcomes (data not shown). No study was deemed insignificant since its removal had no discernible effect on the overall effect (i.e., a change from significant to non-significant). Although there was considerable heterogeneity between RCTs, the moderators that increased the effect of TCE on balance, gait, and motor signs also reduced the analyses' heterogeneity.

Moderator Analysis

The categorical and continuous variables in **Table 4** were used to conduct moderator analyses. PEDro score, type of exercise, type of control group, and number of sessions significantly moderated the effects of TCE on BBS (Q = 48.79, $df = 8$, $p = 0.000$) and gait velocity (Q = 27.77, $df = 10$, $p = 0.001$). Compared to RCTs on TCE with low methodological quality ($g = 0.68$, 95% CI = −0.68–2.04, $p = 0.33$), RCTs on TCE with high methodological quality ($g = 0.88$, 95% CI = 0.38–1.38, $p = 0.001$) significantly improved BBS. Moreover, high-quality methodological RCTs ($g = 0.31$, 95% CI = 0.14–0.47, $p = 0.000$) of TCE significantly improved gait velocity compared with low-quality methodological RCTs on TCE ($g = 0.23$, 95% CI = −0.78–1.24, $p = 0.66$). Additionally, Tai chi ($g = 0.79$, 95% CI = 0.38–1.21; $p = 0.001$) significantly improved BBS compared with Qi gong ($g = 0.89$, 95% CI = −0.36–2.15; $p = 0.16$). The change in gait velocity due to Tai Chi ($g = 0.28$, 95% CI = 0.01–0.54, $p = 0.04$) was more significant than due to Qigong ($g = 0.27$, 95% CI = −0.37–0.92, $p = 0.41$). Active control groups ($g = 0.27$, 95% CI = 0.11–0.43, $p = 0.001$) exhibited significantly improved gait velocity compared with non-active control groups ($g = 0.26$, 95% CI = −0.87–1.39, $p = 0.65$). The number of sessions shows that the effect size of more than 48 sessions ($g = 0.37$, 95% CI = 0.09–0.64, $p = 0.01$) was moderate and significant compared with <48 sessions ($g = -0.02$.,95% CI = −0.21–0.28, $p = 0.38$).

Meta-regression

In the meta-regression (**Table 5** and **Supplementary Material**), covariates that significantly affected UPDRS-III included exercise duration ($\beta = -0.0224$, 95% CI = −0.0443– −0.0006; $p = 0.044$) and number of sessions ($\beta = -0.0108$, 95% CI = −0.0190– −0.0026; $p = 0.01$) in random-effect regression analyses. Session duration was a significant covariate ($\beta = 0.0920$, 95% CI = 0.0212– – 0.1628; $p = 0.011$) on BBS in regression analyses. However, we found that exercise frequency (sessions per work), exercise duration, number of sessions and session duration did not impact other outcomes significantly ($P > 0.05$).

Publication Bias

The Egger's test (**Table 3**) and funnel plot (**Supplementary Material**) were used to assess publication bias. The asymmetrical distribution of the included trials on a funnel plot revealed publication bias for RCTs that reported TUG. The Egger's test showed that Egger's regression intercept = −4.68, $p < 0.05$, and the Duval and Tweedie's trim and fill revealed that five studies were missing on the right side of the mean effect. The adjusted value was as follows: g= −0.38 (95% CI = −0.50– −0.25). As studies with smaller effect sizes were excluded from this meta-analysis, there may be evidence of publication bias.

DISCUSSION

The current systematic review with meta-analysis showed that TCE significantly improved balance outcomes (BBS, TUG, and one-legged blind balance), gait outcomes (gait velocity, 6 WMT, and stride length), and motor symptoms (UPDRS-III) compared with the control group in individuals with PD. Data from 15 RCTs involving a total of 873 participants were

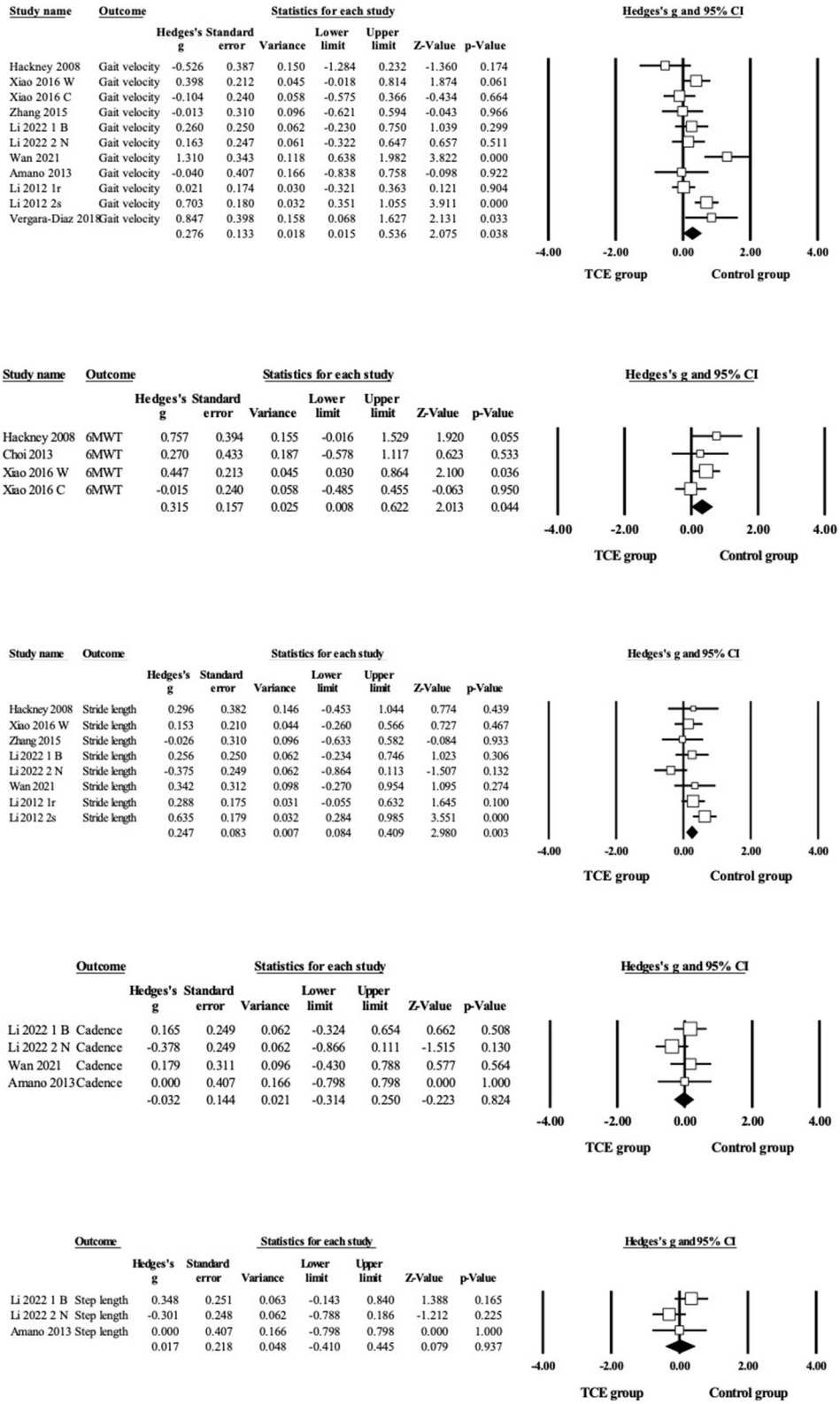


FIGURE 4 | Forest plot showing the effects of TCE vs. control group on gait outcomes: gait velocity, 6 MWT, stride length, cadence, step length.

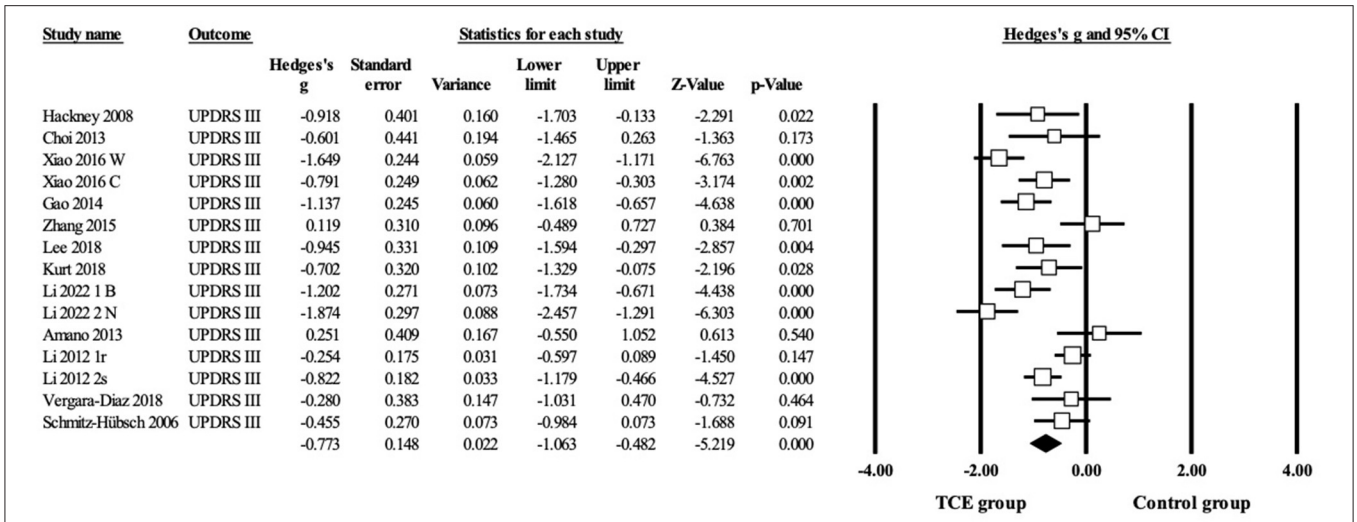


FIGURE 5 | Forest plot showing the effects of TCE vs. control group on motor symptoms: UPDRS-III.

analyzed. The moderator analyses showed the effects of TCE on BBS and gait velocity were moderated by the PEDro score, exercise type, control group type, and number of sessions. Lastly, meta-regression revealed significant relationships between TCE dosage variables (exercise duration, number of sessions, session duration) and observed changes in UPDRS-III and BBS. The safety of the intervention should also be evaluated in future RCTs, regardless of the limited number of reported adverse events.

Common testing tools for balance outcomes include BBS, TUG, and the one-legged blind balance test. Clinicians frequently utilize the TUG test to assess the balance and mobility of patients with movement disorders and the elderly. The time necessary to maintain the body's center of gravity on a single support surface without visual cues is reflected in the one-legged blind balance test. People with PD are more likely to fall due to their movement abnormalities (Lomas-Vega et al., 2017). Strengthening the static and dynamic balancing abilities of patients prone to falls can improve muscle strength in their lower limbs and prevent falls. Tai Chi incorporates a variety of exercises, such as slow weight shifting, body rotation, and single-leg standing in various postures, all of which necessitate sensitive joint control and muscle coordination, resulting in increased proprioceptive stimulation and lower extremity muscle strengthening. Flexion and extension, raising and lowering, opening and shutting the trunk of the limbs, altering breathing according to the action, keeping balance, and continually changing the center of gravity are all techniques used in fitness Qi gong (Subramanian, 2017; Penn et al., 2019). Also, given that a previous review assessed the effect of single TCE on walking ability and balance (Yang et al., 2015; Winser et al., 2018; Wang et al., 2021), the current study found similar results, indicating that TCE could help patients with PD to improve their balance. It reduces nerve exhaustion, relaxes the neural system, strengthens core muscles, enhances joint activity, and improves proprioceptive input to the trunk and lower limbs, all of which help individuals with PD to improve their balance. These findings also suggest that single TCE can help people to increase their aerobic endurance and reduce their chance of falling by improving their balance (Winser et al., 2018). However, they did not apply meta-regression analysis to analyze the effect of factors on trial effect size. Even though they had small sample sizes, none of them calculated effect sizes using Hedges' g statistic. Thus, our findings pool the effects of multiple common TCEs in balance outcomes and reinforce the important role of balance outcomes in individuals with PD.

Concerning the gait outcomes, kinematic gait metrics (such as gait velocity, stride length, and 6 MWT) improved significantly, whereas gait cadence and step length remained the same. The routines chosen from traditional Chinese training can also improve leg muscle strength effectively by focusing on frequent lower limb movements. The research revealed that the gastrocnemius and tibialis anterior muscles substantially impact gait in individuals with PD (Plotnik et al., 2005). These workouts help to improve gait stability, stride length, and gait speed. According to our meta-analysis, the gait velocity and stride length improved following TCE in those with PD, contradicting the results of earlier systematic reviews (Ni et al., 2014; Yang et al., 2014). In contrast, our findings provide more compelling evidence for various reasons. First, all included research had a moderate methodological quality according to the PEDro scale tool. In contrast, most of Ni et al.'s evaluation studies were of low methodological quality (Ni et al., 2014). Second, by including just RCTs in our meta-analysis, we could estimate the magnitude of the effect. Although some studies assessed by Yang et al. were of moderate quality (Yang et al., 2014), the small number of studies and the type of single intervention. Moreover, one of the eight studies in Yang et al.'s meta-analysis had a non-RCT study. Therefore, more research into the benefits of TCE interventions on gait function in people with PD is warranted.

TABLE 4 | Moderator analysis for the effects of TCE on measurement outcomes.

Variables	Balance outcomes			Gait outcomes					Motor symptoms
	BBS Hedges'*g* (95%CI)	OLBB Hedges'*g* (95%CI)	TUG Hedges'*g* (95%CI)	Gait velocity Hedges'*g* (95%CI)	6 MWT Hedges'*g* (95%CI)	Stride length Hedges'*g* (95%CI)	Cadence Hedges'*g* (95%CI)	Step length Hedges'*g* (95%CI)	UPDRS–III Hedges'*g* (95%CI)
PEDro score									
≥6	0.88 (0.38–1.38)	1.11 (0.20–2.03)	−0.80 (−1.2–−0.41)	0.31 (0.14–0.47)	0.41 (0.04–0.79)	0.19 (−0.09–0.46)	−0.09 (−0.41–0.23)	0.02 (−0.30–0.34)	−0.76 (−1.09–−0.43)
<6	0.68 (−0.68 to 2.04)	0.39 (0.01–0.76)	−0.80 (−1.52–−0.08)	0.23 (−0.78–1.24)	0.31 (−0.44 to 1.05)	0.32 (−0.15–0.80)	0.18 (−0.43–0.79)	–	−0.83 (−1.24–0.41)
Exercise type									
Tai Chi	0.79 (0.38–1.21)	–	−0.82 (−1.23–−0.40)	0.28 (0.01–0.54)	0.27 (−0.58–1.12)	0.19 (−0.15–0.53)	−0.09 (−0.41–0.23)	0.02 (−0.30–0.34)	−0.70 (−1.05–−0.35)
Qigong	0.89 (−0.36 −2.15)	0.49 (0.14–0.84)	−0.77 (−1.40–−0.14)	0.27 (−0.37–0.92)	0.34 (−0.07–0.74)	0.23 (−0.09–0.54)	0.18 (−0.43–0.79)	–	−0.97 (−1.50–−0.44)
Type of control group									
Active control	0.73 (0.09–1.37)	0.54 (−0.08–1.15)	−0.77 (−1.19–−0.36)	0.27 (0.11–0.43)	0.23 (−0.22–0.68)	0.19 (−0.09–0.46)	−0.11 (−0.45–0.24)	0.02 (−0.33–0.37)	−0.84 (−1.24–−0.43)
Non-active control	1.04 (0.69–1.38)	0.49 (−0.06–1.04)	−0.95 (−1.27–−0.63)	0.26 (−0.87–1.39)	0.54 (−0.04–1.11)	0.32 (−0.15–0.80)	0.11 (−0.37–0.60)	–	−0.68 (−1.6–−0.29)
Exercise frequency									
≥3 sessions/week	1.07 (0.20–1.93)	−0.62 (0.23–1.02)	−0.96 (−1.43–−0.49)	0.38 (−0.19–0.60)	0.76 (−0.02–1.53)	0.21 (−0.13–0.55)	0.11 (−0.37–0.60)	–	−0.83 (−1.31–−0.36)
<3 sessions/week	0.62 (0.18–1.06)	0.02 (−0.72–0.77)	−0.62 (−1.06–−0.19)	0.23 (−0.08–0.53)	0.25 (−0.06–0.55)	0.21 (−0.09–0.50)	−0.11 (−0.64–0.43)	0.02 (−0.61–0.66)	−0.73 (−1.11–−0.36)
Exercise duration									
>12weeks	0.97 (0.26–1.69)	0.02 (−0.72–0.77)	−0.67 (−1.06–−0.28)	0.22 (−0.03–0.46)	0.32 (0.03–0.61)	0.23 (−0.05–0.50)	−0.09 (−0.41–0.23)	0.02 (−0.41–0.45)	−0.82 (−1.20–−0.44)
≤12weeks	0.66 (0.05–1.27)	0.62 (0.23–1.02)	−0.96 (−1.54–−0.39)	0.64 (−0.66–1.94)	0.27 (−0.58–1.12)	0.16 (−0.28–0.59)	0.18 (−0.43–0.79)	–	−0.67 (−1.13–−0.21)
Number of sessions									
<48 sessions	0.79 (0.24–1.34)	0.50 (0.05–0.92)	−1.05 (−1.63–−0.47)	−0.21 (−0.71–0.28)	0.54 (−0.04–1.11)	0.10 (−0.37–0.57)	–	–	−0.68 (−0.91–−0.45)
≥48 sessions	0.88 (0.05–1.71)	0.48 (−0.13–1.10)	−0.61 (−0.98–−0.24)	0.37 (0.09–0.64)	0.23 (−0.22–0.68)	0.24 (−0.03–0.50)	−0.03 (−0.31–0.25)	0.02 (−0.41–0.45)	−0.85 (−1.30–−0.40)

UPDRS-III, Unified Parkinson's Disease Rating Scale part III; BBS, Berg Balance Scales; OLBB, one legged blind balance; 6MWT, 6min walking test; TUG, time up and go test.

TABLE 5 | Meta-regression of the 15 included studies to predict TCE effects on measurement outcomes.

Variables	Balance outcomes			Gait outcomes				Motor symptoms
	BBS β (95% CI)	OLBB β (95% CI)	TUG β (95% CI)	Gait velocity β (95% CI)	6 MWT β (95% CI)	Stride length β (95% CI)	Cadence β (95% CI)	UPDRS–III β (95% CI)
Exercise frequency (sessions per week)	0.1629 (−0.2710–0.5968)	0.0815 (−0.2583–0.4213)	−0.2382 (−0.5179–0.0415)	−0.1059 (−0.4408–0.2291)	−0.2282 (−0.6442–0.1878)	−0.0359 (−0.3755–0.3036) 0.84	0.0291 (−0.9268–0.9850)	−0.0973 (−0.3788–0.1842)
Exercise duration (weeks)	−0.0013 (−0.0332–0.0306)	−0.1031 (−0.4830–0.2768)	0.0125 (−0.0136–0.0386)	−0.0014 (−0.0239–0.0211)	−0.0248 (−0.0895–0.0400)	−0.0094 (−0.0260–0.0072)	−0.0097 (−0.0255–0.0125)	−0.0224 (−0.0443–−0.0006)
Number of sessions (*n*)	0.0019 (−0.0120–0.0157)	0.0126 (−0.0306–0.0558)	0.0052 (−0.0073–0.0177)	−0.000 (−0.0100–0.0099)	−0.0049 (−0.0159–0.0061)	−0.0045 (−0.0121–0.0032)	−0.0045 (−0.0183–0.0092)	−0.0108 (−0.0190–−0.0026)
Session duration (min)	0.0920 (0.0212–0.1628)	–	−0.0119 (−0.0961–0.0724)	0.0091 (−0.0505–0.0688)	0.0128 (−0.0378–0.0634)	−0.0048 (−0.0501–0.0405)	–	−0.0043 (−0.0403–0.0318)

UPDRS-III, Unified Parkinson's Disease Rating Scale part III; BBS, Berg Balance Scales; OLBB, one legged blind balance; 6 MWT, 6 min walking test; TUG, time up and go test.

The UPDRS-III, which tracks PD motor performance and disability level, is an important outcome measure for evaluating long-term training benefits for motor symptoms. The findings of this meta-analysis revealed that the motor symptoms of individuals with PD improved significantly after TCE. More precisely, TCE moderately affected UPDRS-III ($g = -0.77$). The magnitude of effects of TCE on UPDRS-III is similar to that reported previously (Song et al., 2017; Tang et al., 2019). However, their reviews did not analyze the potential moderators. We discovered moderators that influenced motor symptom correspondence in our studies of motor signs with moderator analysis; however, we need to confirm this conclusion with a larger sample size in the future. Given that UPDRS-III scores are expected to deteriorate with time in patients with PD, the improvements in UPDRS-III scores suggest the possibility of disease-modifying effects (Chung et al., 2020). Furthermore, muscle tension caused by uncoordinated contractions of active and antagonistic muscles affects a range of motor symptoms in patients with PD. During TCE, constant motor alterations and stimulation can increase muscle activity, resulting in improved motor performance (Hawley et al., 2014; Luo et al., 2017).

Our moderator analysis revealed that the effect of TCE on BBS was significantly higher ($g = 0.88$) when only high-quality methodological RCTs were analyzed, but not when low-quality methodological RCTs were analyzed ($g = 0.58$). Additionally, high-quality methodological RCTs ($g = 0.31$) have a greater effect on gait velocity than low-quality methodological RCTs ($g = 0.23$). In clinical research, high-quality RCTs are the primary source of evidence for the safety and efficacy of clinical therapies. They aid in avoiding or mitigating the risk of bias in these trials (Vinkers et al., 2021). As a result, our findings imply that the significant effects of TCE on BBS and gait speed were not based on low-quality RCTs; therefore future studies must utilize high-quality RCTs to evaluate the effects of TCE on BBS and gait speed in PD. As for the type of exercise, BBS and gait movements improved significantly in patients with PD after they performed Tai Chi exercises compared to Qigong exercises. Moderator analysis showed that TCE increased the effect on gait velocity compared with active control groups ($g = 0.27$). Non-active control groups may be ethically untenable as individuals with PD undergo progressive functional decline over time (Kwakkel et al., 2007). Thus, we believe that active control groups should be used as a comparator in future RCTs. Moderator analysis revealed that long sessions affected ($g = 0.37$) gait velocity more significantly than short sessions ($g = -0.21$). This repetitive exercise in motivating surroundings enables patients to become accustomed to comparable tasks over time, allowing them to regain their gait function.

Furthermore, our meta-regression demonstrated that exercise duration and the number of sessions changed in UPDRS-III, meaning that high-intensity long sessions improved UPDRS-III more than low-intensity short sessions after the exercise. A high dose of TCE enhances caudate dopamine release and neurotrophic factor expression, improving the functional connectivity of brain motor circuits and motor skill learning in people with PD (Sacheli et al., 2019). These neurophysiological improvements may have a long-term effect on brain function, reducing motor symptoms and balance function. In terms of session duration, intense training can provide enough of a training effect on BBS to patients with PD. This finding may be equivocal because most of these studies used extended session durations. Further studies are warranted to investigate session duration on the effects of TCE on balance function.

Our systematic review and meta-analysis have some advantages that should be mentioned. It followed the PRISMA statement to the letter, and our review methodology was registered. Only the RCT design was chosen due to its reliability. When the included trials had small sample sizes, we used Hedges' g to ensure an accurate estimation of the overall effect size. Other potential confounding variables were explored to

determine their impact on the effects of TCE. Moreover, we decided to investigate the impact of covariates on the size of trial effects using a random-effects meta-regression model. This novel circumstance may provide additional data for future studies examining the influence of these confounding variables. These strengths contribute to the comprehensiveness and generalizability of our findings.

The current systematic review, however, has several limitations. First, the sample sizes and number of studies evaluating the effects of TCE on executive function and execution subcomponents were both insufficient to assess the effects. Second, we did not examine the long-term effects of TCE treatment on gait and balance outcomes with follow-up data. Third, most studies did not employ a blinding method (i.e., assessor blinding), resulting in subjective expectation bias; however, this is not a limitation of our meta-analysis but rather a problem of studies undertaken on this issue in general. Thus, performance bias was likely inescapable. Furthermore, large sample studies are required and long-term effects should be investigated to gain insight into prospective maintenance effects. An effective exercise program should be established as a promoting strategy in the treatment of PD.

CONCLUSION

Our systematic review found that TCE improved motor symptoms, balance function, and gait function (e.g., gait velocity, 6 MWT, and stride length) in people with PD. Moreover, it did not affect gait cadence and step length. More extensive trials and more rigorous study designs are needed to strengthen the evidence. Lastly, future studies will be able to assess the long-term impact of TCE-based rehabilitation training to ensure its long-term sustainability.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MW, QT, LW, and LZ conceptualized the study. MW, MZ, WS, and LT selected, extracted, and analyzed data. LZ, QT, and LW supervised the study. MW, MZ, and WS drafted the manuscript. MW, LZ, and QT participated in the whole process. LZ and QT made final decisions. All authors contributed to the manuscript's writing and read and approved the final version.

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SUPPLEMENTARY MATERIAL

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Mixed Comparison of Different Exercise Interventions for Function, Respiratory, Fatigue, and Quality of Life in Adults With Amyotrophic Lateral Sclerosis: Systematic Review and Network Meta-Analysis

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease whose primary hallmark is the progressive degeneration of motor neurons in the brainstem, spinal cord, and cerebral cortex that leads to weakness, spasticity, fatigue, skeletal muscle atrophy, paralysis, and even death. Exercise, as a non-pharmacological tool, may generally improve muscle strength, cardiovascular function, and quality of life. However, there are conflicting reports about the effect of exercise training in adults with ALS.

Aims: This systematic review and network meta-analysis aim to conduct a mixed comparison of different exercise interventions for function, respiratory, fatigue, and quality of life in adults with ALS.

Methods: Randomized controlled trials with ALS participants were screened and included from the databases of PubMed, Medline, and Web of Science. Physical exercise interventions were reclassified into aerobic exercise, resistance training, passive exercise, expiratory muscle exercise, and standard rehabilitation. Patient-reported outcome measures would be reclassified from perspectives of function, respiratory, fatigue, and quality of life. The effect size would be transferred into the percentage change of the total score.

Result: There were 10 studies included, with the agreement between authors reaching a kappa-value of 0.73. The network meta-analysis, which was conducted under the consistency model, identified that a combined program of aerobic exercise, resistance exercise, and standard rehabilitation showed the highest potential to improve quality of life (0.64 to be the best) and reduce the fatigue (0.39 to be the best) for ALS patients, while exercise program of aerobic and resistance training showed the highest potential (0.51 to be the best) to improve ALS patients' physical function. The effect of exercise on the respiratory was still unclear.

Conclusion: A multi-modal exercise and rehabilitation program would be more beneficial to ALS patients. However, the safety and guide for practice remain unclear, and further high-quality randomized controlled trials (RCTs) with a larger sample are still needed.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021253442, CRD42021253442.

Keywords: amyotrophic lateral sclerosis, exercise, prom, systematic review, network meta-analysis

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), whose primary hallmark is the progressive degeneration of motor neurons in the brainstem, spinal cord, and cerebral cortex that leads to weakness, spasticity, fatigue, skeletal muscle atrophy, paralysis, and even death, is described first in 1869 (Cleveland and Rothstein, 2001; Byrne et al., 2011). Due to muscle weakness and spasticity, which are the primary symptoms reported in patients with ALS, the functional ability has been damaged in patients with ALS (Jensen et al., 2016). Moreover, musculoskeletal dysfunction would induce respiratory dysfunction, which is the most common cause of death in ALS patients (Corcia et al., 2008).

ALS is one of the most common progressive neuromuscular diseases that is usually regarded as a disease that cannot be completely cured, and the majority of ALS patients are elderly population. The treatments of ALS are often aimed at strengthening the physical function of patients, improving their perceived feelings, reducing the incidence of adverse events, and comprehensively improving their quality of life. Currently, standard rehabilitation (SR) protocols, pathogenetic therapy, and various supportive therapies are prevalent in the clinical practice of ALS treatment. The SR of ALS is usually referred to multi-modal rehabilitation protocols that contain stretching exercises, active proprioceptive exercises, and basic active functional exercise, whereas there are two drugs approved for the pathogenetic therapy of ALS that have been identified to have effects on slowing down the progression of the disease (Beghi et al., 2004).

Physical exercise is one of the most common non-pharmacological tools that might be able to generally improve muscle strength and cardiovascular function of ALS patients and have a positive effect on their quality of life (Garber et al., 2011; Ying et al., 2021). For example, in 2018, a randomized controlled trial conducted by Clawson's team demonstrated that exercise programs contained resistance, endurance, and stretching (or range of motion) exercises are safe to be performed with the specified regimen without any worsening of outcomes as related to ALS function and can be tolerated showing high compliance over a long term (Clawson et al., 2018). A systematic review published in 2021 identified that therapeutic physical exercise could contribute to slowing down the deterioration of the musculature of patients with ALS and facilitating the performance in daily life activities in the short-, medium, and long term (Ortega-Hombrados et al., 2021). In addition, an improved overall functional score, muscle strength, and quality of life in ALS patients had been reported following a period of exercise intervention (Jensen et al., 2017). It seemed highly probable that any form of exercise has an advantageous impact on the quality of life of ALS patients (Tsitkanou et al., 2019).

However, the large heterogeneities within exercise protocols that used in clinical practice make the evidence level of exercise treatments for ALS low. For example, a randomized controlled trial conducted by Zucchi's team in 2019, which explored the effect of high-frequency motor rehabilitation for ALS patients, found that there was no significant difference between the effectiveness of high and usual frequency physical exercise on the ALS Functional Rating Scale—Revised (ALSFRS-R) scores, motor and respiratory functions, survival, fatigue, and quality of life of ALS patients. Moreover, a systematic review and meta-analysis published in 2014 demonstrated that there was limited evidence that inspiratory muscle training leads to the strengthening of inspiratory muscles in ALS. Improvements were minor in only a few parameters, but the survival time was significantly longer in the ALS patients who did inspiratory muscle training (Eidenberger and Nowotny, 2014). Another systematic review and meta-analysis conducted by Rahmati's team found that there was a statistically significant difference in favor of physical exercise in functional ability, overall quality of life, and aerobic capacity for ALS patients, but there was no significant difference in respiratory function, fatigue, pain, and body strength (Rahmati and Malakoutinia, 2021).

Additionally, the potential negative effects of physical exercise, such as accelerating disease progression or increasing adverse events described in the previous studies, might be related to the form of exercise (Mahoney et al., 2004; Harwood et al., 2009; Tsitkanou et al., 2019; Xiang et al., 2022; Xu et al., 2022). For example, a study conducted by Tsitkanou's team in 2019 found that the motor neuronal injuries of ALS patients might increase their risk of falls during physical exercises, such as aerobic exercise (AE) on a treadmill or bicycles. Moreover, a study made by Harwood's team published in 2009 claimed that the dose-response of physical exercise in healthy individuals appears to be changed in ALS patients, leading them to have a greater risk of overtraining when they conduct long-terms of resistance training (RT).

Since there were also conflicting reports about the effect of exercise training in ALS, the best way to exercise for patients with ALS has not been determined, and the effectiveness of exercise training as a treatment for other symptoms of ALS in human

studies is not yet clear. For instance, the effects of respiratory training programs on ALS patients had been addressed in a previous meta-analysis (Ferreira et al., 2016). In 2013, a Cochrane review was conducted to investigate the effect of physical exercise for patients with ALS on the overall functional score, fatigue, muscle strength, and quality of life without considering the form of exercises. The review found that the results of synthesis evidence were unclear because only a few studies were included (Dal Bello-Haas and Florence, 2013).

Many more studies of different physical exercise forms for ALS patients have been conducted recently. Therefore, it was necessary to conduct an updated systematic review to clarify the effects of different physical exercise intervention programs on ALS patients in terms of overall functional score, respiratory function, perceived fatigue, and quality of life. In addition, since the existing studies usually contained different experimental groups and control groups, making it difficult to conduct a pair-wise meta-analysis that could only compare the effectiveness of two kinds of interventions at the same time, a network meta-analysis approach, which was an expansion of pair-wise meta-analysis, could be able to compare more than two interventions for a certain disease synchronously. This systematic review and network meta-analysis were aimed to conduct a mixed comparison of different exercise interventions for function, respiratory, fatigue, and quality of life in adults with ALS.

METHODS

Program and Registration

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) (Moher et al., 2009). Literature screening criteria and study search strategy were proposed and agreed upon by two independent authors (YZ and XY). The PROSPERO registration number of this systematic review and network meta-analysis was CRD42021253442.

Eligibility Criteria

Population/Participants

This systematic review aimed to include all studies with adult ALS patients over 18 years old as participants in trials with the diagnosis criteria of ALS that are defined according to the revised El Escorial Criteria (Brooks et al., 2000).

Intervention(s)

All the interventions in this review were classified into six basic categories according to the definition in these included studies. These basic categories were AE, RT, SR, passive exercise (PE), expiratory muscle exercise (EE), and daily activity (DA). What should be emphasized was that the category SR contained active stretching exercise, active proprioceptive exercises, basic active functional exercise, or any forms of sham (or placebo) treatments, while the category PE represented movement exercise induced by special therapists (Lunetta et al., 2016). Each combined intervention program that contained two or more basic categories was represented by basic categories' abbreviations connected by plus signs, for example, "AE + RT + SR" meant a comprehensive exercise program that included cycling, strength exercises, and proprioceptive exercises. The description of interventions and comparators is provided in **Table 1**.

Comparator(s)

The eligibility criteria of the comparator(s) were the same as the intervention(s). Network meta-analysis was particularly flexible for fitting complex models, including multi-arm trials, and provided credible intervals and rank probabilities for comparing the overall effectiveness of treatments based on the Bayesian approach. All the treatments were ranked by their estimated effect sizes, and then, across all samples, averages for the first rank, second rank, and so on (Lumley, 2002; Chung and Lumley, 2008; Salanti et al., 2011; Wang et al., 2012). These estimated probabilities were plotted against the ranks. Therefore, network meta-analysis was feasible to make mixed and indirect intervention comparisons (Mills et al., 2013).

Outcomes

In clinical practice, clinicians used the patient-reported outcome measures (PROMs) to assess the specific functional abilities and life quality of patients. There were a lot of PROMs tools whose reliability had already been verified in the assessment of ALS patients from different perspectives. The PROMs in this systematic review are listed as follows.

Overall Functional Score

ALSFRS was the most common outcome measure in clinical trials researching ALS patients. There were two kinds of ALSFRS commonly used in clinical practice. One was the ALSFRS-R. The ALSFRS-R included 12 questions and was rated on a 5-point Linkert scale from 0, which referred to being unable to perform the task to 4, which referred to normal ability (Cedarbaum et al., 1999). The other was the original version of ALSFRS, which had 10 questions whose scores ranged from 0 to 4. The total scores of the original version of ALSFRS were between 0, which represented the worst, and 40, which represented the best (Group, 1996).

Respiratory Function

The percent predicted value for forced vital capacity (FVC) was selected to represent the respiratory function of ALS patients.

Perceived Fatigue

The fatigue severity scale (FSS), which was a self-report scale of nine items examining motivation, physical function, responsibilities, work, family or social life, exercise, fatigue, frequency of problems, and priority of symptoms with scores of answers ranged from 1 that referred to strongly disagree to 7 that referred to strongly agree, was selected to represent the perceived fatigue of ALS patients. There was good evidence of its psychometric properties and clinical feasibility in measuring fatigue in various neurological conditions (Tyson and Brown, 2014). Moreover, the Checklist for Individual Strength-Fatigue (CIS-Fatigue), which was a 20-item self-report questionnaire that captured four domains of fatigue, including subjective experience of fatigue, reduction in motivation, reduction in activity,

TABLE 1 | Description of basic interventions/comparators.

Interventions/comparators	Abbreviation	Description
Aerobic exercise	AE	Exercise on a cycle ergometer, treadmill, or rowing machine under an intensity below the lactic acid threshold.
Resistance training	RT	Active muscle exercise of endurance, strength, or power against gravity, external loaded weight, or fitness equipment.
Standard rehabilitation	SR	Rehabilitation protocols that contained stretching, proprioceptive exercises, functional exercise, or any forms of sham (or placebo) treatments.
Passive exercise	PE	Movement exercises induced by special therapists
Expiratory muscle exercise	EE	Expiratory muscle strength training or breathing exercise with the help of expiratory training devices.
Daily activity	DA	Maintaining usual daily activities

and reduction in concentration, was also chosen to represent the perceived fatigue of ALS patients. The CIS-Fatigue had demonstrated satisfactory psychometric properties, including high internal consistency and the ability to discriminate against healthy individuals (Dittner et al., 2004).

Quality of Life

Three kinds of PROMs were used in this systematic review to represent the quality of life. The first one was the Short Form (36) Health Survey (SF-36), an often used, well-researched, and self-reported health measure. The SF-36 comprised 36 questions covering 8 domains of health. Scores for the different domains were converted and pooled using a scoring key for a total score of low to high quality of life. The SF-36 had been found valid, reliable, and responsive to change across diverse clinical populations (McHorney et al., 1994). The second one was the Euro-Qol-5D (EQ-5D), which was widely used in different countries by clinical researchers in various clinical areas. EQ-5D was one of the handful of measures recommended for use in cost-effectiveness analyses and had been translated into most major languages (Rabin and de Charro, 2001). The last PROM for life quality assessment was the McGill Quality of Life (McGill-QoL) questionnaire. The McGill-QoL assessed six domains, including a single item (a single question about the overall quality of life in the past 2 days), physical symptoms or physical problems, psychological symptoms or psychological problems, physical well-being, and existential well-being, and support (Cohen et al., 1995).

Study Design

Only studies of randomized controlled trials were eligible for this systematic review.

Exclusion Criteria

Studies were excluded if: (1) The participants were under18 years old or physical disable; (2) the participants of the trial were from a mixed population with different progressive neuromuscular diseases; (3) the intervention of the trial could not be reclassified into AE, RT, SR, PE, EE, or DA; (4) the participants of the trial took supplementation, such as nitric oxide, creatine, or caffeine, that could improve respiratory function or sporting performance; (5) the participants had clinical exercise contraindication; (6) the study was a published abstract.

Information Sources

Since the revised El Escorial Criteria of ALS diagnosis was published in December 2000, a comprehensive, reproducible search strategy was conducted on the following databases from December 2000 to February 2022: PubMed, Embase, and Web of Science. Reference lists of included studies had also been searched. Gray literature was searched to identify potential studies. The authors were contacted and requested missing data if the original data of articles were insufficient.

Search Strategy

The search terms used in each database were set according to the following logic: (1) contained the term "ALS" or "amyotrophic lateral sclerosis" in the title; (2) contained the term "exercise," "train," or "training" in the title; (3) contained the term "randomized" or "randomised" in title or abstract.

Study Selection

All potential studies were imported into EndNote X9 (Thomson Reuters, Carlsbad, California, USA) after removing duplicates. Title, abstract, and full-text screening were made by two independent authors (YZ and XY). Any disagreement was resolved by a third independent reviewer (YG).

Data Collection Process

Data were extracted by two independent authors (YZ and XY). An independent reviewer was invited to check all the collected data (RX).

Data Items

The following information was collected and recorded. (1) Demographic characteristics, such as mean age and gender ratio; (2) information about intervention programs, such as names of interventions, details of programs, and the categories they could be reclassified; (3) information on each outcome measure, such as the names the of the PROMs scales and their overall scores; (4) data would be used in network meta-analysis, such as sample size of every group and results of each outcome measures in each record point, as well as the number of lost to follow up. All the data is provided in the **Supplementary Material**.

Risk of Bias Assessment

The Cochrane Collaboration Risk of Bias Assessment Tool was used to assess the risk of bias (Robertson et al., 2014). All the included studies were assessed by two independent authors (YZ and XY). Any disagreement would be discussed, and an independent arbitrator (YG) was invited when an agreement could not be met. Agreement between authors was determined by Cohen's Kappa value.

Data Pre-Processing

Data pre-processing and analysis were made by one independent author (YZ) using Microsoft Office Excel (Version 16.0 Microsoft Corporation, Redmond, WA, USA). The overall scores of every PROMs scale in each included study were recorded. Since different PROMs scales had different overall scores, after combining and comparing the results of different PROMs in a unified unit, all the original data was transferred into the percentage of overall score (Mean% ± SD%) by using a mathematical conversion, as shown in Equation (1). Moreover, since some included studies only reported the scores of subscales, mean scores and their standard deviations of every subscale were converted and then pooled together by Equations (2) and (3). Additionally, some outcome measures such as the quality of life and perceived fatigue were measured by different PROMs scales, Equations (2) and (3) were also used to pool scores of different scales after these scores had been transferred into the percentage of overall scores.

$$Mean\% \pm SD\% = \frac{Mean\ Score}{Overall\ Score} \times 100\% \pm \frac{SD}{Overall\ Score} \times 100\% \quad (1)$$

$$Mean_{total} = \sum Mean_{sub} \quad (2)$$

$$SD_{total} = \sqrt{\sum SD_{sub}^2} \quad (3)$$

Another independent author was invited to check all the original data and their pre-processing results to ensure there was no error.

Synthesis of Results

The Aggregate Data Drug Information System (ADDIS V1.16.8 Produced by Drugis.org, http://drugis.org/software/addis/index) was applied to pool all the processed data into network meta-analysis, calculate the effect size, and output results.

Risk of Bias Across Studies

The Cochrane Collaboration Risk of Bias Assessment Tool was used to assess the risk of bias across the included studies (Robertson et al., 2014). The assessment was conducted according to the results of the bias risk assessment of individual studies.

Network Meta-Analysis

Network Geometry

The network geometries provided key information about the strength of evidence and displayed the number and form of interventions by the Bayesian simulation modeling. Every node in the network geometry represented one intervention; the lines referred to a direct comparison between each pair of interventions, while the number of comparison arms was represented by the number on each line (Salanti et al., 2011).

Consistency and Inconsistency Analysis

The consistency of the evidence structure was identified at first since the network meta-analysis was based on the homogeneity, similarity, and consistency hypothesis (Song et al., 2008). If there were closed loops in the evidence structure, the evidence structure was more complex, and the network meta-analysis was called a mixed intervention comparison, and the inconsistency occurred.

There were two approaches to identify the inconsistency. First, the random-effects standard deviations were calculated under both consistency and inconsistency models to determine if there was inconsistency within interventions. If the random-effects standard deviations under the two models were identical, it meant that there was a good consistency with the interventions. Second, the *P*-values calculated in the analysis of the node splitting were checked to determine which model could be used. The node-splitting analysis is an alternative method to assess inconsistency in network meta-analysis. It assessed whether direct and indirect evidence on a split node was in agreement. The node-splitting analysis was performed within a Bayesian framework and was computationally more intensive than other approaches. Whether the identified discrepancy was statistically significant was determined by examining the calculating a respective Bayesian *P*-value. If the *P*-value of all the direct and indirect evidence comparisons were larger than 0.05, the consistency model could be used to conduct the network meta-analysis (Dias et al., 2010).

If there was no relevant inconsistency, or there was no closed loop in the evidence structure, a consistency model was used to conclude the relative effect of the included interventions (Lu and Ades, 2006), and the network meta-analysis was called an adjusted indirect intervention comparison. Under the consistency model, the results were shown in the rank probability plot (Dias et al., 2013).

Ranking of Measures and Probability

A ranking of measures and probability was made to facilitate simultaneous inference regarding interventions. The ranking of treatments was made according to the probability of each intervention being the most effective or the least effective with the overall sum of the percentage in each row or column being 1.00 (100%).

RESULTS

Search Strategy and Information Extraction

The search yielded 1,067 titles and abstracts for screening. After removing 544 duplicated studies, 523 studies were included in the records screening. As only randomized controlled trials (RCTs) would be included in this systematic review, 500 studies that were not RCTs were excluded, and 23 studies were included for full-text article assessment for eligibility. Among the 23 studies, three studies were excluded because of lack of data, five studies were excluded due to their ineligible design, one study was excluded because of its ineligible interventions, and one study was excluded because of its ineligible participants. Eventually, 10 studies were included in the final analysis (Drory et al., 2001; Bello-Haas et al., 2007; Pinto et al., 2012; Lunetta et al., 2016; Braga et al., 2018; Merico et al., 2018; Ferri et al., 2019; Plowman et al., 2019; van Groenestijn et al., 2019; Kalron et al., 2021). The identification process is shown as a flow diagram in **Figure 1**. The information of all included studies is shown in **Table 2**. All the original data was provided in the **Supplementary Material**.

Risk of Bias Assessment

Figure 2 shows the assessment results of the risk of bias. According to the overall bias provided in **Figure 2A**: (1) the risk of performance bias (blinding of participants and personnel) was high (high in 9 studies); (2) the risk of detection bias (blinding of outcome assessors) was moderate (high in 3 studies); (3) the risk of attrition bias (incomplete outcome data) was moderate (high in 4 studies); (4) the risk of selection bias (random sequence generation and allocation concealment) was low (low in all studies); (5) the risk of reporting bias (selective reporting of outcomes) was low (low in 8 studies). According to the Cochrane Collaboration Risk of Bias Assessment Tool, a study with three or more items in high risk would be regarded as having a high risk of bias, a study with five or more items with low risk and 1 item with high risk at most would be regarded as having a low risk of bias, and a study under other conditions would be regarded as having a moderate risk of bias. It was shown in **Figure 2B** that two studies had a high risk of bias, five studies had a moderate risk of bias, and three studies had a low risk of bias. The agreement between authors reached a kappa-value of 0.73.

Network Meta-Analysis

The evidence structures of the mixed interventions comparisons for the overall functional score, respiratory function, perceived fatigue, and quality of life are presented in **Figure 3**, while the results of the consistency and inconsistency analysis are provided in **Table 3**.

According to **Figure 3**, there were nine kinds of interventions included in the network meta-analysis of the effects on overall functions scores with an evidence structure of a mixed comparison; there were seven kinds of interventions included in the network meta-analysis of the effects on respiratory function with an evidence structure of a mixed comparison; there were six kinds of interventions included in the network meta-analysis of the effects on perceived fatigue with an evidence structure of an adjusted indirect comparison; and there were eight kinds of interventions included in the network meta-analysis of the effects on quality of life with an evidence structure of a mixed comparison. Besides, except for the direct comparison of SR and AE + SR, which had two arms, other direct comparisons had only one arm. According to **Table 3**, all the evidence of structures showed good consistency with the random-effects standard deviations calculated under consistency and inconsistency models were fully identical, and the *P*-value of all the direct and indirect evidence comparisons in the node-splitting analysis was more than 0.05. Therefore, the consistency model could be applied to conduct the network meta-analysis of all the outcomes. **Figure 4** and **Table 4** provide the probability rank of every intervention in each mixed comparison. It should be noted that the PROMs of the overall functional score, respiratory function, and the quality of life were continuous data that the higher would be better, while the PROMs of perceived fatigue were continuous data that the lower would be better. Therefore, in the probability rank of perceived fatigue, Rank N would be the best, whereas, in the other three PROMs domains, Rank 1 would be the best. The league table of the network meta-analysis for each outcome is provided in the **Supplementary Material**, the numbers showing the synthesized effect size differences of the comparison between every two interventions.

According to the rank of probability presented in **Table 4**, a combination program of aerobic and resistance exercise had the most potential to be the best intervention choice in improving the overall functional score for ALS patients (0.51 in Rank 1 and 0.01 in Rank 9), while maintaining DA, SR protocols, and EE might have the lowest probabilities to become the best intervention choices for the overall functional score of ALS patients (0.00, 0.00, and 0.03 in Rank 1 and 0.26, 0.14, and 0.40 in Rank 9). When it came to the respiratory function, there were two intervention programs with high potential, one of which was combination programs of AE and RT (0.27 in Rank 1 and 0.06 in Rank 7), and the other was PE (0.29 in Rank 1 and 0.07 in Rank 7). In contrast, programs included AE and SR programs and programs contained PE and SR showed the lowest probability to induce the best positive effectiveness (0.06 and 0.02 in Rank1 and 0.31 and 0.33 in Rank 7). A multi-model intervention program contained AE, RT, and SR, or a program that only contained AE and SR showed the highest potential to bring the largest effect on reducing perceived fatigue for ALS patients (0.39 and 0.32 in Rank 6, 0.04 and 0.05 in Rank 1), while keeping DA showed the lowest potential from this perspective (0.72 in Rank 1 and 0.02 in Rank 6). Additionally, the low potential for creating the best effectiveness of maintaining DA also occurred when it came to improving the life quality for ALS patients (0.52 in Rank 8 and 0.02 in Rank 1), whereas multi-model intervention programs contained AE, RT, and SR seemed to have the highest potential to be the best intervention from this perspective (0.64 in Rank 1 and 0.01 in Rank 8).

DISCUSSION

The objective of this systematic review and network meta-analysis is to conduct a mixed comparison of different exercise

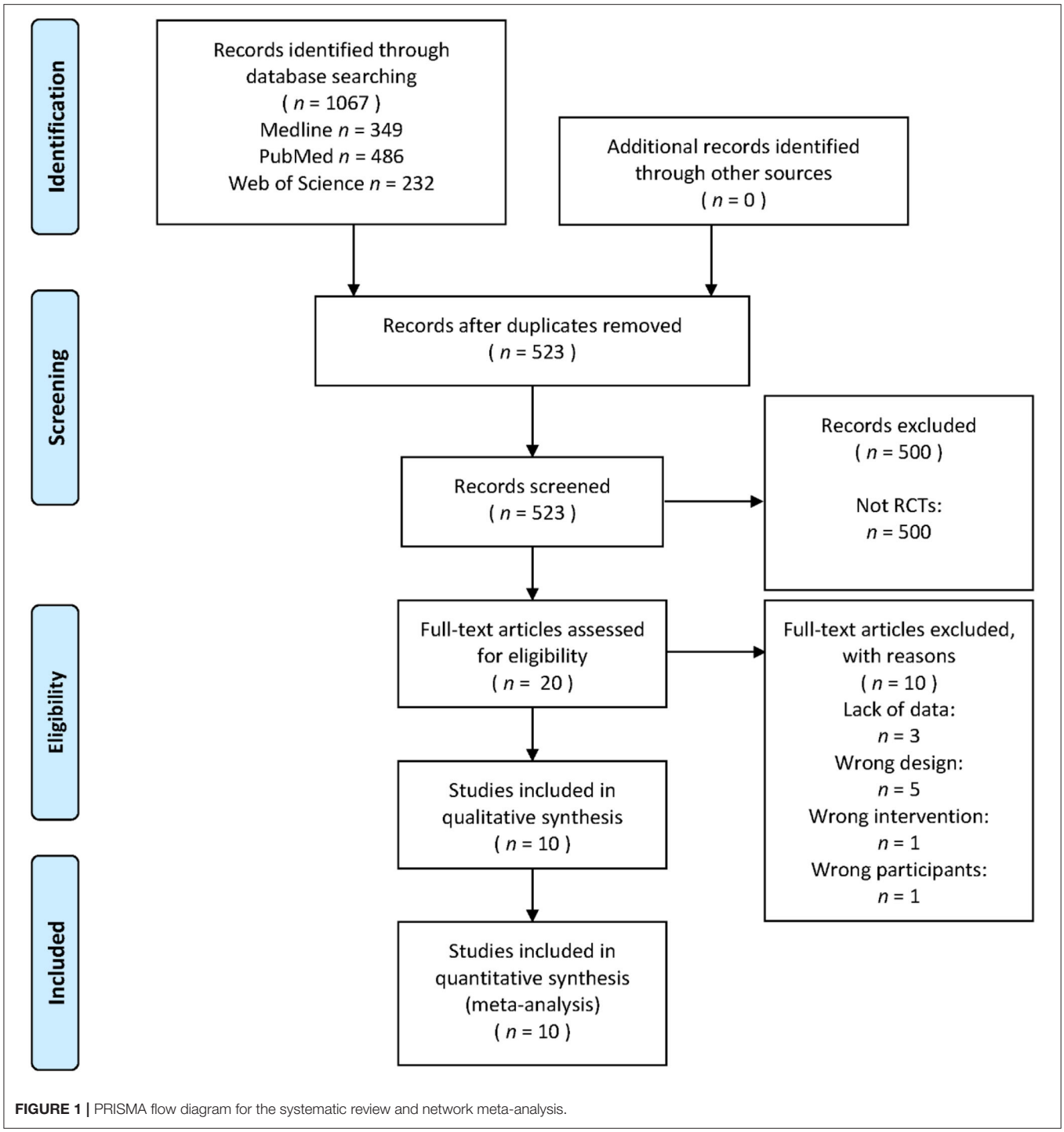


FIGURE 1 | PRISMA flow diagram for the systematic review and network meta-analysis.

interventions for function, respiratory, fatigue, and quality of life in adults with ALS by using the percentage change of PROMs as outcomes. The main findings of this review are as follows. First, for ALS patients, a combined program of AE, resistance exercise, and SR might be the best intervention to improve their quality of life and reduce their perceived fatigue, while exercise programs of aerobic and RT showed the highest potential to improve their overall physical function. Moreover, only maintaining DAs might not be beneficial to ALS patients in relieving perceived fatigue or improving their quality of life. Last, the effect of exercise on the respiratory was still unclear. The main findings indicated that ALS patients could acquire the benefit induced by different exercise interventions without significant interference effect, and the positive effect

TABLE 2 | The information of all included studies.

Study	Interventions			Participants				Outcome measures	
	Exercise	Program	Classification	Mean age	Number	Gender (F/All)	Lost	Measurement	Total score
Drory et al. (2001)	Muscle endurance exercise	15-min muscle endurance exercise for limbs and trunk at home, 2/week	RT	58.0	14	6/14	6	ALSFRS FSS VAS SF-36	40 63 10 100
	Daily routine activity	Keep daily routine activity	DA	60.7	11	5/11	5		
Bello-Haas et al. (2007)	Resistance exercise	Moderate-load-and-intensity resistance exercise and stretching exercise, 3 sessions/week	RT	56.0	13	4/13	5	ALSFRS FSS FVC SF-36	40 63 100 100
	Stretching	Stretching exercise, 3 sessions/week	SR	51.8	14	7/14	4		
Lunetta et al. (2016)	Strictly monitored exercise programs (1)	Active exercise against gravity in six muscle groups in the upper and lower limbs, 3 sets of 3 reps each muscle group + 20-min cycloergometer activity for lower limbs associated with a body ergometer for upper limbs from a sitting position at 60% of maximal power output	AE + RT	61.1	30	9/30	8	ALSFRS-revised FVC McGill-QOL	48 100 140
	Strictly monitored exercise programs (2)	Active exercise program against gravity in six muscle groups in the upper and lower limbs, 3 sets of 3 reps each muscle group	RT						
	Strictly monitored exercise programs (3)	A passive exercise program consisting of 20 min of 20 flexion-extension movements per minute in 6 muscle groups in the upper and lower limbs	PE						
	Home-based passive exercise programs	Usual care program including passive exercises consisting of 20 min of 20 times flexion-extension movements/min, 6 muscle groups in the upper and lower limbs followed by stretching exercise in the four limbs, 2 days/week	PE + SR	60.3	30	13/30	5		
Braga et al. (2018)	Aerobic exercise and standard care	Aerobic exercise on the treadmill and standard care of daily exercises including a range of motion exercises, limbs relaxation, trunk balance, and gait training, 2 sessions/week	AE + SR	63.2	24	6/24	5	ALSFRS-revised	48
	Standard care	Standard care of daily exercises including Range of Motion exercises, limbs relaxation, trunk balance, and gait training + program at home or other rehabilitation, 2 sessions/week	SR	62.0	24	10/24	19		
Merico et al. (2018)	Specific exercise	Individualized strengthening by using rubber bands, 3 reps for bilateral muscle, and 80% max contraction + 15-20 min of aerobic endurance by using cycle ergometer or ergometry arm-leg or treadmill at 65% MHR, 7 sessions/week, 60 min	AE + RT	61.6	23	10/23	8	FIM FSS	126 63

(Continued)

TABLE 2 | Continued

Study	Interventions			Participants				Outcome measures	
	Exercise	Program	Classification	Mean age	Number	Gender (F/All)	Lost	Measurement	Total score
	Standard neuromotor rehabilitation	60-min standard care including stretching exercise, active mobilization, and general muscle reinforcement, 7 sessions/week	SR	59.8	15	4/15	8		
van Groenestijn et al. (2019)	Aerobic exercise	Aerobic cycling exercise program on a cycle ergometer and a step board + Usual careneuropalliative care by multidisciplinary, secondary care teams, 3 sessions/week	AE + SR	60.9	27	9/27	17	ALSFRS-revised CIS-Fatigue VAS FVC SF-36	48 56 10 100 200
	Usual care	Usual care program consists of a rehabilitation medicine consultant, an occupational therapist, physical therapist, speech therapist, dietician, social worker, psychologist, and consultant physicians	SR	59.9	30	8/30	8		
Ferri et al. (2019)	Tailored exercise training	15-min cycling + 25-min strength exercises with 60 % RM + 10-min proprioceptive exercises + 10-min upper and lower body strength exercises, 3 sessions/week	AE + RT + SR	50.7	8	2/8	1	ALSFRS-revised	48
	Usual care	Maintaining usual daily activities	DA	55.5	8	2/8	4		
Pinto et al. (2012)	Respiratory exercise	Inhaling and exhaling through the Threshold-IMT device, 2 times/day, 8 months	EE	57.0	13	8/26	2	ALSFRS FIM FSS FVC EQ5D-VAS	40 126 63 100 100
	Placebo exercise	Follow a placebo exercise program for the first four months and then active exercise for the second four-month period	DA		13		4		
Plowman et al. (2019)	Expiratory Strength Training	Expiratory muscle strength training at 50% of maximum expiratory pressure, at home, 5 times/week + 1 time/week, 5 sets of 5 reps targeted forced exhalations, 8 weeks total	EE	63.1	24	7/24	1	ALSFRS FVC	40 100
	Sham expiratory Strength Training	Placebo training program with a trainer that looked identical to the high physiologic load trainer but had the internal spring removed	DA	60.1	24	12/24	1		
Kalron et al. (2021)	Aerobic and strength training	2 times/week, aerobic training by recumbent cycling, flexibility achieved by stretching and passive exercises, and strength training *via* functional exercises	AE + RT + SR	60.4	16	6/16	2	ALSFRS-revised FSS FVC SF-36	48 63 100 800
	Stretching exercise	Basic stretching exercises of the upper and lower limb at home	SR	56.7	16	5/16	2		

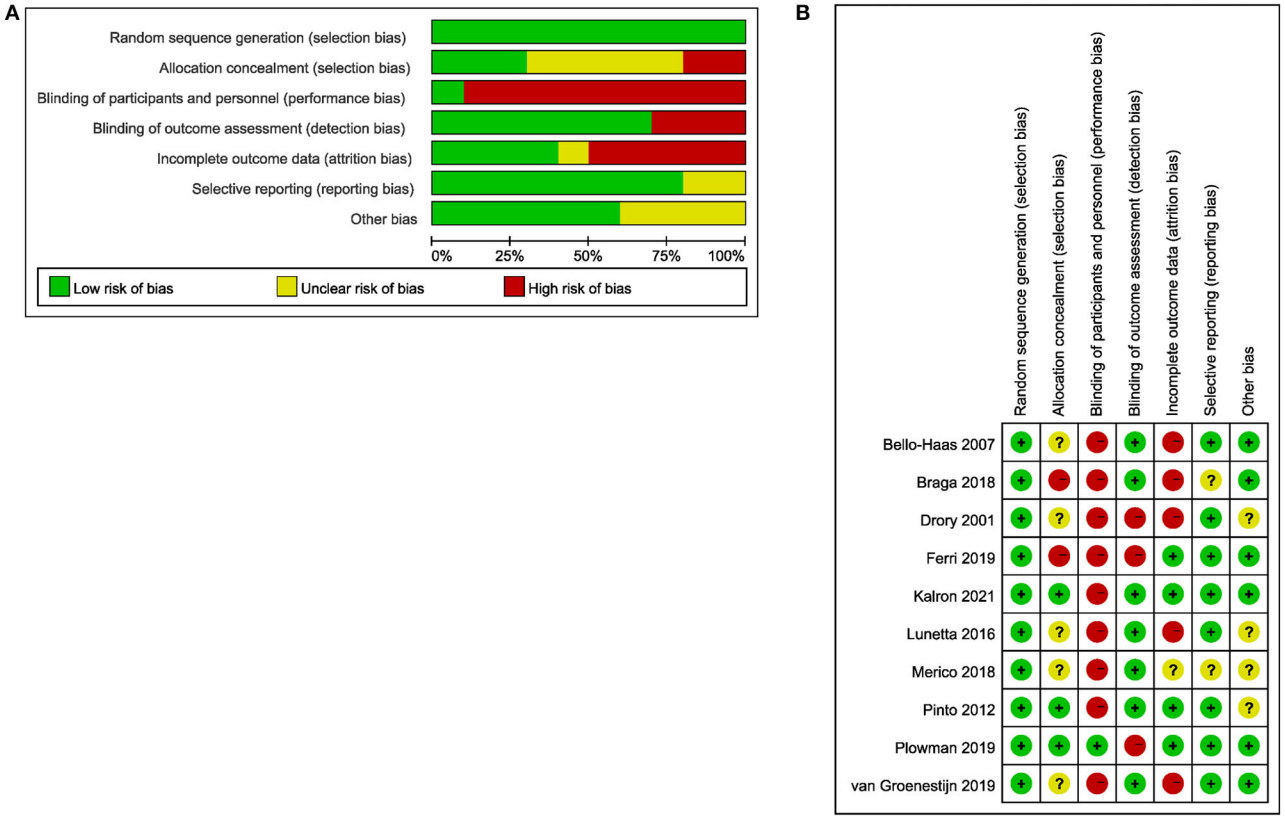


FIGURE 2 | The result of the risk of bias assessment. **(A)** Risk of bias graph; **(B)** Risk of bias summary.

TABLE 3 | The results of the consistency and inconsistency analysis.

Outcome measures	Interventions	Random-effects standard deviations		Node-splitting analysis	
		Consistency model Mean (95%CI)	Inconsistency model Mean (95%CI)	Comparison	*P*-value
Overall functional score	AE + RT, AE + RT + SR, AE + SR, DA, EE, PE, PE + SR, RT, SR	7.99 (0.57, 22.63)	7.01 (0.24, 22.35)	AE + RT + SR vs. DA AE + RT + SR vs. SR DA vs. RT RT vs. SR	0.31 0.30 0.36 0.31
Respiratory function	AE + RT, AE + RT + SR, AE + SR. PE, PE + SR, RT, SR	4.77 (0.42, 9.07)	4.75 (0.29, 9.08)	None	
Perceived fatigue	AE + RT, AR + RT + SR, AE + SR, DA, RT, SR	10.36 (0.47, 20.52)	10.61 (0.68, 20.57)	None	
Quality of life	AE + RT, AE + RT + SR, AE + SR, DA, PE, PE + SR, RT, SR	5.54 (0.46, 10.59)	5.23 (0.03, 10.60)	None	

induced by unimodal interventions might be weaker than multi-modal interventions.

The positive effect of multi-modal exercise interventions that contain AE, RT, and SR programs in improving the quality of life and reducing the perceived fatigue of ALS patients has already been identified by many previous studies and systematic reviews. For example, a preliminary study published in 2010 determined the feasibility, tolerability, safety, and effect size of repetitive rhythmic exercise for ALS patients, concluding that repetitive rhythmic exercise that contained both resistance and stretching movements was feasible, tolerated, and safe and was consistent with improved work capacity and gait function in patients with

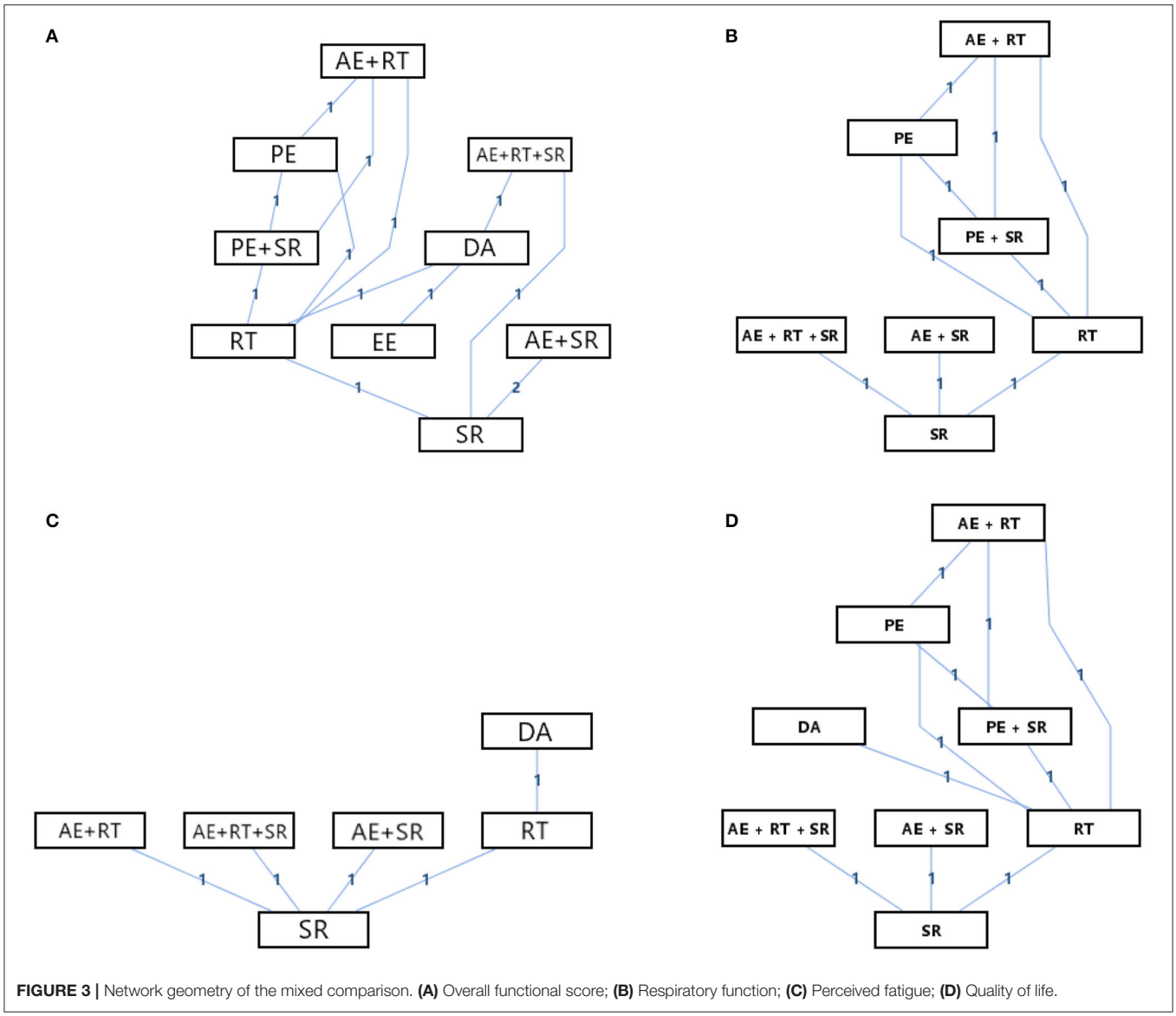


FIGURE 3 | Network geometry of the mixed comparison. **(A)** Overall functional score; **(B)** Respiratory function; **(C)** Perceived fatigue; **(D)** Quality of life.

ALS who are dependent on assistive devices for ambulation (Sanjak et al., 2010). A systematic review published in 2021 demonstrated that physical exercise would be an efficacious and safe therapeutic intervention with a medium-sized effect on the quality of life, a large effect on mood, and a small but significant effect on improving cognition in patients with chronic brain disorders. The effect had a positive dose-response correlation, no matter the exercise was AE, resistance exercise, or concurrent exercise of endurance training and strength training (Dauwan et al., 2021).

The possible mechanism of the multi-modal exercise interventions might come from the following aspects. On one hand, AE training could reduce psychosocial stress, which is an independent risk factor for mortality in patients with chronic diseases (Milani and Lavie, 2009). On the other hand, RT could be an important factor in enhancing the quality of life and survival of patients with chronic diseases by enhancing baroreflex sensitivity by an angiotensin II-dependent mechanism induced by the mechanical tension during training (Mousa et al., 2008). Some animal experiments have also explored the physiological and psychological mechanisms of the multi-modal exercise program, an animal trial with rats as subjects explored the curative effect and possible mechanism by observing the changes in behavior, inflammatory factors, and intestinal flora in rats after exercise, claiming that the mechanism of exercise training to improve the depressive behavior of rats might be related to inhibiting the expression of proinflammatory factors and increasing the number of lactic acid bacteria in the intestine (Yang et al., 2021). When it comes to stretching exercises, stretching exercises could improve flexibility, maintain the extensibility of muscle and soft tissue, improve joint mobility, and prevent contractures. As patients with ALS usually have

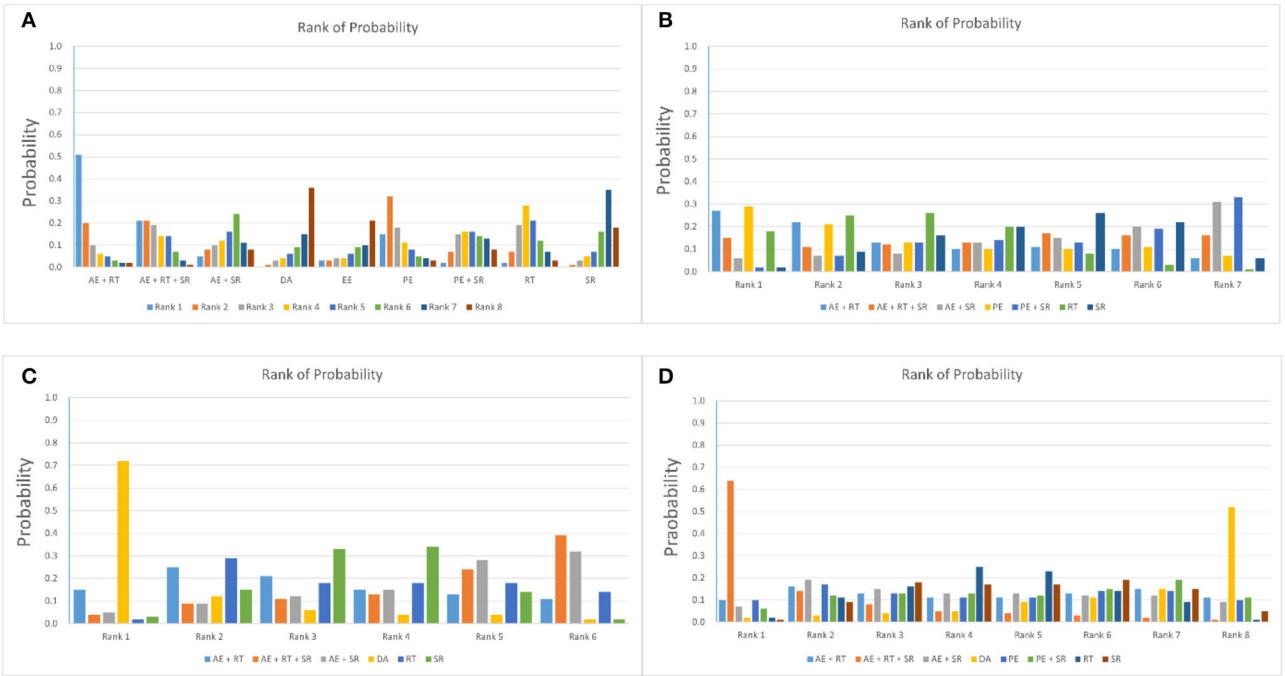


FIGURE 4 | Network geometry of the mixed comparison. **(A)** Overall functional score; **(B)** Respiratory function; **(C)** Perceived fatigue; **(D)** Quality of life.

weaker muscles, they easily get an imbalance between agonist and antagonist muscle groups, predisposing themselves to muscle shortening, joint contractures, and poor posture such as Claw hand deformity. Stretching weakened and unaffected muscle groups could prevent contractures, maintain good alignment of body segments, reduce pain from hypomobility, and help lessen the potential complexities of functional mobility and performing activities of daily living (White and Dressendorfer, 2004).

Besides, the results of this network meta-analysis also demonstrated that exercise programs of aerobic and RT showed the highest potential to improve their overall physical function. This result is correspondent with that of some previous studies, a preliminary study conducted in 2018 demonstrated that structured home-based exercises without supervision by a physical therapist could be used to alleviate functional deterioration in patients with early-stage ALS (Kitano et al., 2018). In 2019, Sivaramakrishnan's team investigated the safety and feasibility of slowing disease progression in ALS and possibly facilitating neuroplasticity, and identified that the effect of a recumbent stepping program for improving the score of ALSFRS was similar to that of common exercise modalities, such as the treadmill and cycle ergometer (Sivaramakrishnan and Madhavan, 2019). Moreover, a narrative review published in 2008 identified that based on human and animal studies of exercise and motor neuron degeneration, it could be concluded that exercise, particularly individualized, monitored, and progressive resistance exercise, was likely to be more beneficial than deleterious for patients with ALS by inducing functional improvement (Chen et al., 2008).

This phenomenon also occurs in many previous studies that explored the effect of aerobic and resistance exercise programs on patients with other progressive neuromuscular diseases. For example, a systematic review published in 2021 claimed that cardiopulmonary exercise has a vast potential for patients with neuromuscular diseases (Barroso de Queiroz Davoli et al., 2021). Moreover, a randomized controlled trial conducted by Holm's team in 2021 identified the positive effect of strength training in addition to neuromuscular exercise and education in neuromuscular disease patients with a dose- and type-specific relationship with their pain sensitization (Holm et al., 2021). Furthermore, another systematic review and meta-analysis published in January 2022 summarized the evidence on the efficacy of AE on aerobic capacity in slowly progressive neuromuscular diseases and found that AE would be safe and leads to moderate improvement of aerobic capacity directly post-intervention in slowly progressive neuromuscular diseases, but the long-term efficacy remained unclear (Oorschot et al., 2022).

The mechanism of these results could be explained by molecular biomechanics. The molecular biomechanical generation of progressive neuromuscular diseases might be from the aggregation and folding of isomers of protein molecules in the brain (Aguzzi and O'Connor, 2010). Physical exercise could directly affect the secretion of neurotransmitters in the brain. For example, Santos-Galduroz's team found that AE under high intensity could induce the increase of neurotrophic factor secretion in the brain, promoting the formation of synapses and neurons, which is closely related to reducing the damage of progressive neuromuscular diseases to the brain of patients

TABLE 4 | The rank probability rank of each mixed interventions comparison.

Outcome measures	Intervention	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9
Overall functional score	AE + RT	0.51	0.20	0.10	0.06	0.05	0.03	0.02	0.02	0.01
	AE + RT + SR	0.21	0.21	0.19	0.14	0.14	0.07	0.03	0.01	0.01
	AE + SR	0.05	0.08	0.10	0.12	0.16	0.24	0.11	0.08	0.06
	DA	0.00	0.01	0.03	0.04	0.06	0.09	0.15	0.36	0.26
	EE	0.03	0.03	0.04	0.04	0.06	0.09	0.10	0.21	0.40
	PE	0.15	0.32	0.18	0.11	0.08	0.05	0.04	0.03	0.02
	PE + SR	0.02	0.07	0.15	0.16	0.16	0.14	0.13	0.08	0.10
	RT	0.02	0.07	0.19	0.28	0.21	0.12	0.07	0.03	0.01
	SR	0.00	0.01	0.03	0.05	0.07	0.16	0.35	0.18	0.14
Respiratory function	AE + RT	0.27	0.22	0.13	0.10	0.11	0.10	0.06		
	AE + RT + SR	0.15	0.11	0.12	0.13	0.17	0.16	0.16		
	AE + SR	0.06	0.07	0.08	0.13	0.15	0.20	0.31		
	PE	0.29	0.21	0.13	0.1	0.10	0.11	0.07		
	PE + SR	0.02	0.07	0.13	0.14	0.13	0.19	0.33		
	RT	0.18	0.25	0.26	0.20	0.08	0.03	0.01		
	SR	0.02	0.09	0.16	0.20	0.26	0.22	0.06		
Perceived fatigue	AE + RT	0.15	0.25	0.21	0.15	0.13	0.11			
	AE + RT + SR	0.04	0.09	0.11	0.13	0.24	0.39			
	AE + SR	0.05	0.09	0.12	0.15	0.28	0.32			
	DA	0.72	0.12	0.06	0.04	0.04	0.02			
	RT	0.02	0.29	0.18	0.18	0.18	0.14			
	SR	0.03	0.15	0.33	0.34	0.14	0.02			
Quality of life	AE + RT	0.10	0.16	0.13	0.11	0.11	0.13	0.15	0.11	
	AE + RT + SR	0.64	0.14	0.08	0.05	0.04	0.03	0.02	0.01	
	AE + SR	0.07	0.19	0.15	0.13	0.13	0.12	0.12	0.09	
	DA	0.02	0.03	0.04	0.05	0.09	0.11	0.15	0.52	
	PE	0.10	0.17	0.13	0.11	0.11	0.14	0.14	0.10	
	PE + SR	0.06	0.12	0.13	0.13	0.12	0.15	0.19	0.11	
	RT	0.02	0.11	0.16	0.25	0.23	0.14	0.09	0.01	
	SR	0.01	0.09	0.18	0.17	0.17	0.19	0.15	0.05	

(Coelho et al., 2014). A trial of mice models also identified that physical exercise could delay the degeneration of central nervous system function, significantly improving the pathological characteristics of beta-amyloid protein and inhibiting the reduction of synaptic proteins as well as neurotrophic factors in the hippocampus and cerebral cortex neurons (Cho et al., 2015). And a systematic review and meta-analysis conducted in 2019 found a significant effect of AE on interleukin-6 and tumor necrosis factor-alpha decrease and positive effects on brain-derived neurotrophic factor expression (Stigger et al., 2019). Moreover, a preliminary study conducted in 2019, in which the researchers correlated clinical scales with molecular data on miRNAs (markers of myogenesis during muscle regeneration and contribute to neuromuscular junction stabilization or sprouting), identified that moderate AE could reduce miRNAs in serum, indicating that circulating miRNAs changed during skeletal muscle recovery in response to physical rehabilitation in ALS (Pegoraro et al., 2019).

The low ranking of maintaining DAs among all interventions is not surprising. Within all these categories of interventions, DA is not a treatment for ALS and is usually set as an intervention in control groups. Besides, this result could indicate that ALS might not be a self-limiting disease whose symptoms would not resolve over time. It means that if patients with ALS do not carry out a particular treatment, only keeping their DAs might not bring any positive effects for them.

What should be paid attention to was that the probability of being the best would not eliminate the uncertainty in the relative intervention effects and could spuriously give higher ranks to interventions for which little evidence is available. The probability of being the best had the disadvantage that it would not reflect the spread of rankings for the treatments, and to consider just the crude figures may be misleading. Therefore, ranking interventions based solely on the probability of each intervention being the best should be avoided (Salanti et al., 2011). At the same time, although there is no serious adverse event reported in the included studies, the safety of exercise interventions should still be worthy of attention. According to what has been mentioned in the introduction of this review, the motor neuronal injuries and induced ALS

might increase the risk of falls during physical exercise, and the change in dose-response of exercise might also increase the risk of overtraining during long-term physical exercises. There are also some limitations of this systematic review. Although there was a meta-analysis published in 2020 claimed that therapeutic exercise appeared beneficial for patients with ALS and exerted more of a cardiopulmonary benefit, as opposed to preventing the progression of limb weakness (Park et al., 2020), the primary limitation is that the EE could not be included in the mix comparison for the respiratory function of ALS patients since there was not any direct comparison between EE and any intervention in the evidence structure of network meta-analysis for respiratory function. According to the specificity principle of training, it could be possible that the effect of EE on respiratory function for ALS patients would be better than other exercise programs since the EE is training specifically designed to improve respiratory function. Further studies of high evidence level clinical trials should be conducted. Another limitation of this systematic review is that, as the weight distribution in network meta-analysis is based on the arms of each direct comparison, rather than the sample size of the included trials, in this network meta-analysis, many direct comparisons have only one arm. At last, in this systematic review, the included studies only referred to the short-term effects assessed immediately after the rehabilitation. Considering the different effects of exercises that are assessed in ALS stages with different severities of symptoms, there is still a lack of knowledge of physical exercise effects on the disease progression and survival. Therefore, the weight distribution of this network meta-analysis might be too average, so the results need to be interpreted with caution.

CONCLUSION

A multi-modal exercise and rehabilitation program that contains aerobic, resistance, and stretching elements would be more beneficial to ALS patients. However, the safety and guide for practice remain unclear, and randomized controlled trials with a larger sample and higher quality are still needed in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ and YG: conceptualization and writing–review and editing. YX, RX, BI, and YG: methodology. YZ, YX, JH, and GF: formal analysis. YZ, YX, and RX: investigation. YZ and YX: data curation. BI, GF, and YG: supervision. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.919059/full#supplementary-material

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Comorbid depressive symptoms can aggravate the functional changes of the pain matrix in patients with chronic back pain: A resting-state fMRI study

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Objective: The purposes of this study are to explore (1) whether comorbid depressive symptoms in patients with chronic back pain (CBP) affect the pain matrix. And (2) whether the interaction of depression and CBP exacerbates impaired brain function.

Methods: Thirty-two patients with CBP without comorbid depressive symptoms and thirty patients with CBP with comorbid depressive symptoms were recruited. All subjects underwent functional magnetic resonance imaging (fMRI) scans. The graph theory analysis, mediation analysis, and functional connectivity (FC) analysis were included in this study. All subjects received the detection of clinical depressive symptoms and pain-related manifestations.

Result: Compared with the CBP group, subjects in the CBP with comorbid depressive symptoms (CBP-D) group had significantly increased FC in the left medial prefrontal cortex and several parietal cortical regions. The results of the graph theory analyses showed that the area under the curve of small-world property ($t = -2.175$, $p = 0.034$), gamma ($t = -2.332$, $p = 0.023$), and local efficiency ($t = -2.461$, $p = 0.017$) in the CBP-D group were significantly lower. The nodal efficiency in the ventral posterior insula (VPI) ($t = -3.581$, $p = 0.0007$), and the network efficiency values ($t = -2.758$, $p = 0.008$) in the pain matrix were significantly lower in the CBP-D group. Both the topological properties and the FC values of these brain regions were significantly correlated with self-rating depression scale (SDS) scores (all FDR corrected) but not with pain intensity. Further mediation analyses demonstrated that pain intensity had a mediating effect

on the relationship between SDS scores and Pain Disability Index scores. Likewise, the SDS scores mediated the relationship between pain intensity and PDI scores.

Conclusion: Our study found that comorbid depressive symptoms can aggravate the impairment of pain matrix function of CBP, but this impairment cannot directly lead to the increase of pain intensity, which may be because some brain regions of the pain matrix are the common neural basis of depression and CBP.

KEYWORDS

comorbid depressive symptoms, chronic back pain, pain matrix, fMRI, resting-state

Introduction

Chronic pain is a debilitating disease that affects physiology and psychology. The World Health Organization's large-scale survey found that the prevalence of chronic pain is very high in both developed (37%) and developing (41%) countries (Tsang et al., 2008), so it greatly increases the cost of medical resources (Henschke et al., 2015). A growing body of literature (Velly and Mohit, 2018) shows that individuals with chronic pain also have a sharply higher risk of developing psychological disorders [Gureje et al. (1998) found that this risk was four times higher in individuals without chronic pain]. However, previous medical views often regarded the patient's body and psychology as independent and separate structures (Gatchel et al., 2007). In the process of diagnosis and treatment of patients with chronic pain, physicians generally pay more attention to the physical complaints of patients with chronic pain and relatively ignore the impaired psychological and social functions of patients.

There is strong evidence that pain is a major risk factor for depression and that depressive symptoms aggravate the progression of chronic pain (Tappe-Theodor and Kuner, 2019). When patients with chronic pain have comorbid depressive symptoms, this comorbidity condition can make the two have mutual promotion of some distresses, such as poor functionality and higher disability rates (Baumeister et al., 2011; Hall et al., 2011). Unfortunately, the underlying mechanism of this reciprocal interaction is unclear yet and needs to be taken seriously.

Some previous preclinical and clinical studies have already paid some attention to the potential neural mechanism of the interaction between depression and chronic pain. For example, a preclinical study has identified a novel neural pathway from the dorsal raphe nucleus (involving 5-hydroxytryptamine projections) to the central nucleus of the amygdala (somatostatin-expressing neurons) that not only mediates depressive symptoms, but also affects painful symptoms (Zhou et al., 2019). A neuroimaging study found that functional connectivity (FC) between the thalamus and dorsolateral prefrontal cortex (involved in the pain descending regulation system) modulated the relationship between depression and chronic low back pain (Li, 2021). A study on heat pain sensitivity found that heat pain sensitivity was associated with thalamic, amygdala, cingulate cortex and sensory cortex activity in both chronic low back pain patients and depressed patients (Rodriguez-Raecke et al., 2014). Moreover, depression-related neuroimaging studies have shown that depression leads to altered FC between a number of brain regions, including the anterior cingulate cortex-thalamus, the anterior cingulate cortex-insula, and the prefrontal-limbic-thalamic circuit, which partially overlap with descending pain modulatory pathway (Gong and He, 2015). These studies suggest that chronic pain and depression have some common neural circuits and partially overlapping functional networks. However, although taking steps in the right direction, the neurological study of depression and pain co-occurrence is still in a preliminary and approximate scope, and there is much room for extending the underlying neural mechanisms of the interaction of chronic pain and depression.

Over the past decade, a great deal of studies have been devoted to understanding how the brain responds to pain and have already demonstrated altered brain structure and function in patients with acute and chronic pain (Apkarian et al., 2004; Ichesco et al., 2014; Lieberman et al., 2014). These wide-ranging cortical and subcortical brain areas, including primarily the thalamus, insula cortex, sensory cortex, and anterior cingulate cortex (ACC), are known as the pain matrix (Legrain, 2011; Geuter et al., 2020). Therefore, since the underlying neural mechanisms by which chronic pain

Abbreviations: fMRI, functional magnetic resonance imaging; SDS, self-rating depression scale; CBP, chronic back pain; CBP-D, chronic back pain with comorbid depressive symptoms; VAS, visual analog scale; PDI, pain disability index; ROI, region of interest; FC, functional connectivity; AI, anterior insula; ACC, anterior cingulate cortex; PG, postcentral gyrus; PPC, posterior parietal cortex; IPL, inferior parietal lobule; SPL, superior parietal lobule; mPFC, medial prefrontal cortex; VPI, ventral posterior insula.

and depression interact are not fully understood, the pain matrix, a core network of pain processing, should deserve focused attention. In addition, little is known about whether depression and chronic pain interact to exacerbate alterations in brain function or structure, which is one of the concerns we are interested in.

Based on the above description, resting-state functional magnetic resonance imaging (fMRI), a recognized objective and non-invasive measure of brain activity, has also been used as a measure of potential biomarkers for detecting various types of pain (Hohenfeld et al., 2018), and was used in this study to explore the changes in brain functions of subjects. Subjects with chronic back pain (CBP) were included in this study and were divided into a group with comorbid depressive symptoms and a group without depressive symptoms. Graph theory analysis methods and FC analysis methods were used in this study to explore the differences in brain function between groups. The self-rating depression scale (SDS) (Zung, 1965) was used to measure the psychological status of the subjects. The Pain Disability Index (PDI) (Pollard, 1984) was used to measure the degree to which patients' daily lives are disrupted by chronic pain. The main objectives of this study are: (1) to explore whether the comorbid depressive symptoms can affect the pain matrix (the core brain network for pain), and (2) to determine whether the interaction between the comorbid depressive symptoms and CBP exacerbate the impairment of brain function. We hypothesized that comorbid depressive symptoms can lead to altered pain matrix function in patients with chronic pain, which in turn affects patients' pain symptoms.

Materials and methods

Participants

To control the covariates, all the subjects were patients with chronic musculoskeletal back pain. Patients with a SDS score $\geq$ 50 were considered to have comorbid depressive symptoms (Zung, 1967; Edelstein et al., 2010). All subjects in this study were able to understand all items on the SDS scale and completed the SDS scale. We recruited 30 patients with comorbid depressive symptoms (CBP-D) and 32 patients without comorbid depressive symptoms (CBP) from Zhujiang Hospital of Southern Medical University and Guangdong Provincial Hospital of Chinese medicine. Two subjects in the CBP group were excluded from this study due to image quality problems or head movement factors. Finally, 30 patients with comorbid depressive symptoms (CBP-D) and 30 patients without comorbid depressive symptoms (CBP) were recruited. The inclusion criteria were: (1) the visual analog scale (VAS) score of pain intensity was greater than or equal to 3 points and the duration was more than 3 months; (2) those who were assessed as normal or abnormal by SDS; (3) no fMRI contraindication; (4) did not receive psychological induction training; and (5) without cerebral lesions. The exclusion criteria were: (1) subjects with life-threatening primary diseases such as those of the cardio-cerebrovascular, liver, kidney, or hematopoietic system; (2) subjects with psychiatric diseases, tuberculosis, tumor, rheumatism, active gastrointestinal ulcers or asthma; (3) subjects with irregular menstrual cycles or currently menstruating; (4) subjects with spinal fracture, dislocation, acute cervical or lumbar disk herniation; (5) subjects with magnetic component objects in their bodies; and (6) body mass index greater than 25 kg/m^2. This experiment was approved by the ethics committee of Zhujiang Hospital of Southern Medical University and Guangdong Provincial Hospital of Chinese medicine. The clinical registration number is ChiCTR2200056929. The research purpose of this manuscript is a part of the whole clinical research project. All participants signed informed consent. We explained the detailed instructions, experimental procedures, possible risks, and discomforts of the study to all subjects, as well as answered their questions in detail.

Data acquisition

All image data were collected by a Philips 3.0 T Ingenia magnetic resonance imager in Zhujiang Hospital, Southern Medical University, and scanned in a standard radio-frequency head coil. Structure data were acquired with a high resolution 3D T1-weighted sequence: repetition time (TR)/echo time (TE) = 7.2/3.3 ms; flip angle = 7°; field of view (FOV) = 256 mm × 256 mm; matrix size = 256 × 256; 1 mm × 1 mm in-plane resolution; slice thickness = 1 mm; 176 slices; slice gap = 0 mm. Functional MRI data were acquired using a T2*-weighted, single-shot, gradient-recalled echo planar imaging sequence, TR/TE = 2000/30 ms; field of view (FOV) = 224 mm × 224 mm; matrix size = 64 × 63; flip angle = 90°; 3.5 mm × 3.5 mm in-plane resolution; slice thickness = 3.5 mm; 33 slices; slice gap = 0.7 mm; number of signals averaged (NSA) = 1.

Measures

The PDI is a self-rating scale that contains seven items that can evaluate the extent to which pain affects seven categories of life activity. Each item is scored on a scale of 0 to 10, with 0 representing no pain induced disability at all and 10 representing that daily life has been totally disrupted by the

pain. The SDS is a 20-item self-assessment scale that is easy to use and visually reflects the patient's subjective feelings. Each item is divided into 4 levels: no or little time, little time, quite a lot of time, and most of the time or all the time. The level of each item refers to the frequency with which the subject experiences the item.

Data preprocessing

The fMRI data preprocessing was carried out in the DPABI toolbox (Yan et al., 2016) based on Statistical Parametric Mapping (SPM12) software[1]. This procedure included data format conversion, discarding the first 10 volumes, slice timing correction, realignment, nuisance covariates regressors, spatial normalization, smoothing, linear de-trending, and filtering (see **Supplementary Material** for the detail). The demographic data (such as age, sex ratio, and pain duration) with significant differences between the two groups were also included in linear regression as covariates.

Functional data analysis

Numerous studies have shown that acute or chronic pain causes alterations in several cortical or subcortical structures, which are collectively referred to as the pain matrix (Legrain et al., 2011; Geuter et al., 2020). Therefore, based on the purpose of our study, the various brain regions of the pain matrix were prior defined as seeds and were extracted as a mask (see **Supplementary Table 1** for the region information of the seeds) using the Human Brainnetome Atlas (Fan et al., 2016). The seeds-to-whole-brain FC analysis and the Fisher's r-to-z transform were then calculated successively. Multiple comparison correction based on Gaussian random field theory (GRF) correction (voxel-level forming statistical threshold of $z = 2.58$, cluster-level $p < 0.05$). After the correction, the results of the seeds-to-whole-brain (significant seeds labeled as 155, 160, and 162 in the Human Brainnetome Atlas, see **Supplementary Table 1** for the region information of regions of interest) were included in the follow-up analysis. The seeds-to-whole-brain results together with the significant seeds were extracted as regions of interest (ROIs, **Supplementary Figure 1**) and calculated for ROI-ROI FC analysis. Finally, an n^*n correlation matrix (n is the number of ROIs) was generated for each subject and the statistical analysis of the inter group was carried out ($q = 0.05$, false discovery rate corrected). The FC map and the correlation coefficient between the significant brain areas were shown by the heat map of the FC correlation coefficient and BrainNet Viewer (Xia et al., 2013).

Graph theory analyses

The graph theory is a mathematical system to study networks. The brain network can be defined as a graph by G (N, K), with N representing the number of nodes (brain regions) and K representing the number of edges (functional or structural connectivity) (Wang et al., 2010). In the current study, we calculated various topological properties to evaluate brain activity. The Human Brainnetome Atlas with 246 brain ROIs was used in the graph theory analysis. The brain was first parcellated into 246 regions according to the template. Pearson correlation of the time series between each brain region was then calculated and generated a 246*246 correlation matrix for each subject. Setting different thresholds will lead to various results, and there is no threshold gold standard at present (Garrison et al., 2015). To avert weak and spurious links in the functional network, the ideal way is to set the threshold to a wider range, then calculate the topological metrics under each threshold, and get the area under the curve (AUC) (Rubinov and Sporns, 2010). In this work, we applied the sparsity threshold from 3 to 30% in steps of 1% into a binary graph (calculated based on the built-in code of the GRETNA toolbox).

We computed five main topological metrics (i.e., global efficiency, local efficiency, nodal efficiency, nodal local efficiency, and small-world property) by using the GRETNA toolbox[2] (see **Supplementary Material** for the detailed definition and the interpretation of equations). To find whether there was any difference in the activity of the key brain regions (pain matrix) between the two groups. We also extracted the nodal efficiency and the nodal local efficiency of all nodes in the pain matrix, as well as calculated the network efficiency and local efficiency of the pain matrix for each participant, and the inter-group comparisons of the topological properties were also carried out ($q = 0.05$, false discovery rate corrected).

Correlation analyses and mediation analyses

The Pearson correlation analyses were used to calculate the correlation between the neuroimaging data with the clinical characteristics results. Spearman correlation analyses were used for correlation analysis of non-normally distributed data. The boxplot method was used to identify outliers of the clinical characteristics and then eliminate them. To further test the summary of the relationships among the pain, the comorbid depressive symptoms, and the neuroimaging findings, mediation analyses were conducted based on the results of correlation analyses. In this study, we designed two main mediating models, in which the mediating variable (M) in model

1 http://www.fil.ion.ucl.ac.uk/spm

2 http://www.nitrc.org/projects/gretna/

1 was the ROI-ROI FC, and the purpose of designing this model was to analyze whether FC could mediate the relationship between pain and comorbid depressive symptoms. Model 2 made pain and comorbid depressive symptoms mutually mediating variables, which was designed to analyze whether the reciprocal interaction between depressive symptoms and pain would affect the clinical characteristics or neuroimaging findings of patients. The mediation analyses were performed using the PROCESS macro for SPSS[3] (Preacher and Hayes, 2004; Williams and Mackinnon, 2008). The bootstrap samples were $n = 5{,}000$, and significant indirect effects were defined by a 95% confidence interval (CI) that does not include zero.

Statistical analysis

The Chi-squared and two-independent sample *t*-tests were employed to conduct the group differences in demographic data by SPSS22.0 (SPSS, Chicago, IL, United States) software. The Shapiro–Wilk test was used to assess the normality of distribution of the data. The Mann–Whitney *U* test was used to compare non-normal distribution data. Analysis of covariance was used to determine whether the difference in pain intensity between groups affected the difference in FC results between groups. All statistical assessments were two-tailed, and the significance threshold was $p = 0.05$.

Results

Demographic and clinical characteristics results

There were no significant differences in age, sex ratio, or pain duration between the two groups (Table 1). Compared with the CBP group, the CBP-D group had significantly higher SDS ($t = 10.360$, $p < 0.001$) scores, self-report pain intensity ($Z = 3.661$, $p < 0.001$), and PDI scores ($t = 4.705$, $p < 0.001$) (Table 1).

The correlation analysis results showed that the SDS scores were significantly positively correlated with pain intensity ($r = 0.4387$, p-FDR < 0.05, p-uncorrected $= 0.0004$) and PDI scores ($r = 0.4811$, p-FDR < 0.05, p-uncorrected < 0.0001). Pain intensity was also significantly positively correlated with PDI scores ($r = 0.7842$, p-FDR < 0.05, p-uncorrected < 0.0001) (Supplementary Figure 2).

Neuroimaging results

Compared with the CBP group, subjects in the CBP-D group had significantly increased right postcentral gyrus (PG1, area 2) FC to the right posterior parietal cortex (PPC), right inferior parietal lobule (IPL), and right superior parietal lobule (SPL). The CBP-D group also showed significantly increased left postcentral gyrus (PG2, area 1/2/3) FC to the right PPC, and significantly decreased right postcentral gyrus (area 1/2/3, trunk region) FC to the left medial prefrontal cortex (mPFC) (Figure 1 and Table 2).

TABLE 1 Demographic and clinical characteristics and behavioral scores of the participants.

	CBP-D ($n = 30$)	CBP ($n = 32$)	Test statistics	*P*-value
Demographic features				
Age, years	40.30 ± 15.39	38.31 ± 14.54	0.523	0.603
Sex ratio, female	21 (70%)	20 (62.5%)	0.398*	0.533
Pain duration, months	24 (45)	18 (28.42)	−0.459**	0.646
Pain symptom severity				
Pain intensity, by VAS	5 (2)	4 (2)	3.661**	<0.001
PDI scores, by VAS	36.63 ± 12.58	20.97 ± 13.57	4.705	<0.001
SDS rating	59.04 ± 7.99	39.14 ± 7.13	10.360	<0.001

**Mann–Whitney *U* test. *Chi-square test. The results satisfying normal distribution were expressed as means ± standard deviations, otherwise were expressed as median (inter-quartile range).

Subjects in the CBP-D group had significantly lower nodal efficiency values in the left ventral posterior insula (VPI) (one of the brain regions of the pain matrix) after multiple comparison correction ($t = -3.581$, $p = 0.0007$) and had lower network efficiency values ($t = -2.758$, $p = 0.008$) and network local efficiency values ($t = -2.475$, $p = 0.017$) in the pre-determined pain matrix (Figure 2 and Table 3). The results of the graph theory analyses showed that the AUC of small-world property ($t = -2.175$, $p = 0.034$), gamma ($t = -2.332$, $p = 0.023$, see Supplementary Material for the detailed definition), and local efficiency ($t = -2.461$, $p = 0.017$) in the CBP-D group were significantly lower, but the global efficiency was not included (Figure 3 and Table 3).

The correlation analysis results (all p-FDR < 0.05, Figure 4) showed that the SDS scores were significantly positively correlated with PG2-SPL connectivity ($r = 0.3895$, $p = 0.0021$), PG2-PPC connectivity ($r = 0.3624$, $p = 0.0044$), PG1-PPC connectivity ($r = 0.4034$, $p = 0.0014$), and PG2-IPL connectivity ($r = 0.4482$, $p = 0.0003$). The SDS scores were also showed significantly negatively correlated with PPC-mPFC connectivity ($r = -0.3165$, $p = 0.0138$). At the same time, there was no significant correlation between pain intensity and FC (Supplementary Figure 3). Similarly, the analysis of covariance did not find that pain intensity had an effect on the difference of FC results between groups (Supplementary Table 2). After multiple comparison, we also found that there was no significant correlation between pain duration and FC, and between pain duration and SDS scores (Supplementary Figure 5, all p-FDR > 0.05). We also carried

3 http://www.afhayes.com

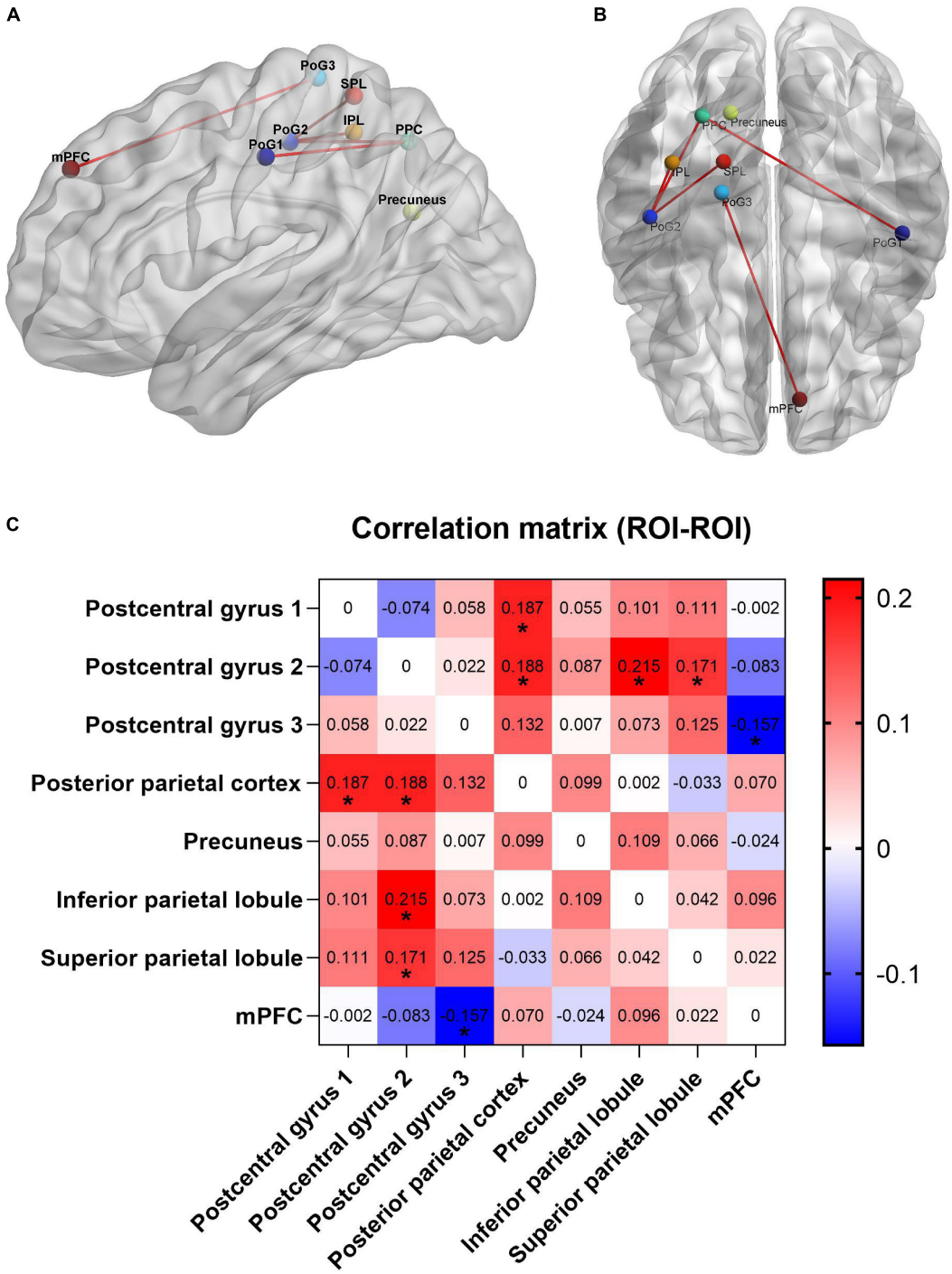


FIGURE 1
Functional connectivity results with significant difference between groups. **(A)** Sagittal view. **(B)** Axial view. **(C)** Heat map of functional connectivity between groups from ROI–ROI analysis. The parameters represent the FC correlation coefficient. *Represents the functional connectivity of brain regions with significant correlation after FDR correction. PPC, posterior parietal cortex; PoG, postcentral gyrus; mPFC, medial prefrontal cortex; SPL, superior parietal lobule; IPL, inferior parietal lobule.

out the correlation analysis of the results of the graph theory analyses with SDS scores and pain intensity, respectively. The results revealed that the most results of the graph theory analyses were significantly negatively correlated with SDS scores (Supplementary Figure 4), but no significant correlation was found with pain intensity.

TABLE 2 The brain regions with significant functional connectivity between groups.

Regions	R/L	BA	Cluster size voxels	MNI			*z*-values
				x-	*y*-	*z*-	
Posterior parietal cortex	R	7	215	27	−63	48	3.6239
Precuneus	R	7	215	27	−63	48	3.6239
Inferior parietal lobule	R	7	158	39	−45	51	4.2427
Superior parietal lobule	R	5, 7	158	39	−45	51	4.2427
mPFC	L	9	147	−9	48	39	−3.9663

BA, Brodmann Area. MNI, Montreal Neurological Institute. R/L, right or left. mPFC, medial prefrontal cortex.

Mediation analyses

Based on the results of correlation analysis, further mediation analyses demonstrated that pain intensity had a mediating effect on the relationship between SDS scores and PDI scores (indirect effect = 0.320, standard error [SE] = 0.119, 95% CI = [0.102, 0.575]). Likewise, the SDS scores mediated the relationship between pain intensity and PDI scores (indirect effect = 1.036, standard error [SE] = 0.483, 95% CI = [0.246, 2.134]) (**Figure 5** and **Table 4**). No mediating effect of FC and the topological properties of the pain matrix on the relationship between SDS scores and pain-related clinical features was found.

Discussion

Some researchers have studied the relationship between chronic pain and depression, but most of these studies are controlled by patients and healthy individuals (Bär et al., 2007; Bilek et al., 2019; Letzen and Boissoneault, 2020). The pain or depression induced by the experiment has a very short impact on the subjects, so it can only be a preliminary study of this interaction (Wiech and Tracey, 2009). This study found that the pain intensity scores and PDI scores in patients of CBP with depressive symptoms were significantly higher than those without depressive symptoms. Moreover, SDS scores were significantly correlated with the pain intensity scores and PDI scores. Follow-up mediation analysis then found that comorbid depressive symptoms could act as a mediator of the relationship between pain intensity and PDI scores, while the pain intensity could act as a mediator of the relationship between comorbid depressive symptoms and PDI scores. These results indicated that, similar to previous studies (Li, 2021), depressive symptoms do affect the clinical characteristics associated with chronic pain. After determining the interaction, we next made two assumptions about the relationship between CBP and depression: (1) CBP and depression accelerate disease progression by affecting the neural basis of each other and (2) CBP and depression fundamentally share some of their neurological underpinnings.

With the development of the graph network theory in neuroimaging, we can explore the topological properties of complex networks. As a complex network, the brain has the characteristics of high information transmission efficiency and high anti-interference ability (Biswal et al., 2010). Previous studies on healthy subjects (Chen and Hu, 2019) and some diseases, such as rheumatoid arthritis (Schrepf et al., 2018) and ischemic leukoaraiosis (Zhu et al., 2020), have been carried out in detail by using the graph theory method, and brilliant achievements have been obtained from the macro aspects of brain work efficiency, which provides a theoretical basis for better study of brain function. In partial accordance with our initial hypothesis, our results showed that the network efficiency and local efficiency of the pain matrix were lower in the CBP-D group. In this regard, the pain matrix network efficiency was significantly negatively correlated with SDS scores, while both topological properties were not correlated with pain intensity. Global efficiency and local efficiency focus on measuring the efficiency of information exchange between remote brain regions and between local networks, respectively (Rubinov and Sporns, 2010). Therefore, according to the research results and the definition of each topological property, we can reckon that comorbid depressive symptoms have led to the disconnection and instability of the FC of the pain matrix in patients with CBP. Our study also found several whole-brain topological properties were lower (uncorrected) in the CBP-D group and were also negatively correlated (uncorrected) with SDS scores but not with pain intensity. These findings demonstrated that co-morbid depressive symptoms can indeed exacerbate impaired function of the pain matrix network. However, subsequent mediation analyses did not find that these significantly different topological properties and FC mediate the interaction of depressive symptoms and CBP, which was inconsistent with our initial hypothesis. Up to this, the first hypothesis mentioned above is then not valid, that is, depressive symptoms cannot exacerbate CBP (at least the pain intensity) by affecting the neural basis of pain.

After identifying depressive symptoms can exacerbate functional impairment of the pain matrix, we next analyzed which brain regions and which functions of the pain matrix are specifically impaired by depressive symptoms in patients

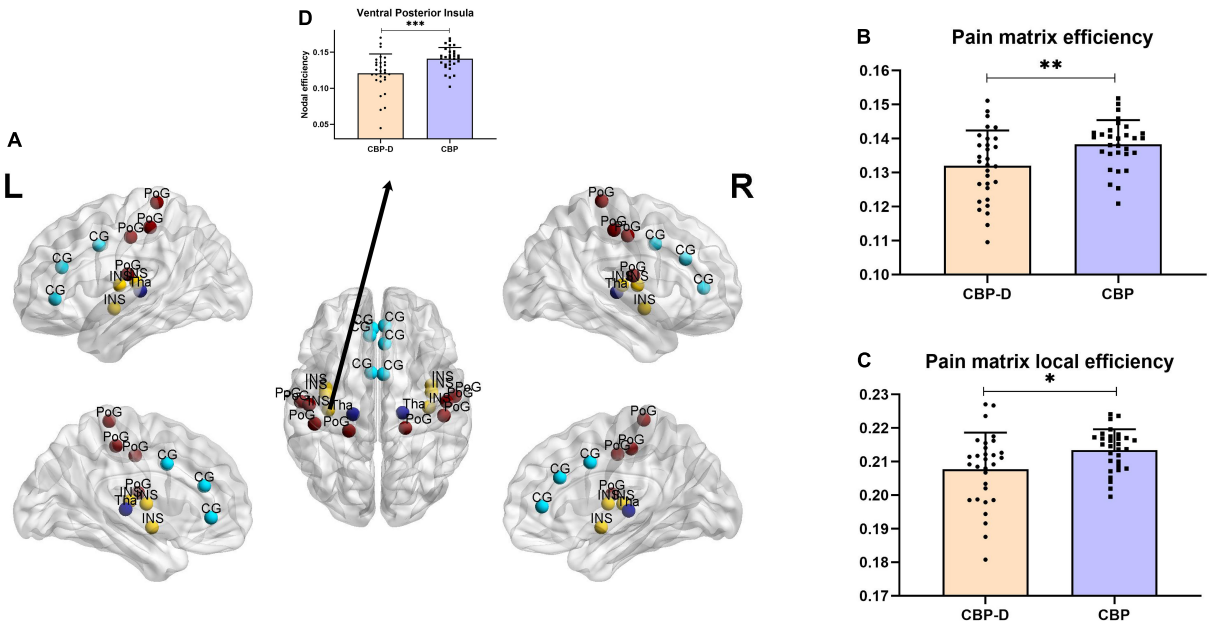


FIGURE 2
Inter group comparison of topological properties of pain matrix. **(A)** Distribution of brain regions in the pain matrix. CG, Cingulate cortex; INS, insula; PoG, postcentral gyrus; Tha, thalamus. **(B)** Comparison of network efficiency of pain matrix. **(C)** Comparison of network local efficiency of pain matrix. **(D)** Brain regions with significant nodal efficiency differences between groups in pain matrix (FDR corrected). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

with CBP. We found that the nodal efficiency in the VPI showed significant between-group differences (FDR corrected), and the FC results also showed significant between-group differences in the FC of several brain regions of the pain matrix, including the mPFC, SPL, IPL, and PPC, and both this topological property and the FC values of these brain regions were significantly correlated with SDS scores (all FDR corrected) but not with pain intensity.

Previous studies have revealed that enhancing the basal neuronal activity of the prefrontal cortex (PFC) enhances its modulation of nociception, whereas patients with chronic pain show reduced neuronal projections from the PFC to the periaqueductal gray matter, decreased PFC glutamate levels, and reduced PFC gray matter density. Our study found that compared with the CBP group, the CBP-D group showed a significantly decreased FC pathway between the left mPFC and the right postcentral gyrus. This suggested that comorbid depressive symptoms aggravate the ability of pain regulation in patients with CBP. However, this FC pathway was significantly negatively correlated with SDS scores but not with pain intensity. It is commonly believed that the diminished prefrontal cortex activity is accompanied by complementary changes in brain regions associated with pain (such as the thalamus and primary somatosensory cortex) when negative emotions regulate pain (Wiech and Tracey, 2009), and a possible reasons for this phenomenon of depressive symptoms regulating pain may imply a partial overlap in the neural basis of the two disorders (Wiech and Tracey, 2009), for instance, the descending pain modulation pathway (Michaelides and Zis, 2019). Since research has shown that monoamine transmitters, such as serotonin and norepinephrine, play a role in reducing pain by acting on this modulation pathway (the PFC is the cortical center of the descending pain modulation pathway), the most commonly prescribed antidepressants (selective serotonin and norepinephrine reuptake inhibitors) are also used to treat neuropathic pain (Ossipov and Morimura, 2014; Sheng and Liu, 2017). These research advances, as well as the results of the present study, remind us that the brain regions in which functional activity was significantly

TABLE 3 Inter group comparison of topological metrics.

	CBP-D	CBP	*t*-value	*P*-value
Pain-matrix topological metrics				
Nodal efficiency (VPI)	0.121 ± 0.027	0.141 ± 0.015	−3.581	<0.001
Network efficiency	0.132 ± 0.01	0.138 ± 0.007	−2.758	0.008
Network local efficiency	0.208 ± 0.01	0.213 ± 0.006	−2.475	0.017
Topological metrics				
Small-world	0.478 ± 0.095	0.530 ± 0.092	−2.175	0.034
Gamma	0.553 ± 0.01	0.614 ± 0.103	−2.332	0.023
Local efficiency	0.195 ± 0.005	0.197 ± 0.003	−2.461	0.017
Global efficiency	0.128 ± 0.008	0.131 ± 0.005	−1.769	0.083

VPI, ventral posterior insula.

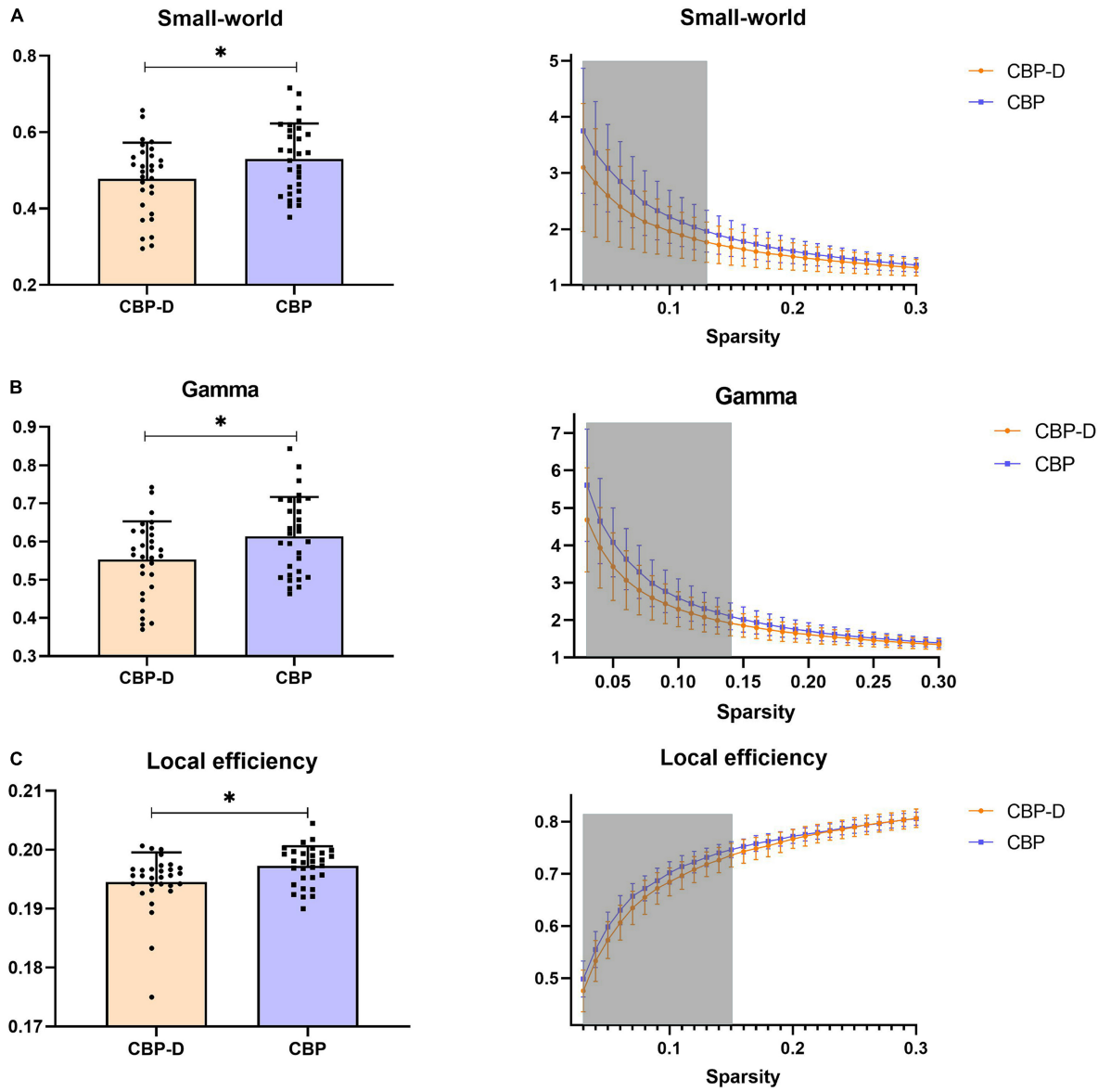


FIGURE 3
Inter group comparison of topological properties of whole brain. **(A)** The left column is the group comparison of the AUC of the small-world property under all sparsity thresholds. The right column is the specific results of the comparison between groups of small-world property under all sparsity thresholds. **(B)** The left column is the group comparison of the AUC of the Gamma property under all sparsity thresholds. The right column is the specific results of the comparison between groups of Gamma property under all sparsity thresholds. **(C)** The left column is the group comparison of the AUC of the local efficiency property under all sparsity thresholds. The right column is the specific results of the comparison between groups of local efficiency property under all sparsity thresholds. Shaded areas represent sparsity thresholds with significant inter-group differences. *$p < 0.05$.

correlated with SDS scores (rather than pain intensity) may be part of the common neural basis for depression and CBP. This implies the possibility that the second hypothesis we mentioned above is valid, that is, CBP and depressive symptoms fundamentally share some of their neurological underpinnings. Not coincidentally, chronic pain and mood disorders appear to share many other neuroendocrine and neurotransmitter changes, including substance P, gamma-aminobutyric acid, glutamate, and dopamine (Yalcin and Barrot, 2014; Pinheiro et al., 2015). In rats with neuropathic pain, microinjections of morphine into the endogenous opioid circuits can induce dopamine release from the nucleus accumbens while relieving pain (LaGraize and Borzan, 2006). In addition, pretreatment of the nucleus accumbens with a non-selective dopamine receptor blocker blocked the action of morphine on the endogenous opioid circuits to relieve pain aversion, and the opioid activity

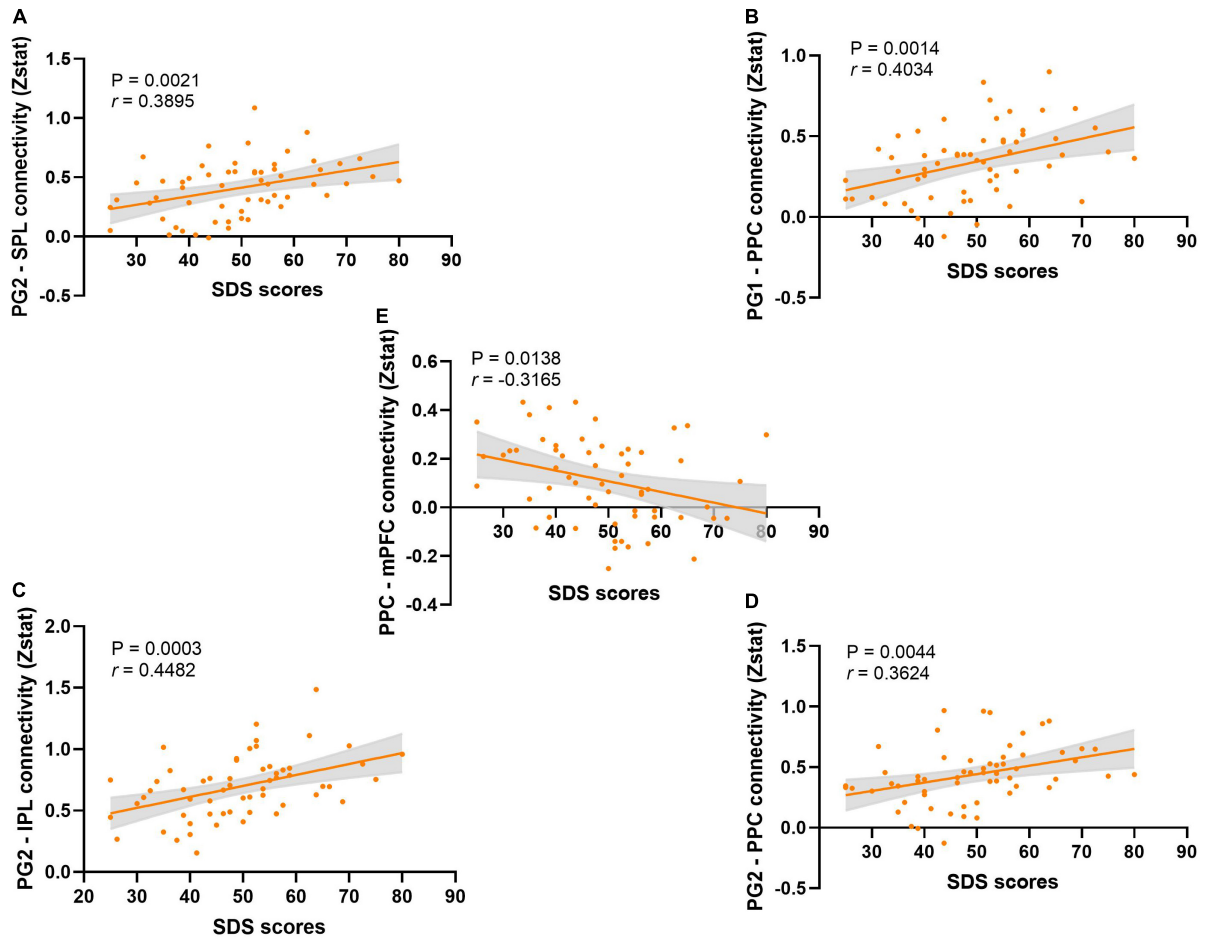


FIGURE 4
The correlation analysis between SDS scores and the functional connectivity. **(A)** The correlation analysis between the SDS scores and the PG2-SPL connectivity. **(B)** The correlation analysis between the SDS scores and the PG1-PPC connectivity. **(C)** The correlation analysis between the SDS scores and the PG2-IPL connectivity. **(D)** The correlation analysis between the SDS scores and the PG2-PPC connectivity. **(E)** The correlation analysis between the SDS scores and the PPC-mPFC connectivity.

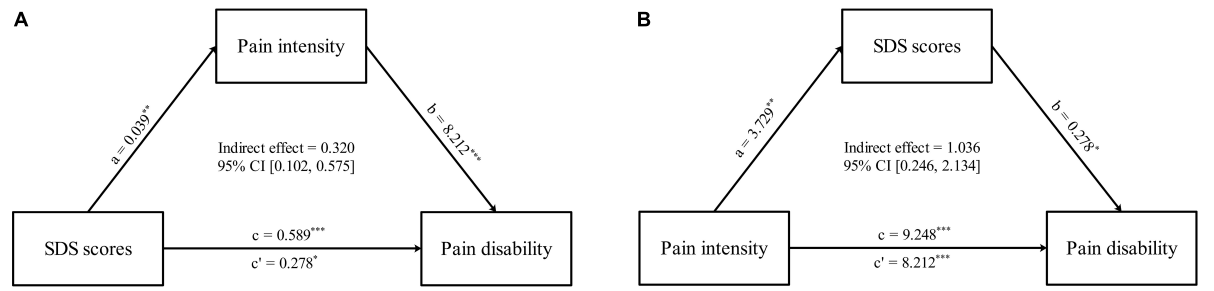


FIGURE 5
Comorbid depressive symptoms-pain intensity-pain disabilities associations. **(A)** The mediation analyses between SDS scores (*X*) and PDI scores (*Y*), with pain intensity as the mediators (M). **(B)** The mediation analyses between pain intensity (*X*) and PDI scores (*Y*), with SDS scores as the mediators (M). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

in the ACC is sufficient and necessary to maintain the increase in dopamine (Navratilova et al., 2015). The dopamine system is unique in the brain. Many depressive symptoms, such as a loss of pleasure and excitement, are directly tied to malfunction of the dopamine system (Eshel and Tian, 2016; Grace, 2016). The interaction between the dopamine system and endogenous opioid circuits can also be regarded as the commonality of pain and depression in neural pathways.

TABLE 4 Detailed results of mediation analysis.

	Effect	SE	*t*-value	*P*-value	95% confidence interval	
					LLCI	ULCI
The mediation analysis between SDS (*X*) and pain disability (*Y*)						
Total effect	0.598	0.142	4.212	<0.001	0.314	0.882
Direct effect	0.278	0.108	2.575	0.013	0.062	0.494
Indirect effect	0.320	0.119			0.102	0.575
The mediation analysis between pain intensity (*X*) and pain disability (*Y*)						
Total effect	9.248	1.021	9.057	<0.001	7.204	11.292
Direct effect	8.212	1.055	7.787	<0.001	6.101	10.324
Indirect effect	1.036	0.483			0.246	2.134

SE, standard error.

Consequently, all these findings can give corresponding support to our research hypothesis.

Our study also found that, compared with the CBP group, there was an enhancement of FC in some parietal brain regions in the CBP-D group, including the SPL, IPL, and PPC. These brain regions are all related to attention, spatial discrimination, and awareness (Teixeira et al., 2014). They are also central to several classical brain networks, involving the ventral and dorsal attention networks, as well as the executive control networks (Smith et al., 2009; Fiebelkorn and Kastner, 2020). The role of the parietal cortex in pain processing has not been clearly clarified, but some researchers believe that it plays a role in maintaining attention to pain and spatial discrimination of noxious stimuli (Carlsson et al., 2006; Oshiro et al., 2007). It was found that the activity of the PPC kept pace with the abnormal increase of central sensitivity of pain (Seifert et al., 2010). According to the experiment, the researchers speculated that this was due to the abnormal increase of spatial attention to harmful stimuli. In addition, a new study has found that stimulation of some areas of the parietal cortex can reduce depression scores (Hou et al., 2021). The increased FC of the parietal cortex in this study is related to depression, indicating that the increased function of the parietal cortex caused by comorbid depression in this study may enhance the attention bias of patients to pain stimuli and enhance the perception of pain. This may also be one of the reasons for the higher pain intensity in patients with comorbid depression and pain.

Previous studies have shown that posterior insula activity can characterize pain to some degree (Mazzola, 2009) and that its increased activity contributes to pain perception control (Tran, 2010), while pain control is impaired in patients with posterior insula lesions (Starr et al., 2009). Our results revealed a significantly lower nodal efficiency in VPI in the CBP-D group compared to the CBP group, and this nodal efficiency was significantly negatively correlated with SDS scores. This suggests that the control of pain representations may be impaired in the presence of depressive symptoms.

Even if our study found some evidence that comorbid depressive symptoms can aggravate the functional changes of the pain matrix in patients with CBP, we must point out some shortcomings of this study to avoid them in the future. Firstly, due to the limited study time and subject population, our sample size is relatively small, which may lead to some evidence not being found. Secondly, anxiety symptoms and some other pain-related clinical characteristics may act as confounders or mediators to influence the study results and need to be included in subsequent in-depth studies in the future. Thirdly, we did not conduct hierarchical analysis on the duration of pain, which is a deficiency of this manuscript, and we hope to include it in the study in the future. Fourthly, excessive inter-individual variation in pain duration is also one of the limitations of this study, and we will analyze subgroups with excessive range of pain duration in future studies. Fifthly, healthy subjects were not included in this study.

Conclusion

This study draws a preliminary conclusion that some brain regions of the pain matrix may be the common neural basis of depression and CBP. Comorbid depressive symptoms do interact with CBP, but depression does not aggravate pain intensity by directly affecting the function of the pain matrix. These results can enrich the theoretical system of chronic pain affected by different comorbid symptoms. Moreover, we hope that our research can stimulate more humanistic care for patients with chronic pain, and pay more attention to the recovery of psychosocial function.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary Material**,

further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Zhujiang Hospital of Southern Medical University and Guangdong Provincial Hospital of Chinese medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. GZ and WW: conceptualization. GZ, JM, WRL, XW, and WW: methodology. GZ, JM, WRL, XZ, and YH: investigation. JM, HZ, and KW: formal Analysis. QC and WL: experimental technology and equipment support. GZ, WRL, HZ, and WL: resources. JM, WRL, and XZ: data curation. GZ, JM, and XZ: writing – original draft. WP, SY, QC, and WL: writing review. QC, WL, and WW: supervision. HZ and WW: funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.935242/full#supplementary-material

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PERSPECTIVE
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Wheelchair Tai Chi Ball Exercise for Improving Neuromuscular Functions of Older Adults With Disability

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The purposes of this perspective article were to summarize Wheelchair or Seated Tai Chi studies related to neuromuscular functions of older adults with disability; to describe the development of Wheelchair Tai Chi Ball (WTCB) exercise — a concept to combine mind-body exercise with strength training; and to propose a new Telehealth WTCB exercise for improving neuromuscular functions of old adults with spinal cord injury (SCI) and disability. With reference to neuromuscular functions, WTC intervention may have positive effects on simple reaction time, range of motion at the shoulder and trunk, static and dynamic sitting balance, handgrip strength, vagal activity, and sympathetic activity among older adults with disability. The developed WTCB intervention is a feasible and safe exercise which combines the mind-body exercise and strength conditioning into one exercise which possesses aerobic, stretching and strength trainings and may facilitate neuromuscular functions of older adults with disability. The proposed Telehealth WTCB 12 forms (TWTCB12) exercise with a "Moving Shadow" method in the telehealth may enable the learner to superimpose learner's image on an expert's demonstrating model to enhance the learning and practice effects. Since wheelchair users will learn and practice TWTCB12 movements in a seated position or sitting on a wheelchair the "Moving shadow" method on Zoom would provide an ideal telehealth learning and practice environment for the wheelchair users to learn and practice TWTCB12 exercise from home more feasible and user friendly.

Keywords: Wheelchair Tai Chi ball, mind-body exercise, strength training, neuromuscular functions, older adults, disability

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INTRODUCTION

There are approximately 65 million people worldwide who have mobility limitations and use wheelchairs as a result of disabling injury or illness (Gurwitz et al., 2021). These individuals with mobility limitations often live a sedentary lifestyle and consequently have issues with cardiovascular, neuromusculoskeletal and bariatric health such as high BMI, and increased body fat percentage (Nooijen et al., 2016). Those compound factors may put older wheelchair users at higher risk of cardiovascular disease, neuromuscular and skeleton disorders which result in lower quality

of life (QOL) among them (Jordaan et al., 2017) and would even increase their risk of chronic disease or premature death (Nooijen et al., 2016).

Older adults who use manual wheelchair experience major limitations in their functional activities (Kaye et al., 2000), however, the access to health and exercise programs are limited for individuals who need to exercise in a sitting position or wheelchair. Lack of exercise can result in significant adverse health consequences. Specifically, among older wheelchair users, a physically inactive lifestyle is associated with conditions such as cardiovascular disease, osteoporosis, respiratory complications, muscle mass loss and strength declining, pain and depression (Hicks et al., 2003; Lan et al., 2013; Wang et al., 2020a). Both the physical and mental benefits of exercises have been well documented (Freeman and Lawlis, 2001; Ko et al., 2006; Haskell et al., 2007; van den Berg-Emons et al., 2011; Nguyen and Kruse, 2012). Hence, a health promotion program or exercise focusing on neuromuscular functions is needed for older individuals who use manual wheelchairs or assistive devices as their primary method of mobility.

Tai Chi, a mind-body harmony exercise, consists of a series of graceful movements with deep and slow diaphragmatic breathing performed while standing (Freeman and Lawlis, 2001; Wang et al., 2004). Tai Chi exercise has been shown to have both physical and psychosocial benefits for the general population (Wang et al., 2004; Nguyen and Kruse, 2012; Wayne et al., 2015; Lu et al., 2016; Varghese et al., 2016). Wang et al. (2017) proposed that Tai Chi was a healing movement combining Qi (vital energy), breathing, and stretching techniques. Physically, the slow, graceful movements allow the body to move with less tension and the lungs to be more relaxed, therefore increasing the intake of oxygen (Wang et al., 2016). Mentally, practicing Tai Chi helps decrease stress and anxiety (Abbott and Lavretsky, 2013; Jiang et al., 2016). However, the studies of WTC for individuals with SCI and disability are limited and there are a few Wheelchair or Sitting Tai Chi studies focused on neuromuscular functions among individuals with SCI and disability (Tsang et al., 2015; Qi et al., 2018, 2020; Wang et al., 2016, 2020a).

The purposes of this perspective article were to summarize Wheelchair (Seated) Tai Chi studies related to neuromuscular functions of older adults with disability, to describe the development of WTCB exercise—a concept to combine mind-body exercise with strength training, and to propose a new Telehealth WTCB exercise for improving neuromuscular functions of old adults with SCI and disability.

RESEARCH OF WHEELCHAIR TAI CHI OR SEATED TAI CHI RELATED TO NEUROMUSCULAR FUNCTIONS AMONG OLDER ADULTS WITH DISABILITY

From the currently available literature, there are a few studies addressing the effects of WTC on the neuromuscular functions among individuals with SCI and disability. Tsang et al. (2015) administrated a sitting Tai Chi intervention to determine its effects on muscle strength, and balance control among individuals with SCI. Eleven participants were engaged in the intervention (90 min/session, 2 times/week for 12 weeks) and eight participants served as controls. The results shown that based on within group comparisons, the sitting Tai Chi group achieved significant improvements in their simple reaction time ($p = 0.042$); in the dynamic sitting balance test: maximum excursion ($p = 0.016$); and directional control ($p = 0.025$) in the limits of stability test after training. Furthermore, they reported that in the sequential weight shifting test: significantly improved their total time to sequentially hit the 12 targets ($p = 0.035$); and significant improvement in handgrip strength ($p = 0.049$) and concluded that 12 weeks of sitting Tai Chi training could improve the dynamic sitting balance and handgrip strength the individuals with SCI (Tsang et al., 2015).

Qi et al. (2018) assessed the effects of wheelchair Tai Chi (WTC) intervention on balance control and QOL among 40 individuals with SCI survivors who were randomly divided into WCTC and control groups. The WCTC group participated in 30-min sessions, 2 sessions/day, and 5 days/week for 6 weeks, while the control group only received the normal rehabilitation intervention. The results shown that the static sitting balance, left handgrip strength, and the psychological domain of QOL improved significantly in the WCTC group (time by group interaction, $p < 0.05$) with comparison to the control group. Therefore, the WCTC exercise may be a feasible, safe, and effective exercise for SCI survivors. Furthermore, Qi et al. (2020) investigated the immediate effect of WTC 16 forms on autonomic nervous modulation among 20 patients with thoracic SCI. The heart rate variability (HRV) of patients at 5 min before and after five consecutive sets of WCTC16 were measured by Equivital-life-monitoring system. The analysis of HRV in the time domain consisted of RR intervals, the standard deviation of all normal R-R intervals (SDNN), and the root mean square of the differences between adjacent NN intervals (RMSSD). The analysis of HRV in the frequency domain consisted of total power (TP) divided into very-low frequency area (VLFP), low-frequency area (LFP), and high-frequency area (HFP) eLF/HF ratio as well as the normalized unit of LFP (LFPnu) and HFP (HFPnu) reflected the sympathovagal balance. Qi et al. (2020) summarized that there was no significant difference in RR interval, SDNN, RMSSD, TP, HEP, VLFP, and LFP of SCI patients before and after WCTC16 exercise ($p > 0.05$). However, LFPnu and HF peak decreased significantly, while HFPnu and LF/HF increased significantly in SCI patients right after WCTC16 exercise ($p < 0.001$). Qi et al. (2020) concluded that the immediate effect of the WCTC16 can improve vagal activity and decrease sympathetic activity, and patients with chronic complete thoracic SCI may achieve the balanced sympathovagal tone.

Our team developed WTC 10 forms in 2008 based on the traditional Tai Chi (Wang et al., 2015). In our pilot study, a 12-week WTC 10 Form (WTC10) intervention was conducted to examine the effect of this WTC10 intervention on selected physical and mental health variables among elderly with disability (Wang et al., 2016). Thirteen in the WTC10 intervention

group and 15 in the control group completed the study. The intervention group practiced WTC10 twice a week and 1 h for each session for 12 weeks. The control group only carried on their routine activities of daily living. The outcome measures were: HR and blood pressure, range of motion of the dominant side upper extremity and trunk, and Pain from Self-Efficacy Questionnaire (PSEQ), Physical Activity Scale from Individuals with Physical Disabilities and physical and mental health from SF-36v2 health survey. The results of this pilot study demonstrated that a 12-week WTC intervention had significant effects on blood pressure, range of motion at the shoulder and trunk, physical activity, and mental health among the elderly with disability (Wang et al., 2016).

There are a limited number of studies to address the effect of WTC on the neuromuscular functions among older adults with disability, and the possible improvements related to neuromuscular functions resulted from WTC interventions may be summarized as follows. Tsang et al. (2015) concluded that WTC exercise could improve simple reaction time, dynamic balance, handgrip strength. Qi et al. (2018, 2020) summarized that WTC may improve static sitting balance and vagal activity and sympathetic activity. Wang et al. (2016) reported that WTC may have positive effect on the range of motion at the shoulder and trunk and physical activity ability. However, the current WTC or seated Tai Chi interventions have not included the direct strength training of the upper extremities (Tsang et al., 2015; Shem et al., 2016; Wang et al., 2016; Qi et al., 2018).

WHEELCHAIR TAI CHI BALL DEVELOPMENT AND A PILOT STUDY

Strength training is a crucial exercise for individuals with mobility limitations. Specifically, within several years of mobility limitations, the average cross-sectional area of sub-lesional skeletal muscle, specific to SCI, and peripheral nerve injury decreases by as much as 18–46% progressively (Yarrow et al., 2014). The lack of physical activity and strength training resulted in negative effects on the muscular, skeletal and cardiovascular systems that might lead to secondary complications or death for individuals with mobility limitations (Davis and Shephard, 1990; Cragg et al., 2015). Strength training not only can decrease muscle mass loss, facilitate rapid gains in volitional function and strength (Jayaraman et al., 2013), but also can provide a wide range of benefits imperative to overall health for individuals with mobility limitation (Bochkezanian et al., 2015).

The rationale for developing WTCB exercise is to take multiple components (physical, mental, and strength conditioning) into consideration. Features of this newly designed ball are: (1) The ball provides resistance for upper extremity strength training; (2) it comes in three sizes (4″, 5″, or 6″) and different weights (1–6 lbs by filling with the weights of 6 mm BB balls) to match individual physical and health conditions (**Figures 1A,B**); and (3) it can be separated into Yin-Yang parts by twisting it thereby equally distributing the weights to left and right hands or combined (with poly-magnets) as a whole in one hand for weight shifting and strength training. Therefore, the use of the Ball during Tai Chi practice may match the traditional Tai Chi movements well, at the same time may facilitate strength training and neuromuscular functions for older adults with disability. The University of Texas at Tyler in United States has applied the patent for this Tai Chi Ball and the patent application has been approved by US Patent and Trademark Office (Patent No. 10765905) (Wang et al., 2020b).

Based on our previously developed WTC 10 forms which took Yin-Yang Balance, Coordination of Breathing, and Movement Dimensions into consideration (Wang et al., 2015), we developed Wheelchair Tai Chi Ball 12 (WTCB12) forms (Wang et al., 2020a). These 12 forms are (1) Commencing Form (Ball-Separated); (2) Part Wild Horse's Mane, (Ball-Separated); (3) Brush Knee and Push Forward, (Ball-Separated); (4) Curling the Arms, (Ball-Separated); (5) Left Grasp the Peacock's Tail (Ball-Together, Ball Transfers from Left to Right Hand); (6) Right Grasp the Peacock's Tail (Ball-Together, Ball Transfers from Right to Left Hand); (7) Wave Hands Like Clouds, (Ball-Together and Leading Arm with Ball); (8) White Crane Spreads Its Wing (Ball-Together, Transfer Ball to Right Hand); (9) Open and Close hands, (Ball-Separated); (10) Appear Closed (Ball-Separated); (11) Crossing Hands (Ball-Separated); (12) Closing Form (Ball-Separated). Tai Chi is rated as a moderate-intensity exercise integrating graceful physical movements, breathing

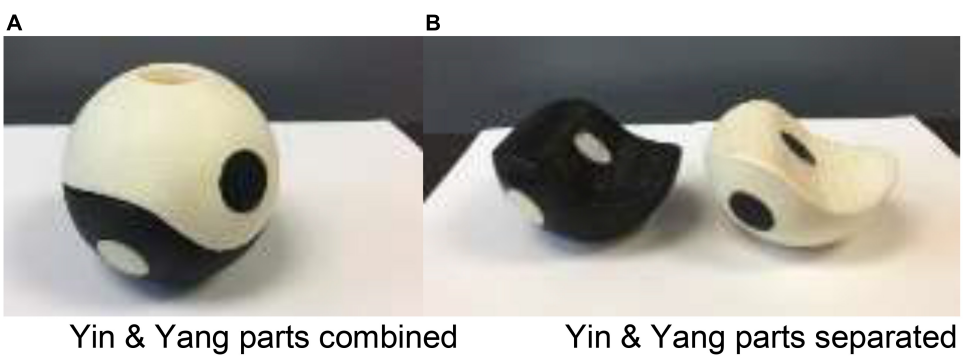


FIGURE 1 | (A) Tai Chi Ball is combined with poly-magnets. **(B)** Tai Chi Ball is separated by twisting it.

TABLE 1 | Means and SDs of the muscle strength of the upper extremity between the WTCB group and control group.

Variable	WTCB group		Control group	
In pounds	**Pre-test (SD)**	**Post-test (SD)**	**Pre-test (SD)**	**Post-test (SD)**
Shoulder				
Flexion	14.67 (3.45)	14.12 (4.75)	14.06 (4.52)	10.15 (5.91)
Extension	19.80 (5.79)	19.61 (7.04)*	16.18 (5.06)	13.28 (5.90)*
Abduction	16.08 (4.87)	14.78 (4.11)*	12.22 (4.15)	9.02 (6.09)*
Adduction	21.65 (6.36)	21.06 (5.78)*	20.14 (5.76)	16.08 (4.42)*
Elbow				
Flexion	16.07 (7.59)	16.76 (7.01)*	11.77 (3.40)	9.91 (4.42)*
Extension	16.24 (6.69)	15.18 (5.98)*	13.77 (6.27)	10.19 (2.80)*
Wrist				
Flexion	11.54 (5.12)	11.33 (5.33)*	8.81 (3.34)	6.36 (2.30)*
Extension	11.52 (5.93)	10.38 (5.16)*	9.32 (2.65)	5.83 (1.45)*

$N_1 = 9$ in WTCB group and $N_2 = 10$ in control group.
**Significance between groups in the post-test test at the $p < 0.05$ level.*

training, and mindful awareness during practice in standing posture (Wayne et al., 2013). When Tai Chi is performed in a seated position the exercise intensity may decrease since not much or no leg movements are involved for wheelchair users. To add the Tai Chi Ball (weight training) to WTC practice would increase exercise intensity. Our pilot data showed that when practicing WTC with and without the Tai Chi Ball for 20 min, the oxygen consumption (VO2) was 20% higher ($p < 0.01$) and the heart rate (HR) was 5% higher ($p < 0.01$) while carrying the Ball than while not carrying the Ball.

In our pilot study, we examined a 12-week WTCB12 intervention on physical and mental health and function abilities among elderly with physical disability (Wang et al., 2020a). Twenty-six elderly persons participated in the study, nine WTCB group participants and 10 control group participants completed the study. The WTCB group practiced WTCB12 twice/week, 1 h each time for 12 weeks. The control group did their daily routine. The outcomes measures were: PSEQ, physical and mental health from SF-36v2, HR, blood pressure, range of motion, and muscle strength of the dominant arm at the shoulder, elbow and wrist joints. The results between groups demonstrated that the WTCB12 intervention may have significant effects on: (1) PSEQ in the activities of daily living; (2) general physical and mental health; and (3) maintaining the upper extremity muscle strength for the activities of daily living. From observations of the upper arm muscle strength data in **Table 1**, we found that the muscle strengths at the shoulder, elbow and wrist joints of the WTCB group remain about the same between the pre-test and post-test, but those of the control group decreased significantly in the post-test (Wang et al., 2020a).

DISCUSSION

The results of the upper extremity muscle strengths in the WTCB study might indicate that the WTCB intervention as a combination of both mind-body exercise and strength training may help to maintain upper extremity muscle strengths of the elderly (average 84 years old) with disability. The term "use it or lose it" may well reflect on the strength training in the elderly. Numerous studies have demonstrated that strength training can improve or maintain muscle mass and strength in older adults (Guizelini et al., 2018; Bennie et al., 2019). Furthermore, WTCB exercise is accessible, safe and inexpensive. It is a type of client self-initiated rehabilitation program and could be used in regions where there is a prevalent shortage of resources for hospital- and community-based rehabilitation (Bethge et al., 2014; Zheng et al., 2018).

The key innovation for the WTCB exercise lies in (1) WTCB combines the mind-body exercise and strength conditioning into one exercise which possesses aerobic, stretching and strength training; and (2) the Tai Chi Ball can be split into Yin-Yang parts or combined into one during WTCB exercise so that the use of the Tai Chi Ball during Tai Chi practice may match the traditional Tai Chi movements well, at the same time may facilitate upper extremity strength training and neuromuscular functions. The weight of the ball can be customized for the user, based on the participant's upper arm strength and physical condition. To our limited knowledge, the WTCB intervention may be the first attempt to combine mind-body and strength training into one exercise and the data of our pilot study showed promising results that the WTCB exercise had positive effects on self-efficacy pain management, general physical health, and maintain upper extremity muscle strength and was a feasible exercise for elderly with disability (Wang et al., 2020a).

There are several factors limit wheelchair users' access to exercise facilities such as transportation to gyms or clinics, and lack of home exercise equipment (Meyers et al., 2002;

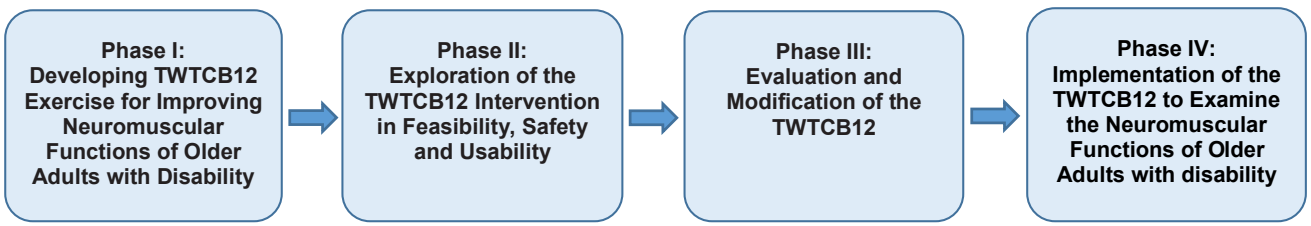


FIGURE 2 | Medical Research Council (MRC) framework for TWTCB12 intervention in four phases for improvement of neuromuscular functions for older adults with disability modified conceptual framework based on the model of Craig et al. (2013).

Cardinal and Spaziani, 2003). Many individuals with mobility limitations do not leave home because they are disabled, and the pandemic situation significantly decreased wheelchair users' daily activities and their engagement in physical activity and exercise. In recent years, telehealth and virtual rehabilitation become feasible and practical (Escalante-Gonzalbo et al., 2021; Gajarawala and Pelkowski, 2021). Therefore, we propose to add telehealth concept to WTCB12 exercise—to convert WTCB to Telehealth Wheelchair Tai Chi Ball (TWTCB12) and use a "Moving Shadow" method in telehealth that enables the learner to superimpose her/his image on an expert's demonstrating model to enhance the learning and practice effects. In order for the designed TWTCB12 intervention to improve the neuromuscular functions of older adults, the conceptual framework of the process of development-exploration-evaluation-implementation in four different phases is presented in **Figure 2**, a modified model of Craig et al. (2013) in order to determine the effects of the TWTCB12 on neuromuscular functions for older adults with disability.

Our *working hypothesis* is that applying the concepts of telehealth and "Moving Shadow" method in TWTCB intervention will make the intervention safe, feasible and user friendly for older wheelchair users with disability. The "Moving shadow" for TWTCB12 intervention demonstrating model is generated by three of the software: Zoom (providing a platform for TWTCB12), ManyCam (adding animation background as the moving shadow for expert's demonstrating), and OBS Studio (making the participant-self half transparent for superimposing on the demo image). The advantages of this "Moving Shadow" telehealth (online) methods are: (1) Tai Chi is a slow movement and the mirror shadow movements is performed by the Tai Chi master so that it is easy for learner to learn TWTCB12following the shadow by superimposing her/him onto the expert's image; and (2) The "Moving shadow" method on Zoom would provide an ideal telehealth environment for the wheelchair users to learn and practice WTCB12 exercise from home more feasible and user friendly.

We will conduct a pilot study of TWTCB12 Intervention to examine the neuromusculoskeletal functions of older adults with disability. The outcome measures in this pilot study would be the proprioception and motor coordination (e.g., eye-hand coordination, bilateral coordination, etc.), postural sway, spinal reflex excitability, central nervous system (CNS) responses (e.g., EEG, fMRI, TMS, fNIRs, or reflexes, etc.), muscle size or volume, muscle fiber typing and medical imaging methods (e.g., MRI, CT or ultrasound) in additional the outcome measures in aforementioned literature review. In order to meet the physical conditions of the individuals with limited mobility or SCI, three different weight levels (1–2 lbs; 3–4 lbs; 5–6 lbs) of the Tai Chi Ball are used to meet the physical conditions. Furthermore, we will develop a short form such as "Telehealth Wheelchair Tai Chi Ball 6 Forms (TWTCB6)" which included the TWTCB12 forms 1–3 and forms 10–12 for those who cannot learn and practice the full set of TWTCB12 due to very limited mobility or physical function. Meanwhile, we may also first conduct the TWTCB6 exercise without a Ball for individuals with more limited mobility based on a baseline physical condition evaluation such as the range of motion and muscle strength of the upper extremities. After the participants get stronger, we may engage them in TWTCB12 exercise. We anticipate that the TWTCB12 exercise will be an effective and feasible intervention for the improvement of neuromusculoskeletal functions for older adults with disability.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

TL wrote the outline and draft of the manuscript. X-WK made the literature search and wrote a brief summary. YW guided and revised the first version, the second version and the final version. All authors contributed to the article and approved the submitted version.

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Exploring the effects of peripheral sensibility on visuospatial and postural capacities during goal-directed movements in long-term Tai Chi practitioners

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Background: Falls are directly related to visuospatial ability and postural stability. Perturbations of upper body movements pose a challenge to older adults and may cause falls. This study investigated visuospatial ability and postural stability during goal-directed upper body movements between the Tai Chi and control groups and tried to connect them with their sensations.

Materials and methods: Thirty-seven older adults were recruited to perform the touch (TT) and blind touch (BTT) tasks. The target positioning error (TPE), ankle proprioception, tactile sensation, time to stabilization (TTS), and maximum displacement (D_{max}) of the center of pressure trajectory were compared between the groups during the tasks. The relationships of visuospatial ability and postural stability to proprioception and tactile sensation were investigated.

Results: D_{max} in the mediolateral (D_{maxML}) direction decreased during BTT compared to TT among the Tai Chi group but not the control group. Compared to the control group, less D_{max} in the anterio-posterior (D_{maxAP}) direction, and shorter TTS in AP/ML (TTS_{AP}/TTS_{ML}) directions were observed among the Tai Chi group. Compared to TT, D_{maxAP} decreased during the BTT. The Tai Chi group had less TPE in the vertical (TPE_V) direction and in three-dimensional space. Among the Tai Chi group, TPE_V, TTS_{ML}, and D_{maxAP} were correlated to their proprioception during plantarflexion; TTS_{AP} was correlated to tactile sensation at the great toe during the TT and BTT; D_{maxAP} was correlated to tactile sensation at the great toe during the TT. Among the control group, TTS_{ML} was correlated to ankle proprioception during dorsiflexion and plantarflexion during the BTT.

Conclusion: Long-term Tai Chi practitioners exhibited superior visuospatial ability and postural stability during goal-directed upper body movements, which was associated with sensitive proprioception and tactile sensation.

KEYWORDS

coordination, postural balance, proprioception, tactile sensation, Tai Chi quan

Introduction

Falls in older adults pose a severe problem and are the fifth leading cause of death, following cancer, heart disease, stroke, and respiratory diseases (Canada, 2011). Standing with goal-directed upper body movements (reaching and fitting) is an important activity in daily life and is closely associated with motor, sensory, or cognitive functions among older adults (Hyndman et al., 2002; Pan et al., 2016). Goal-directed upper body reaching movements require the visuospatial ability of individuals (Hondzinski et al., 2010), and the perturbations of upper body movements under such tasks challenge the postural stability among older adults (Pan et al., 2016).

Falls are directly related to visuospatial ability (Naslund, 2010) and postural stability (Liu et al., 2012), especially during goal-directed upper body movements. Visuospatial ability is often used in describing how the mind organizes and understands two- and three-dimensional spaces (Pinker, 1984) and is one of the essential abilities in daily life (Martin et al., 2009). Poor visuospatial ability is associated with a greater risk of falls among older adults (Naslund, 2010). The target positioning error (TPE) measured during a blind touch task (BTT) could be used as an important indicator for evaluating visuospatial ability (McIntyre et al., 2000), indicated by a distance between the participant's pointed position by memory and the original target position after the target was removed. Less TPE indicated better visuospatial ability (McIntyre et al., 2000). Postural stability was often used to reflect an individual's ability to control their posture during locomotion (Kang and Dingwell, 2006). A proper postural control strategy was needed to restore the body's stability when needed (Haddad et al., 2012). Greater postural stability enhanced the ability to resist perturbations, thereby reducing the risk of falls (Latash et al., 2010). Postural stability could be reflected by time to stabilization (TTS) (Ross and Guskiewicz, 2003, 2004; Fransz et al., 2015) and maximum displacement (D_{max}) of the center of pressure (COP) trajectory during goal-directed upper body movements (Prieto et al., 1996; Pan et al., 2016). Shorter TTS (Fransz et al., 2015; Sherrington et al., 2019) or the less D_{max} indicated better postural stability and reduction in fall risk (Prieto et al., 1996; Pan et al., 2016).

A few types of physical activities are effective in reducing fall risk among older adults (Bangsbo et al., 2019). As a traditional Chinese multi-genre fitness exercise, Tai Chi might be an option for improving visuospatial ability and postural stability. Visuospatial ability (Nemoto et al., 2020) and postural stability (Ghai et al., 2017) requires combinations of cognition and movement coordination. Tai Chi encompasses motor (a series of body movements) and mental (mind concentration) elements (Wayne et al., 2014; Song et al., 2018), and has been proven to improve motor and cognitive functions among older adults (Solianik et al., 2021). Further, practicing Tai Chi improved the sensitivity of proprioception and tactile sensation (Sun et al., 2015; Hu et al., 2021), which were positively related to visuospatial ability (Hondzinski et al., 2010) and postural stability (Zhang et al., 2015). Moreover, Tai Chi involves upper body movements supported by lower extremities to maintain postural stability, similar to the goal-directed upper body movements. Therefore, visuospatial ability and postural stability during goal-directed upper body movements may benefit from Tai Chi practice.

As individual ages, their visuospatial ability and postural stability decline rapidly, twice as fast as the decline in memory (Murre et al., 2013; Lee et al., 2019). Therefore, a suitable exercise that delays or reverses a decline in visuospatial ability and postural stability among older adults is urgently needed. Although the relationship of visuospatial ability and postural stability to sensations has been investigated, the different roles of its two main components, proprioception, and tactile sensation, have yet been fully understood. Therefore, the purpose of this study was to investigate the benefits of Tai Chi practice for visuospatial ability and postural stability during goal-directed upper body movements and their relationship to practitioners' visuospatial ability and postural stability were related to their proprioception and tactile sensations. It is hypothesis that 1. compared to the control group, Tai Chi practitioners have better visuospatial ability and postural stability; 2. The visuospatial ability and postural stability are positively correlated with the sensitivity of proprioception and tactile sensation.

Materials and methods

The study design is analytical cross-sectional.

Participants

An *a priori* power analysis (G*Power Version 3.1) indicated that a minimum of 15 participants was needed in each group to obtain an alpha level of 0.05 and a beta level of 0.80 based on a previous report, in which the TTS was compared after the matched bias (2.75 ± 0.85) or unmatched bias (3.76 ± 1.01) exercises (Tulloch et al., 2012). The current study recruited 37 older adults aged 65∼77 years through flyers, leaflets, and advocacy from local communities (**Table 1**). The inclusion criteria were as follows: age ≥ 65 years, long-term Tai Chi practice experience (at least four times per week, 1 h each time, for more than 5 years) for the Tai Chi group, and absence of regular exercise (total exercise time less than 1 h per week in the past 3 years) for the control group. The exclusion criteria were movement disorders or nervous system diseases, recent lower extremity and dominant arm surgery, cardiovascular pathologies, diabetes or hepatorenal syndrome, coordination function disorders, peripheral neuritis, Parkinson's disease, Alzheimer's disease, and Mini-Mental State Examination (MMSE) scores < 24. All participants were right arm dominant, defined by the outstretched hand to reach an object (Haddad et al., 2008). All the participants signed informed consent forms before the formal test. The project was approved by the Ethics Committee of Shandong Sports University (2020108) and in accordance with the Declaration of Helsinki.

Testing protocol

Touch task and blind touch task

Each participant wore experimental shoes provided by the laboratory (Flattie, Qingdao Luzhong Co. Ltd., Qingdao, China). A reflective marker (Marker-1) was attached to a metal bar (height = 2 m, diameter = 1.5 cm) with a solid base; another reflective marker (Marker-2) was attached to the tip of the index finger of a participant's dominant arm. The metal bar was removable, and the height of Maker-1 was adjustable. A force plate (AMTI 600*900, AMTI Inc., Watertown, MA, United States) was used to collect force data at 1,000 Hz. A 12-camera motion analysis system (Vicon, Oxford Metrics, Yarnton, England) was used to collect the markers' three-dimensional data at 100 Hz. The force plate and motion analysis system were collected via the Vicon system with internal synchronization.

The location of the marker-1 is adjustable. The horizontal location could be adjusted by moving the bar forward or backward, the vertical location could be adjusted by attaching the marker to the high or low part of the bar. The height of Marker-1 was adjusted to the participant's shoulder joint

TABLE 1 Basic information of the participants in Tai Chi and control groups.

Tai Chi group						Control group				
Sex	**Height (cm)**	**Weight (kg)**	**BMI (kg/m^2)**	**Age (years)**	**EXP (years)**	**Sex**	**Height (cm)**	**Weight (kg)**	**BMI (kg/m^2)**	**Age (years)**
Male	181	93.4	28.51	72.7	8.1	Male	170	68.2	23.60	75.2
Male	165	66.5	24.43	68.6	8.9	Male	162	63.6	24.23	65.0
Male	161	60.6	23.38	70.5	5.2	Female	156	71.3	29.30	71.8
Male	180	76.0	23.46	77.3	10.8	Female	156	71.4	29.34	67.7
Male	170	75.0	25.95	72.9	19.6	Male	160	62.1	24.26	66.3
Male	164	66.1	24.58	76.4	20.4	Male	168	82.9	29.37	70.2
Male	171	86.0	29.41	65.4	5.4	Female	153	44.7	19.10	67.8
Male	171	78.0	26.67	67.4	9.6	Male	177	89.9	28.70	69.6
Male	168	71.1	25.19	65.2	5.3	Male	164	64.7	24.06	76.0
Female	156	71.9	29.54	65.6	6.0	Male	164	56.3	20.93	65.4
Male	174	72.8	24.05	65.3	5.7	Female	152	64.0	27.70	67.2
Male	173	81.0	27.06	73.1	11.8	Female	154	56.3	23.74	68.7
Female	158	56.3	22.55	72.6	21.2	Male	176	90.8	29.31	66.1
Male	176	76.7	24.76	75.4	20.3	Male	166	75.1	27.25	65.7
Female	155	48.6	20.23	67.7	5.5	Male	175	84.8	27.69	65.6
Male	171	74.3	25.41	66.9	8.2	Male	166	76.3	27.69	69.7
Female	157	57.6	23.37	66.4	9.2	Male	164	71.1	26.44	65.5
Male	181	59.1	18.04	65.6	9.8	Male	168	75.2	26.64	66.4
–	–	–	–	–	–	Male	175	91.0	29.71	66.1
AVE	168.4	70.6	24.81	69.7	10.6	AVE	164.5	71.4	26.2	68.2

EXP, experience; BMI, body mass index; M, male; F, female; AVE, average.

height with 1.3 times the dominant arm length to the shoulder joint horizontally. The metal bar location was adjusted to allow participants to stand on the center of the force plate. Each participant was asked to complete 2 tasks in a fixed order, namely, touch task (TT) and BTT. During the TT (**Figure 1A**), each participant stood quietly on the force plate for 30 s for stabilization. When the command "start" was given, the participants raised their dominant arms and used Marker-2 to touch Marker-1 at a comfortable speed, then brought their arms back to the initial position and stood still for another 30 s. During the BTT (**Figure 1B**), the metal bar with Marker-1 was removed from sight manually about 1 s before individual movement, and the participants could see the process of moving out (Hondzinski et al., 2010). The participants raised their dominant arms and used Marker-2 to point to the remembered position of Marker-1, and then return to a stable standing position as soon as possible. Five trials were performed for each task. Rests were taken between each round of data collection for as long as requested by the participant (Hondzinski et al., 2010). Before data collection, the participants had 10 min to familiarize the test protocol, and their height, weight, dominant arm length, and shoulder height were recorded. The protocol was similar to a previous study, in which the effects of aging and sensory deficits were examined (Hondzinski et al., 2010).

Proprioception test

The proprioception threshold at the ankle joint of the dominant leg was assessed using a proprioception test device (AP-II, Sunny Co. Ltd., Jinan, China) (**Figure 1C**). Good test-retest reliability (ICC value, 0.74∼0.94) for the device has been reported previously (Sun et al., 2015). The dominant leg was defined as the preferred leg for kicking a football in the lab. The minimum angular motion that the patient can detect during ankle dorsiflexion/plantarflexion was collected by using the proprioception test device. The device consists of a box and a platform that can rotate within the frontal and sagittal planes. Two electric motors drive the platform at an angular velocity of 0.4°/s (Song et al., 2021). The movement of the platform can be stopped at any time by a hand switch controlled by the participants. An electronic goniometer in the device recorded the angular displacement of the platform. Each participant was seated on a height-adjustable chair with the foot placed on the platform. During the ankle proprioception test, the knee and hip joints were flexed at 90°, and the leg was perpendicular to the surface of the platform when the platform was placed in a horizontal position. Approximately 50% of the participant's lower extremity weight was rested on the platform using the thigh cuff suspension system to control unwanted sensory cues from the contact between the platform and the plantar surface of the foot. The participant sat with their eyes closed

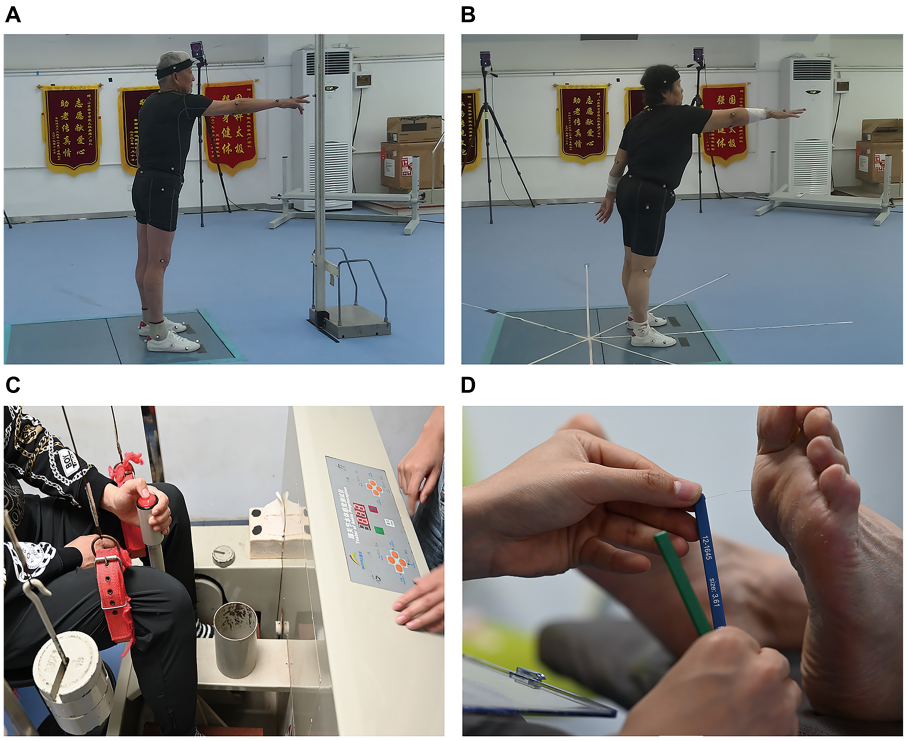


FIGURE 1
The illustration about the actual testing protocol. **(A)** Touch task; **(B)** blind touch task; **(C)** proprioception test; **(D)** tactile sensation tests.

and wore headphones with light music playing to eliminate potential environmental visual and auditory stimulation. The participant was instructed to concentrate on their foot and press the hand switch to stop the movement of the platform when they could sense motion, followed by identification of the rotation direction. The motor was operated to rotate with a random time interval ranging from 2 to 10 s after an indication to start a trial. At least five trials were performed for each direction to reduce random measurement errors.

Tactile sensation test

The dominant foot's tactile sensation was tested with the participants while lying supine on the treatment table with a set of Semmes-Weinstein monofilaments (six piece foot kit, North Coast Medical, Inc., Morgan Hill, CA, United States) (**Figure 1D**), which showed good test-retest reliability (ICC value, 0.83∼0.86) (Collins et al., 2010). Monofilaments of 6 different sizes used in this study were 2.83, 3.61, 4.31, 4.56, 5.07, and 6.65 that applies 0.07, 0.4, 2, 4, 10, and 300 grams of force when being pressed into a C-shape (bent 90°). The filament size was log10 (10 × force in milligrams). The filaments were applied to the skin on the bases of the great toe, 1st and 5th metatarsals, arch, and heel in random order (Song et al., 2021). These touches were performed for 1 s and with two repetitions. Randomized null-stimuli were added to ensure that the participants could not anticipate the application of the filaments. Plantar sensitivity was determined by the initial application of the thin filaments, progressing to the thicker filaments until the participants were able to detect the touch (Song et al., 2021). The participants were asked to provide a verbal response about the localization of the area tested when they perceived the stimulation. The sensitivity threshold was determined by the minimum monofilament gauge detected correctly. A less sensitivity threshold indicates better plantar tactile sensation.

Data reduction

Force plate data were used in calculating ground reaction force (GRF) and D_{max} of COP trajectory. COP was measured in the anterior-posterior (AP) and mediolateral (ML) directions. The GRF and COP data were filtered using a lowpass fourth-order Butterworth digital filter with a cut-off frequency of 50 Hz (Pan et al., 2016). The 20 s GRF data after the Marker-2 detached from the Marker-1 (or detached from the position of the removed Marker-1) were used in calculating the TTS. Two time-windows of the last 10 s (10∼15 s, 15∼20 s) of the AP and ML components of the GRF were analyzed. The windows with the smallest absolute GRF range for the AP and ML components were regarded as the optimal range of variation values (Ross and Guskiewicz, 2004). The 20 s COP data were collected from each participant after they began to move Marker-2 to Marker-1 (or removed Marker-1) (Prieto et al., 1996; Pan et al., 2016). The hand movement onset was taken as the moment when hand velocity exceeds 5% of the maximal hand speed at the beginning of the movement (Kubicki et al., 2012). The hand movement offset was calculated when the hand velocity fell below 5% of the maximal hand speed (the maximum speed of the Marker M2) at the end of the movement (Kubicki et al., 2012). Marker-2 position data were filtered with a 5 Hz fourth-order lowpass Butterworth filter (Hondzinski et al., 2010) and used in calculating TPE in the AP, ML, and vertical directions and three-dimensional space.

Variables

The TPE was calculated in the EXCEL as the distance between a participant's pointed position by memory (Marker-2) and the position of Marker-1 before it was removed. The TPE in 3D space is the 3D spatial distance between the marker 2 and the position of Marker-1 before it was removed. Final Marker-2 location was determined as the average of five frames after the movement offset (Hondzinski et al., 2010). TTS was defined as the time from Marker-2 detached from Marker-1 until the body regains stability, i.e., the starting moment when the smoothed GRF was within the optimal range of variation values for at least 0.5 s (Tulloch et al., 2012). The D_{maxAP}/D_{maxML} was defined as the maximum displacement (maximum-minimum) of COP trajectory in the AP/ML direction.

Data analysis

All statistical analysis was conducted using the SPSS software package (26.0, SPSS Inc., Chicago, IL, United States). Descriptive analysis results were presented as mean ± standard error in TTS, proprioception, and tactile sensation. The normality of all variables was tested using the Shapiro-Wilk test. Independent sample *t*-test (normally) or the Mann–Whitney U (non-normally) test was used to analyze TPE, proprioception, and tactile sensation thresholds. Two-way analysis of variance with repeated measures (normally) or Scheirer-Ray-Hare test (non-normally) was used to determine differences in TTS and D_{max} of COP trajectory.

A Bonferroni-adjusted *post-hoc* analysis was conducted when significant Group-by-Task interaction was detected. Partial eta squared (η^2_p) was used to represent the effect size of the main effect and interaction of the two-way analysis of variance. The thresholds for η^2_p were as follows: <0.06, small; 0.06∼0.14, moderate; >0.14, large (Pierce et al., 2004). Cohen's *d* was used to represent the effect size of the *post-hoc* pair comparison. The thresholds for Cohen' *d* were as follows: <0.20, trivial; 0.20∼0.50, small; 0.51∼0.80, medium; >0.80, large (Cohen et al., 1988). Pearson (normally) or Spearman (non-normally) correlations were used for testing the relationships of

visuospatial ability and postural stability to proprioception and tactile sensation. The thresholds for the correlation coefficient (r) were as follows: <0.10, trivial; 0.10∼0.30, weak; 0.31∼0.50, moderate; >0.50, strong (Cohen, 1988). A Type I error rate of less than 0.05 was used as an indication of statistical significance.

Results

Of the 37 participants, 18 were included in the Tai Chi group (female = 4, male = 14, age = 69.7 ± 3.9 years, weight = 70.6 ± 11.0 kg, height = 1.68 ± 0.08 m, BMI = 24.8 ± 2.9 kg/m^2, MMSE scores = 28.83 ± 1.01, Tai Chi experience = 10.6 ± 5.6 years), and 19 were included in the control group (female = 5, male = 14, age = 68.2 ± 3.3 years, weight = 71.4 ± 12.4 kg, height = 1.65 ± 0.08 m, BMI = 26.2 ± 3.1 kg/m^2, MMSE scores = 27.11 ± 2.38). The basic information of each participant in Tai Chi or control groups is shown in Table 1. Independent *t*-tests showed no significant differences in age, weight, height, and BMI between the groups.

The Shapiro-Wilk test showed that most variables were normally distributed, except the TPE in the ML and vertical directions and tactile sensation thresholds.

The TPE between Marker-1 and Marker-2 is shown in Figure 2. The bar chart with error lines represented the mean and standard error of the TPE among the Tai Chi and control groups. Compared with the control group, the Tai Chi group had significantly less TPE in the vertical direction (TPE_V; Tai Chi group: 20.3 ± 3.9 mm; control group: 34.9 ± 4.4 mm, $p = 0.019$, $d = 0.848$) and in three-dimensional space (Tai Chi group: 61.0 ± 6.9 mm; control group: 101.3 ± 10.3 mm, $p = 0.003$, $d = 1.065$) during the BTT.

The descriptive statistics and subgroup comparisons of the TTS are presented in Table 2. No Group-by-Task interaction was observed. Significant group effects were detected in TTS in the AP (TTS_{AP}; $p = 0.001$, $\eta^2_p = 0.458$) and ML (TTS_{ML}; $p < 0.001$, $\eta^2_p = 0.557$) directions. The control group took a longer time to be stabilized compared to the Tai Chi group.

The descriptive statistics and subgroup comparisons of D_{max} of COP trajectory in the AP (D_{maxAP}) and ML (D_{maxML}) directions were presented in Figure 3. Significant Group-by-Task interactions were detected in D_{maxML} ($p = 0.025$, $\eta^2_p = 0.278$). Pairwise comparisons showed that D_{maxML} direction was larger during the TT than during the BTT among the Tai Chi group ($p = 0.001$, $d = 0.975$); And less during the TT ($p = 0.037$, $d = 0.498$) and BTT ($p < 0.001$, $d = 1.364$) among the Tai Chi group compared with the control group. Significant group and task effects were detected in D_{maxAP} ($p = 0.002$, $\eta^2_p = 0.477$; and $p = 0.015$, $\eta^2_p = 0.316$), which was larger among the control group and TT than the Tai Chi group and BTT.

The differences in ankle proprioception and tactile sensation thresholds between the TC and the control groups are presented in Table 3. Participants in the Tai Chi group had less ankle proprioception thresholds during both dorsiflexion ($p = 0.029$, $d = 0.886$) and plantarflexion ($p = 0.012$, $d = 1.025$), and less tactile sensation thresholds at the great toe ($p = 0.015$, $d = 0.932$), arch ($p = 0.019$, $d = 0.855$) and heel ($p = 0.027$, $d = 0.930$), compared to people in the control group.

The relationships between TPE, TTS, D_{max} and proprioception/tactile sensation thresholds are presented in Table 4. Among the Tai Chi group, sensitive ankle proprioception during plantarflexion was strongly correlated to less TPE_V ($r = -0.515$, $p = 0.029$), TTS_{ML} ($r = 0.587$, $p = 0.01$) and D_{maxAP} during the TT ($r = -0.629$, $p = 0.005$). Sensitive tactile sensation at the great toe was strongly correlated to less

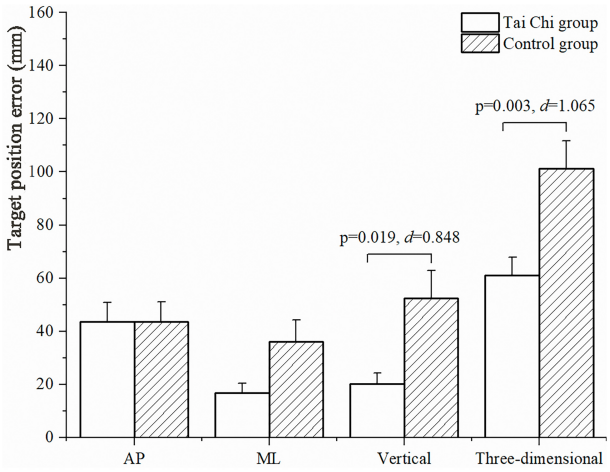


FIGURE 2
Target positioning error (TPE) between the finger marker and the removed bar marker in the AP, ML, vertical directions, and in three-dimensional space during the blind touch task (BTT). AP, anterior-posterior; ML, mediolateral.

TABLE 2 Time to stabilization (TTS) in the anterior-posterior (AP) and mediolateral (ML) directions during the touch task (TT) and blind touch task (BTT).

Variables	Task	Group		Group-by-task interaction		Task effect		Group effect	
		Tai Chi (N = 18)	Control (N = 19)	p	η^2_p	p	η^2_p	p	η^2_p
TTS_{AP} (s)	TT	2.63 ± 0.83	3.03 ± 0.47	0.258	0.075	0.152	0.117	**0.001**	0.458
	BTT	2.25 ± 0.66	2.93 ± 0.66						
TTS_{ML} (s)	TT	2.07 ± 0.83	3.20 ± 0.65	0.266	0.072	0.417	0.039	<**0.001**	0.557
	BTT	2.16 ± 0.75	2.88 ± 0.71						

Values are presented as mean ± SD.
Bold and highlighted: $p < 0.05$, compared with control group.
AP, anterior-posterior; BTT, blind touch task; ML, mediolateral; TTS, time to stabilization; TT, touch task.

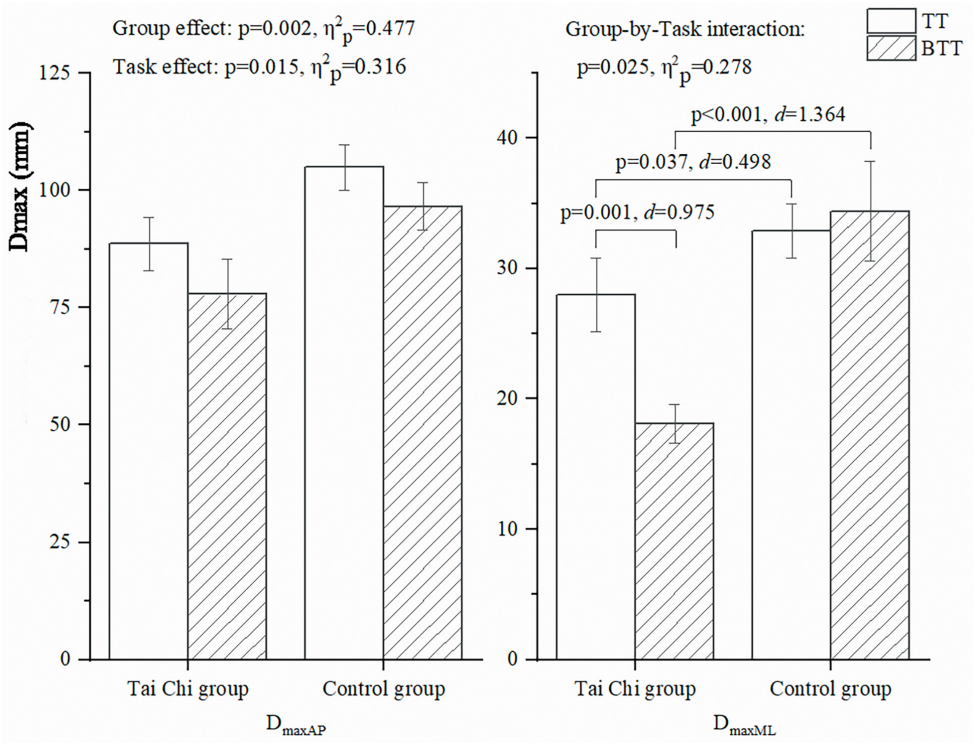


FIGURE 3
D_{max} in the AP and ML directions during the TT and BTT. AP, anterior-posterior; BTT, blind touch task; D_{max}, maximum displacement; ML, mediolateral; TT, touch task.

TTS_{AP} during the TT (r = 0.550, p = 0.018) and BTT (r = 0.564, p = 0.015), and moderately correlated to D_{maxAP} during the TT (r = –0.468, p = 0.05); Among the control group, sensitive ankle proprioceptions during dorsiflexion (r = 0.492, p = 0.033) and plantarflexion (r = 0.519, p = 0.021) were moderately to strongly correlated to less TTS_{ml} during the BTT.

Discussion

This study investigated the differences in visuospatial ability and postural stability between the Tai Chi practitioners with more than 5 years' experience and their controls during the TT and BTT. The relationship between visuospatial ability and postural stability with proprioception and the tactile sensation was also explored. The results supported our hypotheses. The TPE was significantly less, the time to recover from an unstable state was significantly shorter, and the D_{max} was significantly less among the Tai Chi group compared to the control group. The Tai Chi group decreased D_{maxML} during the BTT compared to TT; Compared to the control group, the Tai Chi group was more sensitive in proprioception and tactile sensation.

The TPE provided the following key data: 1. The Tai Chi and control groups did not reach Marker-2 far enough to the

TABLE 3 Proprioception and tactile sensation thresholds.

Sensations		Tai Chi group	Control group	*p*	*d*
Proprioception (°)	Dorsiflexion	1.58 ± 0.82	2.98 ± 2.08	**0.029**	0.886
	Plantarflexion	1.47 ± 0.73	3.24 ± 2.33	**0.012**	1.025
Tactile sensation (gauge)	Great Toe	3.93 ± 0.51	4.32 ± 0.30	**0.015***	0.932
	Metatarsal 1	4.13 ± 1.04	4.38 ± 0.22	0.162	0.333
	Metatarsal 5	4.27 ± 0.25	4.48 ± 0.60	0.380	0.457
	Arch	4.10 ± 0.44	4.54 ± 0.58	**0.019***	0.855
	Heel	4.25 ± 0.47	4.86 ± 0.80	**0.027***	0.930

Values are presented as mean ± SD.
Bold and highlighted: $p < 0.05$, compared with control group.
*Significant difference from the Mann–Whitney U test, or else from the independent sample *t*-test.

TABLE 4 Relationship of TPE, TTS, D_{max} to proprioception and tactile sensation.

Correlation coefficient (r)		TPE (mm)	TTS (s)				D_{max} (mm)
			TT		BTT		TT
		Vertical	AP	ML	AP	ML	AP
Tai Chi group							
Proprioception (°)	Dorsiflexion	0.008	0.053	0.049	0.082	−0.383	−0.200
	Plantarflexion	**−0.515**	−0.022	**0.587**	0.313	0.003	**−0.629**
Tactile sensation (gauge)	Great toe	−0.323	**0.550***	−0.003	**0.564***	0.064	**−0.468***
Control group							
Proprioception (°)	Dorsiflexion	−0.283	−0.116	0.085	0.206	**0.492**	−0.095
	Plantarflexion	−0.242	−0.050	0.038	0.182	**0.519**	0.086

AP, anterior-posterior; BTT, blind touch task; D_{max}, maximum displacement; ML, mediolateral; TPE, target positioning error; TT, touch task.
Bold and highlighted: $p < 0.05$, significantly correlated.
*Significant correlated from Spearman correlation, or else from Pearson correlation.
Adjusted for age, weight, and height.

original position of Marker-1 during the BTT; 2. Less TPE in the vertical direction and three-dimensional space were detected during the BTT among the Tai Chi group, compared to the control group; 3. The TPE was correlated to ankle plantarflexion proprioception among the Tai Chi group. The further the practitioner stretched, the more forward the center of gravity was, and the greater disturbance of postural stability was. Therefore, those practitioners selected a more conservative strategy to maintain their postural stability during the BTT and prevent falls. TPE was correlated to participants' gaze direction (Kennedy and Inglis, 2002; Meyer et al., 2004) and sensation (Liu et al., 2012). The effects of Tai Chi practice on gaze stability (McGibbon et al., 2004), proprioception, and tactile sensation (Hu et al., 2021) had been proven, and this study further indicated that the proprioception among the Tai Chi group was correlated to the TPE. Among the Tai Chi group, the TPE was correlated to ankle proprioception during plantarflexion, but not dorsiflexion. During the tasks, the participants needed to lean forward to touch the marker, and ankle plantarflexors, such as soleus and gastrocnemius, were stretched. The proprioceptive receptors in these muscles provide spatial and temporal afferent information to maintain postural stability (Hogervorst and Brand, 1998). In the plantarflexion proprioceptive test, the same muscles were stretched and the sensitivity of proprioception was also determined by the function of the proprioceptive receptors in these muscles (Hogervorst and Brand, 1998). It is reasonable to indicate that Tai Chi practitioners used their better proprioception to reduce their TPE. The less TPE reflected the higher positioning accuracy of the Tai Chi group.

The results of TTS showed that 1. The Tai Chi group had shorter TTS than the control group; 2. TTS was correlated to proprioception and tactile sensation among the Tai Chi group and correlated to proprioception only among the control group. 3. TTS was correlated with proprioception during the BTT among the control group. TTS was defined as the time that a participant returns to a stable state from an unstable condition (Ross and Guskiewicz, 2003, 2004; Fransz et al., 2015) and could be used in evaluating postural stability (Ross and Guskiewicz, 2003). A shorter TTS indicated improved posture

stability and low fall risk (Fransz et al., 2015; Sherrington et al., 2019). Individuals with functional ankle instability had longer TTS than the healthy controllers, and long TTS might be caused by poor neuromuscular functions (Ross and Guskiewicz, 2004). Our study pointed out that both proprioception and tactile sensation were correlated to TTS. Ross and Guskiewicz (2004) supported the relationship by showing that ankle joint proprioception was highly correlated to an individual's TTS. Konradsen and Ravn (1991) suggested that proprioceptive defects at the ankle joint weaken the reflex contraction of the muscles that stabilize the body. This is the first study that revealed the relationship between tactile sensation and TTS to the best of our knowledge. Song et al. (2021) indicated that tactile sensation was only correlated to postural control when body movements were restricted. During the TT and BTT, older adults fixed their feet on the ground, so their body movements were relatively limited. In this circumstance, the position of the plantar COP changes as the subtle variation of GRFs, the perception of forces under the feet during the stance could be used to generate an internal estimate of the body center of mass location (Meyer et al., 2004). Tactile sensation afferents could provide valuable feedback to the central nervous system regarding ankle torque production, weight transfer, and limb loading (Meyer et al., 2004). From this viewpoint, a better tactile sensation might help to reduce the TTS among the Tai Chi group. In addition, this study showed that only the tactile sensation at the great toe was correlated to TTS. The tactile sensation is different between foot sole sites due to the notable differences in cutaneous receptor distribution, firing characteristics (Kennedy and Inglis, 2002), and the mechanical properties of the skin, like its hardness and thickness (Strzalkowski et al., 2015). Previous studies showed that the arch and great toe were thin and soft plantar regions (Strzalkowski et al., 2015) with better sensitivity, which was correlated to static balance control (Song et al., 2021). In our study, only tactile sensation at the great toe, rather than at the arch, was correlated with the postural stability. As one of the areas with the highest pressure during walking, great toe is subjected to much greater pressure loads than the arch (Mao et al., 2006b). It could be inferred that more pressure signals at the great toe could be transmitted to the central nervous system, so the correlation of TTS to tactile sensation at the great toe was detected, rather than at the arch. In our study, only the tactile sensation at the great toe, but not the arch, was correlated with postural stability. As one of the areas with high pressure during walking, the great toe is subjected to a much higher weight load than the arch (Mao et al., 2006b). It can be inferred that more pressure signals at the great toe could be transmitted to the central nervous system, so that significantly correlation of TTS with tactile sensation at the big toe was detected, but not at the arch. Among the control group, TTS was correlated with proprioception during the BTT, but not TT. Proprioception and vision can be compensated for each other by sensory weighting in the central nervous system (Rand et al., 2013), so the participants may rely more on proprioception to maintain postural stability during the BTT, where there was less visual information.

The outcomes of the D_{max} of COP trajectory showed that: 1. The Tai Chi group showed significantly less D_{max} in the AP direction during the TT and BTT compared with the control group. 2. The Tai Chi and control groups showed significantly less D_{max} in the AP direction during the BTT than during the TT. 3. Significant Group-by-Task interaction showed that the Tai Chi group had decreased D_{max} in the ML direction during BTT than during TT, while the control group did not have similar changes. 4. D_{max} was correlated to proprioception and tactile sensation among the Tai Chi group. One of the previous studies supported our first discovery by indicating that the Tai Chi group showed significantly less postural sway than the brisk walking and control groups during goal-directed upper body movements (Pan et al., 2016). The better postural control could explain the less D_{max} (Hondzinski et al., 2010; Zhang et al., 2011; Hu et al., 2021; Song et al., 2021). The less Dmax in the AP direction during the BTT may be explained by the fact that the Tai Chi and control groups reached their hands less forward and produced a small postural sway in the AP direction during the BTT. The Group-by-Task interaction in the D_{max} indicated that the Tai Chi group increased their postural stability in the ML direction during BTT compared to that during TT. Compared with normal walking, Tai Chi has more variety movements and greater plantar loading in the ML direction (Mao et al., 2006a), so it is not surprising that the Tai Chi group showed better postural stability in the ML direction. Compared to TT, the effects of vision on postural control were reduced during the BTT because the target was removed, and individuals relied more on sensations to compensate for the decreased vision effects. The outcomes of this and previous studies well-documented that proprioception and tactile sensation were better among the Tai Chi group (Li et al., 2019; Hu et al., 2021). It was reasonable to assume that the Tai Chi group took advantage of their better sensations to control their movements more precisely and decreased the disturbance in the ML direction during BTT than during TT.

The differences in proprioception and tactile sensation between the Tai Chi and control groups and the relationships of proprioception and tactile sensation to visuospatial ability and postural stability showed that: 1. Most of the proprioception and tactile sensation thresholds were significantly less among the Tai Chi group than among the control group; 2. Compared with the control group, more correlations of proprioception to visuospatial ability and postural stability were detected among the Tai Chi group; and 3. No correlations of tactile sensation to visuospatial ability and postural stability were detected among the control group. The positive effects of Tai Chi exercise on proprioception and tactile sensation had

been extensively investigated and well-explained previously (Hondzinski et al., 2010; Zhang et al., 2011; Hu et al., 2021). We investigated the relationship of proprioception and tactile sensation to visuospatial ability and postural stability. The proprioceptive receptors in and around joints provided important spatial and temporal afferent information regarding the positions and movements of body segments and information between body segments in space (Hogervorst and Brand, 1998; Relph and Herrington, 2016). Proprioceptive receptors afferent information was transmitted to the central nervous system, and these receptors, in turn, were organized and managed in various high-order areas. Therefore, proprioception had an important role in visuospatial ability and postural stability. One study measured the postural sway in 74 healthy subjects from different age groups. It reported that all groups were more dependent on proprioception than on other sensations to maintain balance control (Colledge et al., 1994). It is reasonable to assume that individuals prefer proprioception over vision to precisely control their movements. Hence, the Tai Chi group relied more on their better proprioception and performed better during upper body movements. Moreover, our outcomes indicated that proprioception was only correlated to postural stability during BTT, but not during TT.

In this study, the tactile sensation was better among the Tai Chi group. One previous study supported our observations and further indicated that Tai Chi intervention significantly improved tactile sensation among older adults by altering ring the plasticity of the sensory-motor system to increase somatosensory information from the plantar sensory (Hondzinski et al., 2010). Skin receptors in the foot sole are sensitive to contact pressure and potential changes in the distribution of pressure, provide important information about the body's status with respect to the supporting surface (Kennedy and Inglis, 2002). Tai Chi practitioners used their better tactile sensation, felt the slight changes of plantar pressure distribution, and finally improved their visuospatial ability and postural stability. This study confirmed the relationship of visuospatial ability and postural stability to proprioception and tactile sensation. This finding has clinical implication. Exercises that enhance sensations should be included in the exercise prescriptions for fall prevention among older adults.

This study has several limitations. First, considering the size of the sample and the heterogeneity in the number of years of practicing Tai Chi, it could be specified that it is an exploratory study. Second, this is an analytical cross-sectional study, rather than a randomized controlled trial, only one measurement of the study variables was made, and no variables were assessed over time, that might cause some participant selection bias. Therefore, future studies should be designed by randomized controlled trials. Third, this study only examined the relationship of proprioception and tactile sensation with the visuospatial ability and postural stability, other contributors, such as the central nervous system, visual, vestibular, or cognitive functions, could also influence them. Fourth, some observations of this study could not to be explained by our limited understanding, e.g., only proprioception during plantarflexion, instead of during dorsiflexion, was correlated to visuospatial ability and postural stability among the Tai Chi group, and only proprioception during the BTT, instead of during the TT, was correlated to postural stability among the control group. Therefore, further investigations can be designed based on our new and innovative report.

Conclusion

During goal-directed upper body movements, long-term Tai Chi practitioners exhibited superior visuospatial ability and superior postural stability, along with better proprioception and tactile sensation. Compared with those of the control group, Tai Chi practitioners' better sensations enhanced their superior visuospatial ability and postural stability.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Sports Science Ethics Committee of Shandong Sport University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

ZS participated in the design of the study and contributed to the data collection, reduction, and analysis. LL and QS participated in the design of the study. WS participated in the design of the study and contributed to the data collection. MM contributed to the data reduction and analysis. CZ contributed to the data analysis and interpretation of results. All authors contributed to the manuscript writing, read and approved the final version of the manuscript, and agreed with the order of presentation of the authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Effect of Wearable Sensor-Based Exercise on Musculoskeletal Disorders in Individuals With Neurodegenerative Diseases: A Systematic Review and Meta-Analysis

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Background: The application of wearable sensor technology in an exercise intervention provides a new method for the standardization and accuracy of intervention. Considering that the deterioration of musculoskeletal conditions is of serious concern in patients with neurodegenerative diseases, it is worthwhile to clarify the effect of wearable sensor-based exercise on musculoskeletal disorders in such patients compared with traditional exercise.

Methods: Five health science-related databases, including PubMed, Cochrane Library, Embase, Web of Science, and Ebsco Cumulative Index to Nursing and Allied Health, were systematically searched. The protocol number of the study is PROSPERO CRD42022319763. Randomized controlled trials (RCTs) that were published up to March 2022 and written in English were included. Balance was the primary outcome measure, comprising questionnaires on postural stability and computerized dynamic posturography. The secondary outcome measures are motor symptoms, mobility ability, functional gait abilities, fall-associated self-efficacy, and adverse events. Stata version 16.0 was used for statistical analysis, and the weighted mean difference (WMD) was selected as the effect size with a 95% confidence interval (CI).

Results: Fifteen RCTs involving 488 participants with mean ages ranging from 58.6 to 81.6 years were included in this review, with 14 of them being pooled in a quantitative meta-analysis. Only five included studies showed a low risk of bias. The Berg balance scale (BBS) was used in nine studies, and the pooled data showed a significant improvement in the wearable sensor-based exercise group compared with the traditional exercise group after 3–12-week intervention (WMD = 1.43; 95% CI, 0.50 to 2.36, P = 0.003). A significant change in visual score was found both post-assessment and at 1-month follow-up assessment (WMD = 4.38; 95% CI, 1.69 to

7.07, $P = 0.001$; I2 = 0.0%). However, no significant differences were found between the two groups in the secondary outcome measures (all $p > 0.05$). No major adverse events were reported.

Conclusion: The wearable sensor-based exercise had advantages in improving balance in patients with neurodegenerative diseases, while there was a lack of evidence in motor symptoms, mobility, and functional gait ability enhancement. Future studies are recommended to construct a comprehensive rehabilitation treatment system for the improvement in both postural control and quality of life.

Systematic Review Registration: http://www.crd.york.ac.uk/prospero/, identifier CRD42022319763.

Keywords: neurodegenerative diseases, Parkinson's disease, Alzheimer's disease, wearable sensor-based exercise, musculoskeletal disorders, balance, dynamic postural control

INTRODUCTION

Neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, motor neuron diseases, or amyotrophic lateral sclerosis) are caused by the progressive degeneration of neurons and/or their myelin sheaths and mainly characterized by the deposition of proteins showing altered physicochemical properties in the brain and in peripheral organs (Dugger and Dickson, 2017; Kovacs, 2017), such as degeneration and death of dopaminergic neurons in substantia nigra, or tangle of intracellular neurofibrillary. Symptoms of neurodegenerative diseases vary depending on the mechanism of degeneration and the corresponding brain region (Erkkinen et al., 2018). As degeneration increases, patients may develop different types of dysfunctions, including cognitive or motor impairments (Pender et al., 2020; Aarsland et al., 2021). Moreover, neurodegenerative diseases are among the most serious health problems affecting the life expectancy of millions of people worldwide (Kingwell, 2019; Dommershuijsen et al., 2020), with an estimated incidence rate from approximately 17 per 100,000 to 11.08 per 1000 person-years in Parkinson's disease (PD) (Hirsch et al., 2016) and Alzheimer's disease (AD) (Niu et al., 2017), respectively.

Previous study suggested that the main motor symptom, which was associated with neurodegeneration, increases gradually as the disease progresses (Ray and Agarwal, 2020), is the postural control abnormalities because the degeneration of the nervous system influences the integration of sensory information, the formation of motor patterns (which can be understood as the central nervous system generating the imagination of the movement), and the disorder of muscle control (Ryan et al., 2014). A growing body of research demonstrated that patients with neurodegenerative diseases may present with decreased balance, abnormal gait (Morel et al., 2020), a higher tendency to fall (Schell et al., 2019), and frailty (Swanson and Robinson, 2020; Waite et al., 2021), which brings about higher morbidity and mortality and also turns into significant healthcare concerns.

Cass et al. proposed that the ability to control postural balance is essential to perform most of the daily life activities, allowing people to maintain an active lifestyle, and avoiding falls (Cass, 2017). Motor intervention is a critical pathway for improving both balance and postural control in people with neurodegenerative diseases. The traditional exercise protocol consists of repeated balance training and gait relearning under the guidance of the therapist (Ni et al., 2018; Meng et al., 2020; Okada et al., 2021), while wearable systems are a promising solution to provide quantitative and meaningful clinical information about progress in a rehabilitation pathway, with personalized biofeedback or tele-therapy that can be administered in the comfort of settings for those with progressive neurological conditions (Porciuncula et al., 2018). Well-documented evidence suggested that the involvement of wearable sensor-based exercise, which means a cueing rehabilitation based on devices providing visual, auditory, or vibrotactile biofeedback (Carpinella et al., 2017), can provide patients with instant and sensitive biofeedback about the user's performance and build an interactive environment for supporting motor learning (Argent et al., 2019). The sensors can accurately measure body motion and capture the tendency of incorrect action patterns to promote the learning of postural control (Carpinella et al., 2017; Jakob et al., 2021; Meng et al., 2021). Studies have supported that a wearable sensor-based intervention model is well suited to impact a movement disorder in people with mild cognitive impairment (Schwenk et al., 2016), as they can serve as a "sixth sense," promote the central organization of multiple sensory inputs through external feedback (Gomez-Pinilla and Hillman, 2013; Gera et al., 2018), guide the formation of movement patterns in the brain (internal feedback) to control posture (Donath et al., 2016; Shih et al., 2016; Conradsson et al., 2017; Silva et al., 2017), and give a motivating effect due to game-based features (Horak et al., 2015).

Overview articles have discussed the potential of wearable sensor-based exercise for improving clinically relevant motor performances, such as postural stability or gait, which are important for safe ambulation and mobility-related quality of

life (Horak et al., 2015), and a previous meta-analysis, including eight randomized controlled trials (RCTs), provided evidence for a positive effect of wearable sensor-based exercise on static steady-state balance of healthy and various patient populations in studies with usual care controls and studies with conventional balance training controls (Gordt et al., 2018). However, to our knowledge, it remains unclear whether the wearable sensor-based exercise can effectively improve musculoskeletal disorders in individuals with neurodegenerative diseases. Therefore, the purpose of this study was to clarify the effectiveness of wearable sensor-based exercise for musculoskeletal concerns in patients with neurodegenerative diseases.

METHODS

The Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to structure our review. PROSPERO was used to enroll the protocol for this meta-analysis (No. CRD42022319763).

Search Strategy

Two reviewers (Xin Li and Zhengquan Chen) independently conducted an extensive search in five health science databases, including PubMed, Cochrane Library, Embase, Web of Science, and Ebsco Cumulative Index to Nursing and Allied Health, up to March 2022. The following search terms and their synonyms: "neurodegenerative diseases," "Parkinson's disease," "Alzheimer's disease," "motor neuron diseases," "amyotrophic lateral sclerosis," "biofeedback," "sensor," "exercise," and "postural control" (**Table 1**), were used. The search strategies are given in **Supplementary Appendix 1**.

We also searched the reference lists of the included studies and reviews of similar topics to identify additional eligible studies. This systematic review only included RCTs written in English. If there was a disagreement, the full text of the article was checked and discussed, if necessary, with third-party adjudication (Meiwen Zhu).

Eligibility Criteria

The following criteria that followed PICOS strategy were used to determine whether studies were eligible: (1) population: patients who were diagnosed with neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, motor neuron diseases, and amyotrophic lateral sclerosis; (2) intervention: wearable sensor-based exercise, including self-developed sensors or commercial sensors, which can provide visual, auditory, or vibrotactile biofeedback; (3) comparisons: therapeutic exercise without the use of sensors; (4) outcome measures: primary outcome being balance and secondary outcomes being motor symptoms, mobility ability, functional gait abilities, and fall-associated self-efficacy; and (5) study design: RCTs.

TABLE 1 | Terms used in the search strategy.

Search strategy
#1 Neurodegenerati* OR Parkinson* OR PD OR Alzheimer* OR "Amyotrophic Lateral Sclerosis" OR ALS OR "Motor Neuron Diseases"
#2 Biofeedback OR Sensor* OR Inertial OR IMU OR Acceleromet* OR Actigraph* OR Gyroscope* OR Magnetometer* OR "Virtual Reality" OR Exergam*
#3 Exercise* OR Physical Activity OR Sport* OR Training
#4 Balance OR Postur* OR "Motor Control" OR Gait OR Propriocepti*
#5 random* OR allocation OR placebo OR "single-blind" OR "double-blind" OR RCT
#6 #1 AND #2 AND #3 AND #4 AND #5

** Is used as a wildcard for truncated word retrieval.*

Study Selection

Two reviewers (Yiming Yue and Shuangyu Gu) independently screened the studies using the eligibility criteria. The titles and abstracts were initially screened, and then, the full texts of the remaining articles were extensively reviewed. Disagreements were resolved by discussion and rechecking the articles.

Outcome Measurements and Data Extraction

Considering the progression of neurodegenerative diseases, changes in the outcomes were compared between the wearable sensor-based exercise and controls. A change in balance was the primary outcome for extraction. Balance was assessed by evaluated by the Berg balance scale (BBS) or sensory organization test (SOT). A change in motor symptoms evaluated by the Unified Parkinson's Disease Rating Scale-III (UPDRS-III), mobility ability evaluated by the timed "Up and Go" test (TUG), 10-meter walking test (10MWT), and 39-item Parkinson's Disease Questionnaire (PDQ-39), functional gait abilities evaluated by the dynamic gait index (DGI), and fall-associated self-efficacy evaluated by the activities-specific balance confidence (ABC) scale were also extracted as the secondary outcomes.

Two reviewers (Qing Du and Haibin Guo) were paired up to retrieve the information and data from the included RCTs. Disagreements were resolved by discussion with a third reviewer (Xin Li). The following data were extracted: first author, published year, country, the number, gender, and age of participants; the duration, severity, and medication of the neurodegenerative diseases; sensor type; outcome measures; time points; and dropout rate. The details of the intervention methods (frequency, intensity, time, and type of exercise) in both the control group and sensor-based intervention group were also extracted. Adverse events were also collected to determine the safety of the wearable sensor-based exercise protocols.

Mean, standard deviation (SD), and the sample size were extracted for the outcome measures in each group (i.e., active and sham) for the pooled analysis. Published protocols were referenced and the corresponding authors were contacted for additional data when data were not directly available from the article.

Risk of Bias Assessment

The two reviewers (Xuan Zhou and Jing Tao) independently used the Cochrane risk of bias assessment tool (RoB 2.0) for

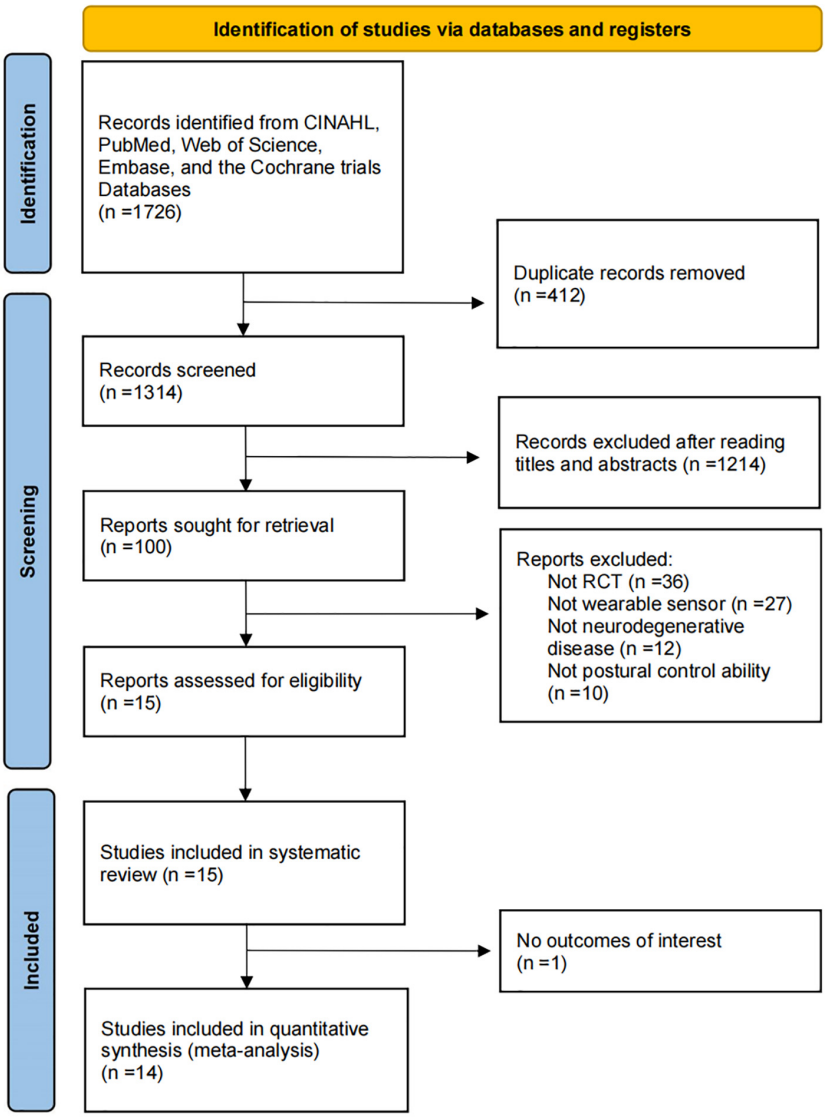


FIGURE 1 | Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.

RCTs to assess the methodological quality of the included studies. RoB 2.0 provides five domains and gives the overall risk of bias evaluation at the end. The five domains in RoB 2.0 are (1) the randomization process, (2) deviations from the intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. For missing outcome data in individual studies, we stipulated a low risk of bias for loss to follow-up of less than 10% and a difference of less than 5% in missing data between intervention and control groups. Publication bias was assessed through visual inspection of funnel plots for each outcome in which 10 or more eligible studies were identified.

Meta-Analysis and Subgroup Analyses

We used Stata version 16.0 (Stata Corp., College Station, TX, United States) to conduct this meta-analysis. The weighted mean difference (WMD) with 95 percent confidence intervals (Cls) was calculated to represent the effect size. The I^2 test was used to estimate the heterogeneity. A random-effects model was adopted when there was a significant heterogeneity ($I^2 > 50\%$); otherwise, a fixed-effects model was used. Egger's test was used to identify the publication bias of the main outcome measures. The p-value at the 0.05 level was considered statistically significant. Moreover, a sub-group analysis was performed on outcome measures of different follow-up time points according to the included studies.

Quality of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was conducted in this systematic review and meta-analysis to determine the quality of the evidence provided by RCTs. Detailed GRADE guidance was used to assess the overall risk of bias, imprecision, inconsistency,

indirectness, and publication bias and to summarize the results. We categorized each piece of evidence as high, medium, low, or very low quality (Atkins et al., 2004).

RESULTS

Identification of Studies

We found 1726 relevant articles from five health science databases. After removing duplicates, 1314 article titles and abstracts were screened for relevance. Eventually, 1299 articles were excluded due to not meeting the inclusion criteria or satisfying the exclusion criteria, and 15 articles were included. All these studies were randomized clinical trials. The flowchart of the study selection process is shown in **Figure 1**.

Participant and Study Characteristics

The demographic variables, type of sensors, time point, outcome measures, and dropout rate are given in **Table 2**. The frequency, intensity, time, and type of the exercise protocols in the intervention group and control group are presented in **Table 3**. A total of 15 articles involved 488 participants with mean ages ranging from 58.6 to 81.6 years, with 14 of them being pooled in a quantitative meta-analysis. The selected RCTs were performed in patients with PD (n = 13) (Yen et al., 2011; Nanhoe-Mahabier et al., 2012; Pompeu et al., 2012; van den Heuvel et al., 2014; Liao et al., 2015a,b; Yang et al., 2016; Carpinella et al., 2017; Gandolfi et al., 2017; Ribas et al., 2017; Cikajlo and Potisk, 2019; Santos et al., 2019; Kafle and Rizvi, 2021) and AD (n = 2) (Padala et al., 2012; Ugur and Sertel, 2020). Most studies included patients with mild-to-moderate Parkinson's disease (Hoehn and Yahr stages I to III).

The included trials were carried out in China (n = 4), Brazil (n = 3), Italy (n = 2), Netherlands (n = 2), India (n = 1), Slovenia (n = 1), Turkey (n = 1), and the United States (n = 1) (**Table 2**). Nine studies used the Nintendo Wii Fit (Yen et al., 2011; Padala et al., 2012; Pompeu et al., 2012; Liao et al., 2015a,b; Gandolfi et al., 2017; Ribas et al., 2017; Ugur and Sertel, 2020; Kafle and Rizvi, 2021) connected to a large screen. Four studies (van den Heuvel et al., 2014; Yang et al., 2016; Cikajlo and Potisk, 2019; Santos et al., 2019) played sports games based on VR technology, one study (Carpinella et al., 2017) used a Gamepad system comprising six wearable inertial sensors, and one study (Nanhoe-Mahabier et al., 2012) conducted a balance training session with a real-time vibrotactile biofeedback system containing angular velocity sensors. One trial reported an immediate effect of one-time biofeedback program on trunk sway of PD (Nanhoe-Mahabier et al., 2012), while the rehabilitation process of other 14 trials was completed over 2 months with a minimum of 10 sessions and a maximum of 40 sessions. Besides, the dedicated time per training session ranged from 20 to 60 min; in three studies (Nanhoe-Mahabier et al., 2012; Santos et al., 2019; Kafle and Rizvi, 2021), the treatment time was not given. Regarding treatment frequency, most studies reported a frequency between two and five times a week, and only one study (Kafle and Rizvi, 2021) provided no information about intervention frequency. Two studies (Yang et al., 2016; Gandolfi et al., 2017) were carried out in the home circumstance, involving 99 participants.

Risk of Bias and Quality of Evidence Appraisal

The risk of bias is reported in **Supplementary Table 1**. Most of the studies (more than 75%) present an unclear risk of bias in deviations from the intended interventions (effect of assignment to intervention). More than 50% included studies presented a low risk of bias in the randomization process, missing outcome data, measurement of the outcome, and selection of the reported result. The quality of evidence appraisal is given in **Supplementary Table 2**, and the quality ranged from low to moderate.

Outcome Measurements

Primary Outcome: Balance

The Berg balance scale is a comprehensive scale for postural stability assessment. Patients diagnosed with neurodegenerative diseases were assessed for static and dynamic postural control tasks using the BBS (Downs, 2015). The BBS was reported in nine studies (Padala et al., 2012; Pompeu et al., 2012; van den Heuvel et al., 2014; Yang et al., 2016; Carpinella et al., 2017; Gandolfi et al., 2017; Ribas et al., 2017; Santos et al., 2019; Kafle and Rizvi, 2021), with the duration from 3 to 12 weeks. When post-intervention data from nine randomized controlled studies were pooled, a significant improvement was found [WMD = 1.43; 95% CI, 0.50 to 2.36, P = 0.003; I^2 = 0.0%, **Figure 2**(2.1)]. After 0.5–2 months of follow-up, no significant differences were found between the wearable sensor-based exercise and control [≤1-month follow-up, WMD = −0.26; 95% CI, −2.21 to 1.69, P = 0.79; >1-month follow-up, WMD = −0.14; 95% CI, −1.19 to 0.91, P = 0.80, **Figures 2**(2.2; 2.3)]. Besides, the overall result of this pooled analysis is not significant (WMD = 0.63; 95% CI, −0.03 to 1.28, P = 0.061; I^2 = 0.0%, **Figure 2**). In addition, Egger's test revealed no evidence of publication bias (P = 0.815).

The SOT is used to quantify sensory integration ability for balance using computerized dynamic posturography. It can provide information related to the integration of vision, somatosensory, and vestibular systems for maintaining postural stability (Gera et al., 2016). Only two studies (Yen et al., 2011; Liao et al., 2015b) from China with 78 participants used the SOT, and the results showed no significant effect of wearable sensor-based exercise on the somatosensory score (WMD = −0.63; 95% CI, −1.62 to 0.37, P = 0.216; I^2 = 35.0%) (**Figure 3A**) or the vestibular score (WMD = −5.43; 95% CI, −24.58 to 13.73, P = 0.579; I^2 = 93.3%) (**Figure 3C**). However, a significant change in visual score was found both post-assessment and at 1-month follow-up assessment (WMD = 4.38; 95% CI, 1.69 to 7.07, P = 0.001; I^2 = 0.0%) (**Figure 3B**).

Secondary Outcomes

Motor Symptoms

The UPDRS is the most used comprehensive scale of PD severity. The scale has four sub-scales: I = Motivation,

TABLE 2 | Characteristics of the included studies.

	Author, year	Country	No. of participants (% men)	Age (y), Range/ Mean (SD)	Disease severity (mean ± SD)	Diagnosis	Disease duration (year) mean (SD)	Drug usage	Sensor type	Outcome measures	Time points	Dropout rate
1	Carpinella et al., 2017	Italy	T:37 A:17 (82.3%) C:20 (45.0%)	A: 73.0 (7.1) C:75.6 (8.2)	Hoehn and Yahr stages II to III UPDRS-III (0–56): A:16.6 (6.8) C:22.3 (7.3)	Parkinson's Disease	A:7.5 (3.2) C:10.3 (5.7)	–	Inertial sensors (TMA); 3D accelerometer, gyroscope, and magnetometer	BBS; 10MWT; UPDRS-III; TUG; ABC; FOGQ; PDQ-39; cop ML sway; cop AP sway	Baseline Intervention: 6–7 weeks Follow-up: 1-month	Post-treatment: 0% End of follow-up: 13.5%
2	Cikajlo and Potisk, 2019	Slovenia	T:20 (45%) A:10 (50%) C:10 (40%)	A:67.6 (7.6) C: 71.3 (8.4)	Hoehn and Yahr stages II to III	Parkinson's Disease	A:7.1 C:7.1	Dopamine	3D VR Oculus Rift CV1 head-mounted device	BBT; UPDRS; tfftte, atom, IB, tnot, ATI, atips	Baseline Intervention: 3 weeks	Post-treatment: 0% End of follow-up: 0%
3	Gandolfi et al., 2017	Italy	T:70 A:38 (60.5%) C:38 (73.6%)	A:67.45 (7.18) C: 69.84 (9.41)	Modified Hoehn and Yahr (H&Y) stages 2.5 to 3 UPDRS score: A:44.13 (24.05) C:50.76 (24.12)	Parkinson's Disease	A:6.16 (3.81) C:7.47 (3.90)	–	TeleWii balance training + VR telerehabilitation	BBS; falls; ABC; 10MWT; DGI; PDQ-8	Baseline Intervention: 7 weeks Follow-up: 1 month	Post-treatment: 7.9% End of follow-up: 7.9%
4	Kafle and Rizvi, 2021	India	T:60 A:30 (50.0%) C:30 (43.3%)	A:72.17 (8.19) C:72.40 (6.71)	Hoehn and Yahr stages I to II UPDRS A:30.90 (8.33) C:31.27 (7.78)	Parkinson's Disease	–	Levodopa or its synergists	Nintendo Wii gaming console	BBS;UST;UPDRS	Baseline Intervention: 7 weeks	–
5	Liao et al., 2015a*	China	T:36 A:12 (50%) C:12 (50%)	A:67.3 (7.1) C: 65.1 (6.7)	Hoehn and Yahr stages I to III A: 2.0 ± 0.7 C:2.0 ± 0.8	Parkinson's Disease	A:7.9 (2.7) C:6.9 (2.8)	–	VR-based Wii Fit exercise	TUG, PDQ-39, and FES-I	Baseline Intervention: 6 weeks Follow-up: 1 month	Post-treatment: 0% End of follow-up: 2.8%
6	Liao et al., 2015b*	China	T:36 A:12 (50%) C:12 (50%)	A:67.3 (7.1) C: 65.1 (6.7)	Hoehn and Yahr stages I to III A: 2.0 ± 0.7 C:2.0 ± 0.8	Parkinson's Disease	A:7.9 (2.7) C:6.9 (2.8)	–	VR-based Wii Fit exercise	Gait: Level walking velocity; Stride length; FGA; Sensory organization test	Baseline Intervention 6 weeks Follow-up: 1 month	Post-treatment: 0% End of follow-up: 2.8%
7	Padala et al., 2012	United States	T:22 (27%) A:11 (27%) C:11 (27%)	A:79.3 (9.8) C: 81.6 (5.2)	–	Alzheimer's Dementia	–	–	Nintendo Wii Fit console	BBS; TT;TUG; ADL; IADL; QOL-AD	Baseline Intervention: 8 weeks	–
8	Pompeu et al., 2012	Brazil	T:32 (53.1%) A:16 C:16	T:67.4 (8.1)	Hoehn and Yahr stages I to II UPDRS: T:9.5 (3.4) A:10.1 (3.8) C:8.9 (2.9)	Parkinson's Disease	–	Levodopa or its synergists	Nintendo Wii Fit console	UPDRS II; BBS	Baseline Intervention7 weeks Follow-up: 60 days	–
9	Ribas et al., 2017	Brazil	T:20 (60%) A:10 (40%) C:10 (40%)	T:61 (9.11) A:61.7 (6.83) C:60.2 (11.29)	UPDRS: A: 22.5 (11.5–32) C:20.5 (13.5–27.5)	Parkinson's Disease	A:6.5 (4) C:7 (2.79)	Dopaminergic medication	Nintendo Wii Fit console	BBS; 6MWT Quality-of-life scores: PDQ-39 Mobility	Baseline Intervention: 12 weeks Follow-up: 60 days	Post-treatment: 0% End of follow-up: 0%
10	Santos et al., 2019	Brazil	T:41 A:13 (84.6%) C:14 (78.6%)	A: 61.7 (7.3) C: 64.5 (9.8)	Hoehn and Yahr stages I to III A:1.4 (0.6) C: 1.3 (0.3)	Parkinson's Disease	A:7.0 (2.8) C:6.5 (2.0)	Levodopa	VR-based Wii Fit exercise	BBS; DGI; TUG Quality-of-life score (PDQ-39): Total	Baseline Intervention8 weeks Follow-up: 2 months	Post-treatment: 0% End of follow-up: 0%

(Continued)

TABLE 2 | (Continued)

	Author, year	Country	No. of participants (% men)	Age (y), Range/ Mean (SD)	Disease severity (mean ± SD)	Diagnosis	Disease duration (year) mean (SD)	Drug usage	Sensor type	Outcome measures	Time points	Dropout rate
11	Ugur and Sertel, 2020	Turkey	T:32 A:16 (68%) T:16 (75%)	A:73.75 (5.16) C:73.13 (3.54)	–	Alzheimer's Dementia	–	–	VR-based Wii Fit exercise	Tinetti Gait and Balance Test (Balance); five-time Sit-to-Stand Test; Gait Speed	Baseline Intervention: 6 weeks	Post-treatment: 0% End of follow-up: 0%
12	van den Heuvel et al., 2014	Netherlands	T:33 (60.6%) A:17 (70.6%) C:16 (50%)	A:66.3 (6.39) C:68.8 (9.68)	Hoehn and Yahr stages II and III UPDRS (Total): A:46.0 (19.81) C:52.0 (21.11)	Parkinson's Disease	–	A: One patient received intestinal levodopa infusion. One patient received an acetylcholine sterase inhibitor	Inertial sensors (Xsens, Enschede, Netherlands)	FRT; BBS; Single-leg test;10MWT; UPDRS; FES PDQ-39 mobility	Baseline Intervention 6 weeks Follow-up: 12 weeks	Post-treatment: 3.0% End of follow-up: 6.1%
13	Yang et al., 2016	China	T:23 (60.9%) A:11 (63.6%) C:12 (58.3%)	A:72.5 (8.4) C:75.4 (6.3)	Hoehn and Yahr stages II and III UPDRS: A:22.5 (12.1) C:21.7 (14.4)	Parkinson's Disease	A:9.4 (3.6) C:8.3 (4.1)	–	Custom-made virtual reality balance training system	BBS; DGI; Timed Up-and-Go test; PDQ-39; UPDRS-III	Baseline Intervention 6 weeks Follow-up: 2 weeks	Post-treatment: 13.0% End of follow-up: 13.0%
14	Yen et al., 2011	China	T:42 A:14 (85.7%) C:14 (85.7%) Untrained control group: 14 (64.3%)	A:70.4 (6.5) C:70.1 (6.9) Untrained control group:71.6 (5.8)	UPDRS-III: A:15.1 (3.2) C:15.9 (2.4)	Parkinson's Disease	A:6.0 (2.9) C:6.1 (3.3)	Dopamine agonists or dopamine replacement antiparkinsonian medications	Dimensional (3D) VR Balance Training System	SOT	Baseline Intervention 6 weeks Follow-up: 4 weeks	Post-treatment: 9.5% End of follow-up: 23.8%
15	Nanhoe-Mahabier et al., 2012	Netherlands	T:20 (80%) A:10 (80%) C: 10 (80%)	A:59.3 (2) C:58.6 (2.5)	UPDRS-III: A:17.9 (2.7) C:15.4 (1.1)	Parkinson's Disease	A:3.7 (0.8) C:3.9 (0.8)	levodopa equivalent	Balance biofeedback system	Duration until completion of the walking tasks, the 90% range of pitch and roll sway angle and the 90% range of pitch and roll sway angular velocity	Baseline; post-training	None

*SD, standard deviation; TUG, Timed Up and Go test, ABC, Activities-specific Balance Confidence scale; FOGQ, Freezing Of Gait Questionnaire; PDQ-39, Parkinson's Disease Questionnaire-39; COP, Center of Pressure; BBT, Box Blocks Test; tfftte, Time from first touch to the end; atom, Average time of manipulation; IB, Inserted boxes; tnot, Total number of tries; ATI, Average tremor indicator; atips, Average tremor indicator per second; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale—Motor Examination III; BBS, Berg Balance Scale; falls, number of falls in the previous month; 10MWT, 10-Meter Walking Test; DGI, Dynamic Gait Index; PDQ-8, Parkinson's Disease Quality-of-Life questionnaire; UST, Unipedal Stance Test; FGA, functional gait assessment; DC, directional control; ME, maximal excursion; MV, movement velocity; SOT, sensory organization test; TE, traditional exercise; FES-I, Falls Efficacy Scale—International; TT, Tinetti Test; ADL, activities of daily living; IADL, instrumental activities of daily living; QOL-AD, quality of life-Alzheimer's disease; MMSE, Mini-Mental State Examination; ST, Single task; DT, dual task; MFI, multidimensional fatigue inventory; HY, Hoehn and Yahr stage; PG, posture and gait subscore; FRT, functional reach test; HADS, hospital anxiety and depression scale; SOM, somatosensory; VIS, vision; VES, vestibular; PREF, preference. * The participants of the two articles were from the same population, but there were differences in the outcome measures between the two articles.*

TABLE 3 | Interventions in the included trials.

	Author, year	Intervention group FITT	Control group ITT	Adverse events
1	Carpinella et al., 2017	Frequency: 45-min sessions three times a week Intensity: mild Time: 20 sessions Type: balance and gait training with biofeedback Gamepad system (changing the reference values of the exercise, including more difficult tasks, changing the perceptive context) (e.g., altering proprioception through foam pads under feet), and/or including a dual task (e.g., walking holding a tray with a ball above)	Frequency: 45-min sessions three times a week Intensity: Mild Time: 20 sessions Type: Conventional physiotherapy [5 min of muscle stretching (hamstrings, quadriceps, and calves) and mobilization exercises (e.g., trunk rotation, hip abduction, flexion), followed by 40 min of balance and gait exercises similar to those performed by the experimental group]	Not mentioned
2	Cikajlo and Potisk, 2019	Frequency: 30-min sessions 10 times in 3 weeks Intensity: mild Time: 3 weeks Type: using immersive VR (3D) called "10Cubes" exergaming system to finish the VR task five times to pick and place the 10 virtual cubes in the virtual environment into the open treasure chest using the more affected hand.	Frequency: 30-min sessions 10 times in 3 weeks Intensity: Mild Time: 3 weeks Type: using a non-immersive environment (2D) (a laptop) to move to manipulate the virtual cubes.	None
3	Gandolfi et al., 2017	Frequency: 50 min 3 days/week Intensity: mild Time: 7 weeks + 1-month follow-up Type: in-home VR balance training called TeleWii consisted of 21 sessions of balance exercises to finish 10 exergames selected by the physiotherapist	Frequency: 50 min 3 days/week Intensity: Mild Time: 7 weeks + 1-month follow-up Type: in-clinic sensory integration balance training (SIBT) consisted of 21 sessions of balance and gait exercises under different sensory conditions (free vision, blindfolded, wearing a visual-conflict dome, firm/compliant surfaces, and neck extensions)	None
4	Kafle and Rizvi, 2021	Frequency: no information Intensity: no information Time: no information Type: using Nintendo Wii FitTM console.	Frequency: no information Intensity: no information Time: no information Type: global exercise	Not mentioned
5	Liao et al., 2015a	Frequency: 45-min sessions two times a week Intensity: moderate Time: 6 weeks + 1-month follow-up Type: virtual reality-based Wii Fit exercise included 10 min of yoga exercises, 15 min of strengthening exercises, and 20 min of balance games	Frequency: 45-min sessions two times a week Intensity: moderate Time: 6 weeks + 1-month follow-up Type: traditional exercise included 10 min of stretching exercises, 15 min of strengthening exercises, and 20 min of balance exercises	None
6	Liao et al., 2015b	Frequency: 45-min sessions two times a week Intensity: moderate Time: 6 weeks + 1-month follow-up Type: VR-based Wii Fit exercise included 10 min of yoga exercises, 15 min of strengthening exercises, and 20 min of balance games	Frequency: 45-min sessions two times a week Intensity: moderate Time: 6 weeks + 1-month follow-up Type: traditional exercise included 10 min of stretching exercises, 15 min of strengthening exercises, and 20 min of balance exercises	None
7	Padala et al., 2012	Frequency: 30-min sessions five times a week Intensity: moderate Time: 8 weeks Type: Wii Fit program included 10 min of yoga, 10 min of strength training, and 10 min of balance games.	Frequency: 30-min sessions five times a week Intensity: moderate Time: 8 weeks Type: walking group walked at their own pace as a group of three or four subjects at any given time with research personnel.	None
8	Pompeu et al., 2012	Frequency: 60-min sessions two times a week Intensity: moderate Time: 7 weeks + 60-day follow-up Type: 30 min on global exercises (10 min of warming, stretching, and active exercises; 10 min of resistance exercises for limbs; and 10 min of exercises in diagonal patterns for trunk, neck, and limbs) + 30 min on Wii-based motor and cognitive training (playing 10 Wii Fit games included static balance, dynamic balance, and stationary gait)	Frequency: 60-min sessions two times a week Intensity: moderate Time: 7 weeks + 60-day follow-up Type: 30 min on global exercises (10 min of warming, stretching, and active exercises; 10 min of resistance exercises for limbs; and 10 min of exercises in diagonal patterns for trunk, neck, and limbs) + 30 min on Wii-based motor and cognitive training (the same movements without the provision of external cues, feedback, and cognitive stimulation)	None
9	Ribas et al., 2017	Frequency: 30-min sessions two times a week Intensity: moderate Time:12 weeks + 60-day follow-up Type: seven Wii Fit games: Table Tilt, Tilt City, Penguin	Frequency: 30-min sessions two times a week Intensity: moderate Time: 12 weeks + 60-day follow-up Type: conventional exercise program: warming, stretching	

(Continued)

TABLE 3 | (Continued)

	Author, year	Intervention group FITT	Control group ITT	Adverse events
		Slide, Soccer Heading, Basic Run, Obstacle Course, and Basic Step (a Nintendo video game console with a Wii Balance Board)	and active exercises (10 min); resistance exercises for the limbs (10 min); and diagonal exercises for the trunk, neck, and limbs (10 min).	None
10	Santos et al., 2019	Frequency: 50 min a day, two times a week Intensity: moderate Time: 8 weeks Type: played four games in two sessions (Wii Sport and Wii Fit) standing up. In the first session, they played Boxing and Soccer Heading, and in the second session Golf and Running. Each session was performed for 20 min, with intervals of 1-min rest every 5 min of activity.	Frequency: 50 min a day, two times a week Intensity: moderate Time: 8 weeks Type: 30 min of specific diagonals [being superior limbs (flexion–abduction external rotation/extension–adduction–internal rotation); scapula (elevation and posterior depression), pelvis (anterior elevation/posterior depression), lower limbs (flexion–abduction–external rotation/internal extension–adduction–rotation) and 10 min of walking training in orthostasis or trunk extension training in ductus dorsal], with intervals of 1-min rest every 5 min of activity.	Not mentioned
11	Ugur and Sertel, 2020	Frequency: 30 min, two times a week Intensity: moderate Time: 6 weeks Type: training with games selected from different categories (soccer heading, tilt table, tightrope tension, perfect 10, cycling, tilt city, jogging plus, hula hoop, step basics, and penguin slide) with Nintendo Wii virtual reality device	Frequency: no clear Intensity: no clear Time: no clear Type: routine medical treatments	Not mentioned
12	van den Heuvel et al., 2014	Frequency: 60 min, two times a week Intensity: moderate Time: 5 weeks + 12-week follow-up Type: Visual feedback (VFT) training, the dynamic balance exercises focused on controlling body posture in the forward, backward, and sideward directions, exploring limits of stability, shifting weight from one foot to another, sit-to-stand movements, and included dual-task exercises.	Frequency: 60 min, two times a week Intensity: moderate Time: 5 weeks + 12-week follow-up Type: Conventional balance training, focused on training standing balance and included exercises while standing on one leg or with eyes closed, stepping exercises, dual-task exercises, sit-to-stand exercises, and exercises on the balancing beam or other challenging support surfaces.	None
13	Yang et al., 2016	Frequency: 50 min, two times a week Intensity: moderate Time: 6 weeks + 8-week follow-up Type: a 10-min warm-up stretching, three 10-min blocks of balance training [practiced the static posture maintaining with the VR balance training system (10 min) and dynamic weight shifting (2 × 10-min blocks)], and two 5-min breaks between blocks.	Frequency: 30 min, two times a week Intensity: moderate Time: 6 weeks + 8-week follow-up Type: In conventional balance training, participants practiced static posture maintaining (10-min block) and dynamic weight shifting (2 × 10-min blocks; **Supplementary Appendix 2**). The therapist in the control group guided the training and provided verbal instructions to correct the participants' movements.	Not mentioned
14	Yen et al., 2011	Frequency: 30 min, two times a week Intensity: moderate Time: 6 weeks + 4-week follow-up Type: undergo 10 min of stretching exercises as a warm-up and 20-min VR challenges (including 10 min of the 3D ball-rolling game and 10 min of indoor-outdoor virtual activities.)	Frequency: 30 min, two times a week Intensity: moderate Time: 6 weeks + 4-week follow-up Type: Conventional balance training, undergo 10 min of stretching exercises and 20 min of intervention [(1) static stance, (2) dynamic weight shifting, and (3) external perturbations]	None
15	Nanhoe-Mahabier et al., 2012	12-task balance training with a real-time vibrotactile biofeedback, which was provided at a frequency of 250 Hz by eight vibrotactile sensors spaced equally around the headband. Activation thresholds were set at 40% of the 90% ranges of pitch and roll sway angular velocity derived during the second balance assessment of the first session, for each subject and for each task separately.	The same 12-task balance training without any biofeedback	Not mentioned

Behavior, and Mood; II = ADL; III = Motor Examination; and IV = Complications of Therapy (Goetz et al., 2008). The pooled results of four studies (van den Heuvel et al., 2014; Yang et al., 2016; Carpinella et al., 2017; Kafle and Rizvi, 2021) did not show a significant effect of wearable sensor-based exercise on the UPDRS-III either at the post-intervention or 0.5–1.5-month

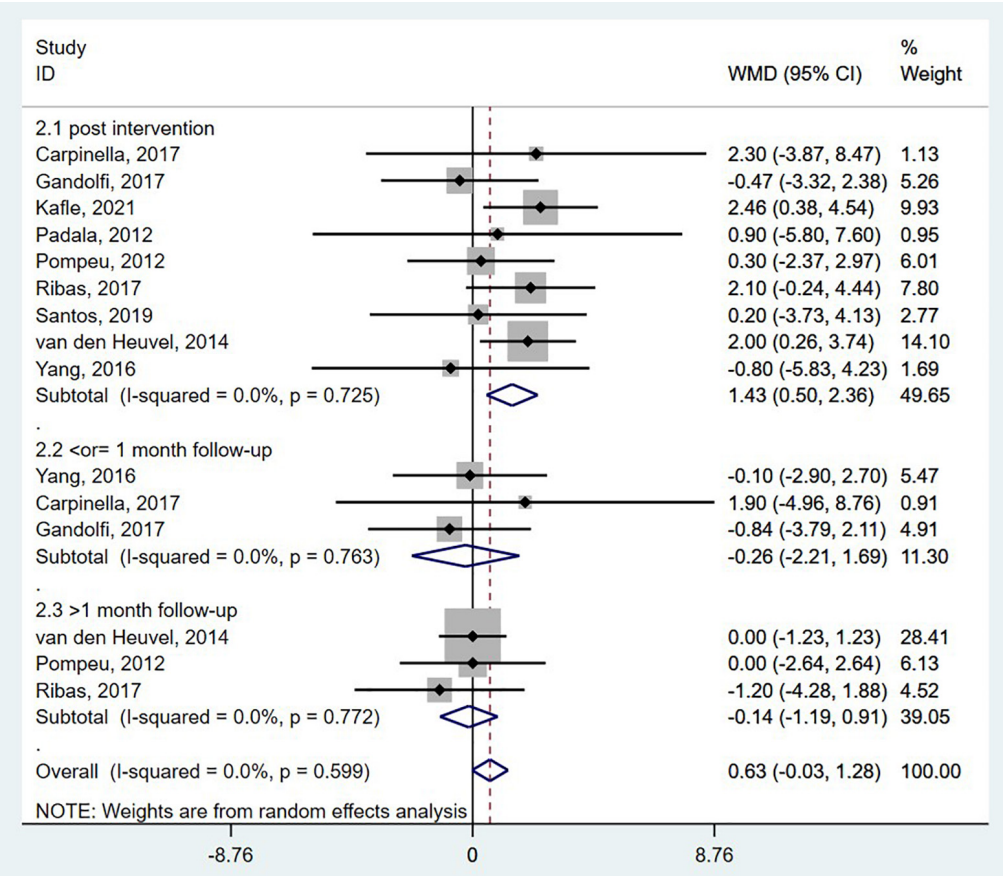


FIGURE 2 | Forest plot of pooled results for the Berg balance scale.

follow-up (WMD = −0.00; 95% CI, −2.79 to 2.78, P = 0.997; I^2 = 46.9%) (**Figure 4**).

Mobility Ability

Five studies (Padala et al., 2012; Liao et al., 2015a; Yang et al., 2016; Carpinella et al., 2017; Santos et al., 2019) used the TUG to evaluate functional mobility. In the TUG, the participants were timed as they stood up from a backrest chair, walked with a normal gait 3 meters forward, and then sat down and leaned back (de Oliveira Silva et al., 2019; Yoo et al., 2020). The pooled analysis showed no significant effect of wearable sensor-based exercise on the TUG test (WMD = −1.06; 95% CI, −2.17 to 0.06, P = 0.589; I^2 = 0%) (**Figure 5**). Three studies (van den Heuvel et al., 2014; Carpinella et al., 2017; Gandolfi et al., 2017) measured the effects on functional mobility by the 10MWT. Our analysis revealed no significant effect of wearable sensor-based exercise on the 10MWT (WMD = 0.01; 95% CI, −0.07 to 0.08, P = 0.481; I^2 = 0%) (**Figure 6**).

Parkinson's disease questionnaire-39 is a self-reported quality-of-life questionnaire evaluating mobility and social functions in people with Parkinson's disease based on a five-point Likert scale (Neff et al., 2018). The PDQ-39 was reported in four studies (Liao et al., 2015a; Yang et al., 2016; Carpinella et al., 2017; Santos et al., 2019), and the pooled analysis showed no significant effect of wearable sensor-based exercise on PDQ-39 scores (WMD = 0.21; 95% CI, −4.24 to 4.66, P = 0.926; I^2 = 0%, **Figure 7A**). The mobility scores of the PDQ-39 were reported in two studies (van den Heuvel et al., 2014; Ribas et al., 2017), and the pooled analysis did reveal no significant effect of wearable sensor-based exercise on these scores (WMD = −0.87; 95% CI, −6.43 to 4.70, P = 0.760; I^2 = 0%, **Figure 7B**; Peto et al., 2001).

Functional Gait Abilities

Dynamic gait index (DGI) has emerged as a valid indicator of functional gait abilities for people with balance and vestibular disorders. Scores on the DGI range from 0 to 24, with higher scores indicating better performance (Bloem et al., 2016). Three RCTs (Yang et al., 2016; Gandolfi et al., 2017; Santos et al., 2019) evaluated the effect of wearable sensor-based exercise on gait performance using the DGI. However, the pooled results did not reveal a significant effect (WMD = −0.55; 95% CI, −1.27 to 0.17, P = 0.135; I^2 = 0%) (**Figure 8**).

Fall-Associated Self-Efficacy

Activities-specific balance confidence (ABC) scale measures balance confidence in particular postural control tasks. The ABC scale was employed in two studies (Carpinella et al., 2017; Gandolfi et al., 2017), and there was no significant difference

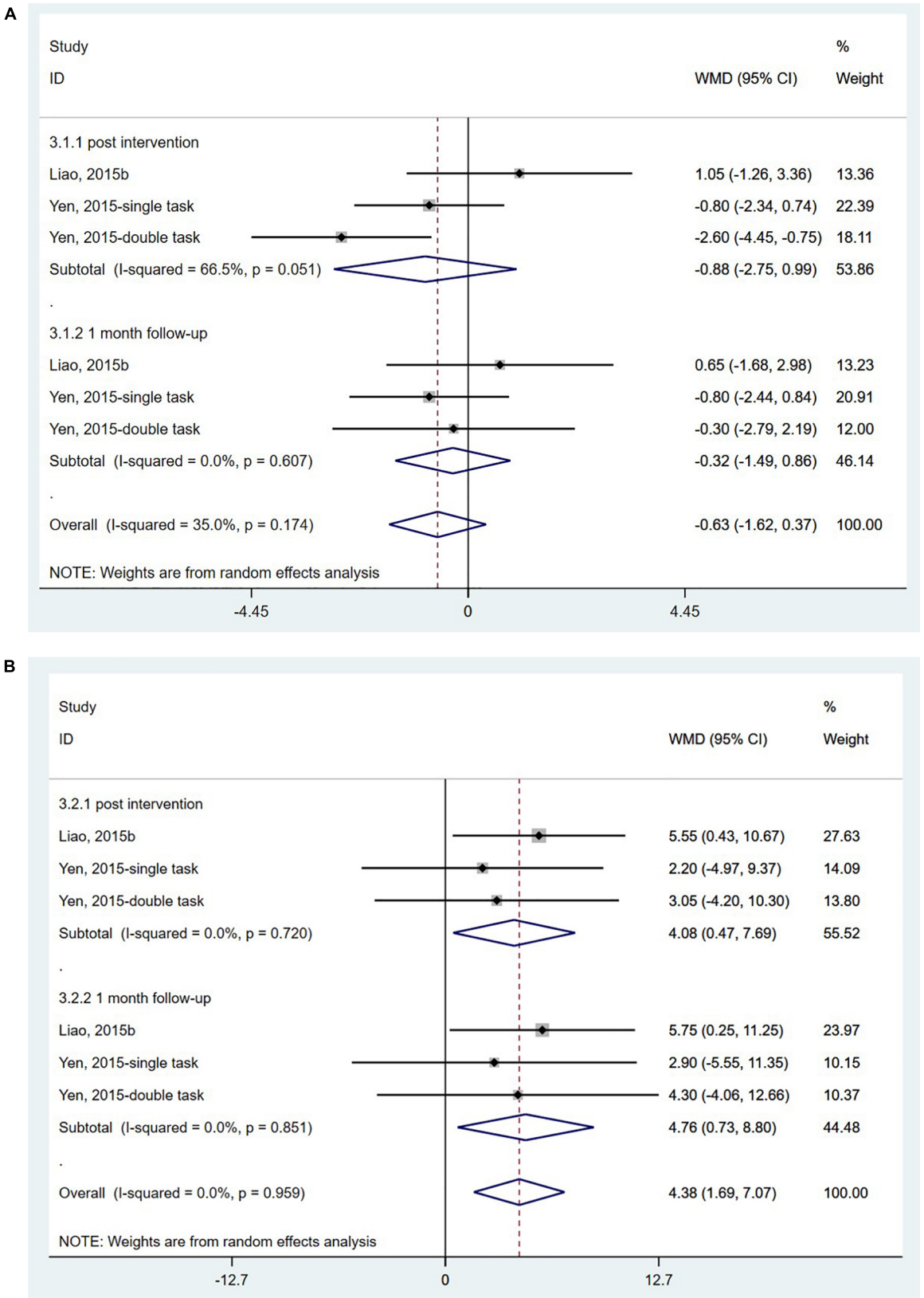


FIGURE 3 | (Continued)

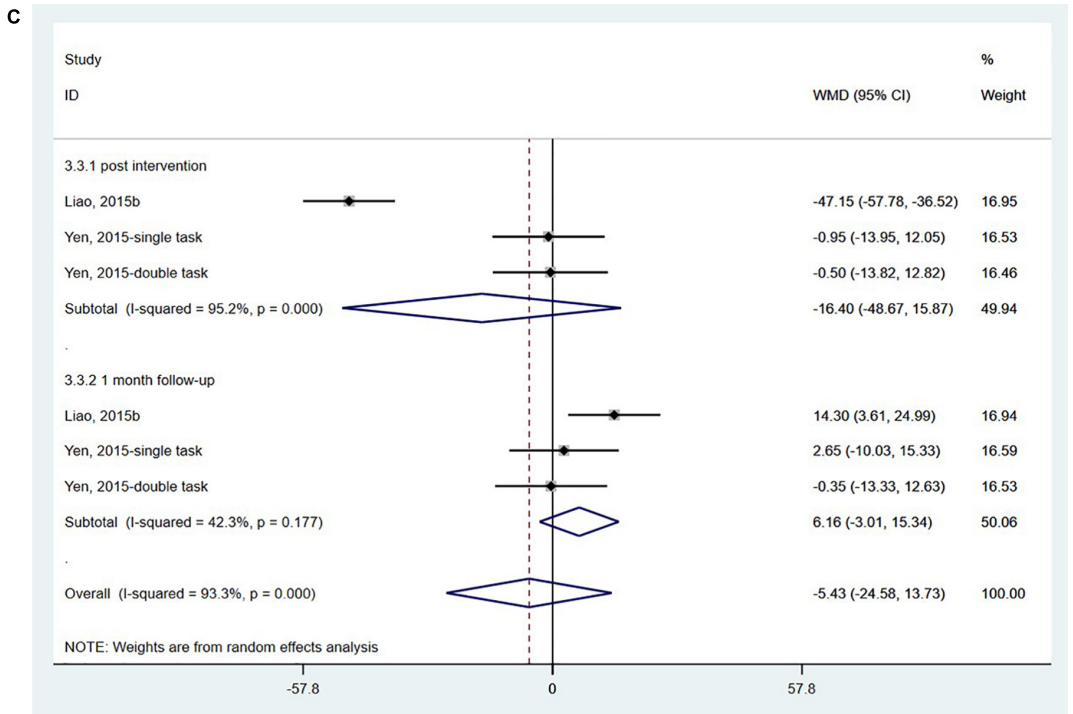


FIGURE 3 | Forest plot of pooled results for sensory organization test. **(A)** Somatosensory scores. **(B)** Visual scores. **(C)** Vestibular scores.

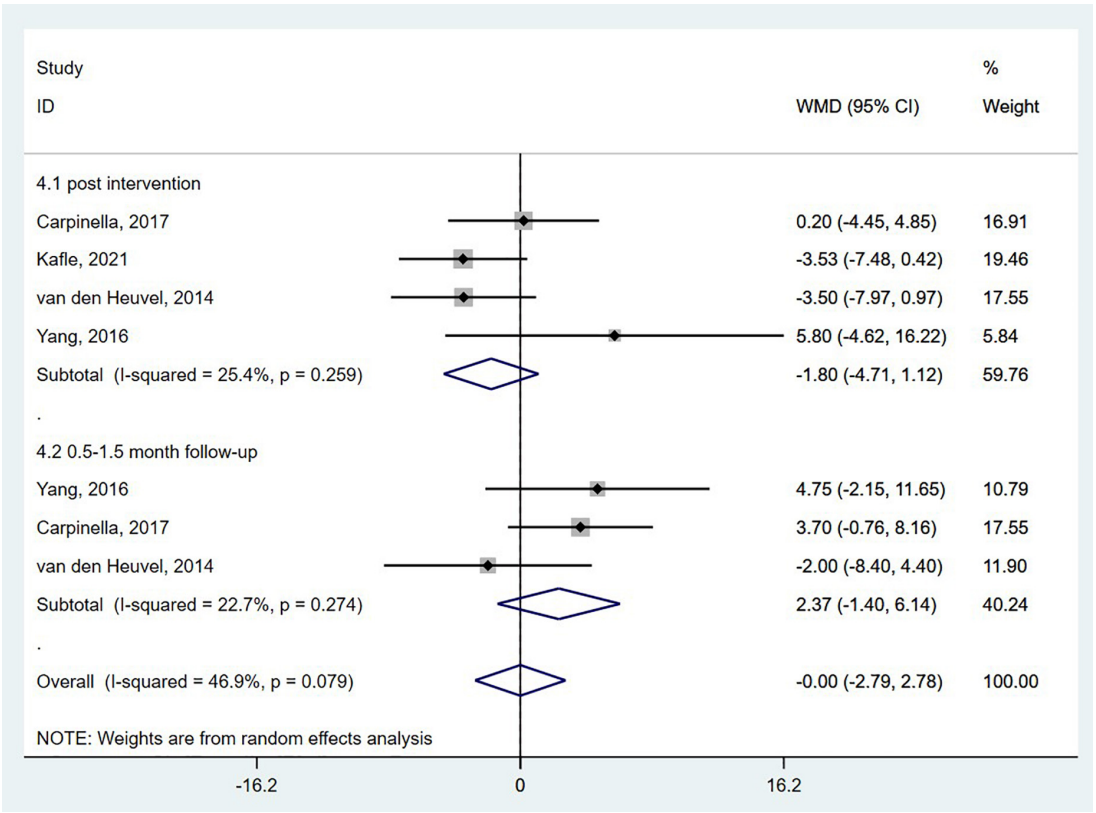


FIGURE 4 | Forest plot of pooled results for Unified Parkinson's Disease Rating Scale-III.

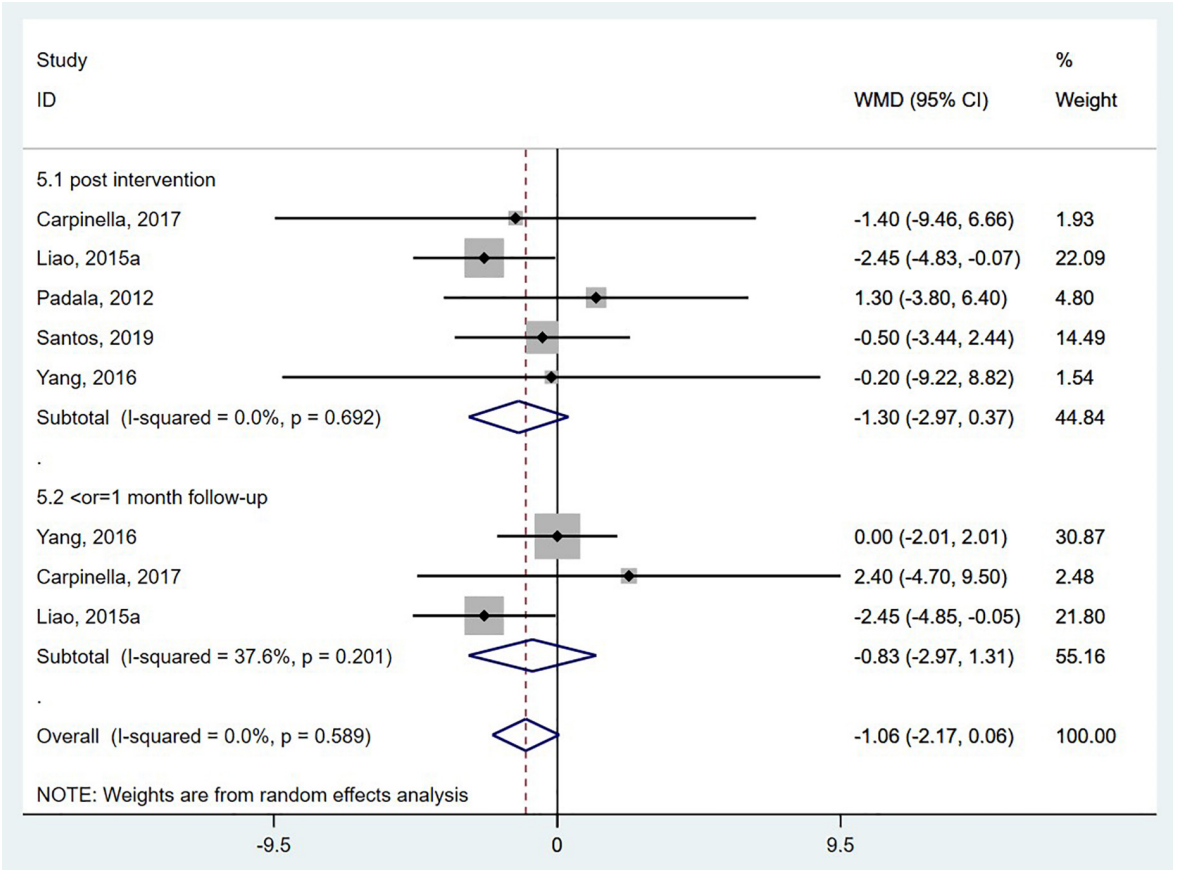


FIGURE 5 | Forest plot of pooled results for timed "Up and Go" test.

between the wearable sensor-based exercise group and the control group (WMD = 0.40; 95% CI, −4.73 to 5.53, $P = 0.879$; $I^2 = 0\%$, **Figure 9**).

Adverse Events and Acceptability

None of the included RCTs reported any adverse events, such as falling, during study duration. The dropout rate ranged from 0 to 23.5% (**Tables 2**, **3**). One study evaluated the satisfaction of the subject with the wearable sensors, found most of the participants were positive about the device, and considered this a beneficial, reliable, easy to use, comfort, and safe technology (Carpinella et al., 2017).

DISCUSSION

This systematic review explored the effect of wearable sensor-based exercise on improving postural control in patients with neurodegenerative diseases compared with traditional exercise. The results of the meta-analysis including 14 studies indicated that the wearable sensor-based exercise could induce a significant short-term effect on balance, especially for an increased visual gain in the SOT. However, the 3–12-week wearable sensor-based exercise did not seem to improve mobility ability, functional gait abilities, and fall-associated self-efficacy, as the changes did not reach statistical significance. Overall, the wearable sensor-based exercise increases balance in patients with neurodegenerative diseases, but the evidence is lacking to improve postural control during daily activities, such as walking.

The movement disorders associated with neurodegeneration may be explained by various perspectives, such as oxidative stress or mitochondrial dysfunction (Borsche et al., 2021; Dionísio et al., 2021). Due to the complexity of neurodegeneration with many potential intervention targets, the research progress of drug treatment is slow, and the current drug treatment mainly focuses on improving motor symptoms (Armstrong and Okun, 2020; Dar et al., 2020). In contrast, an exercise intervention is a more direct protocol to improve motor symptoms, and the benefits of intervention can also delay the speed of neurodegeneration and improve the quality of life (Bonavita, 2020; Sujkowski et al., 2022). However, traditional exercise interventions often require the involvement of specialists, such as rehabilitation physicians and physical therapists. The quality of the intervention often depends on the experience of the specialists and the patient's compliance (Botros et al., 2019; Schootemeijer et al., 2020). The involvement of sensor-based equipment brings new possibilities for an exercise intervention (Jahn et al., 2019). The instant biofeedback provided by sensors and the combination with exergame can form a standardized and interesting exercise protocol for patients with

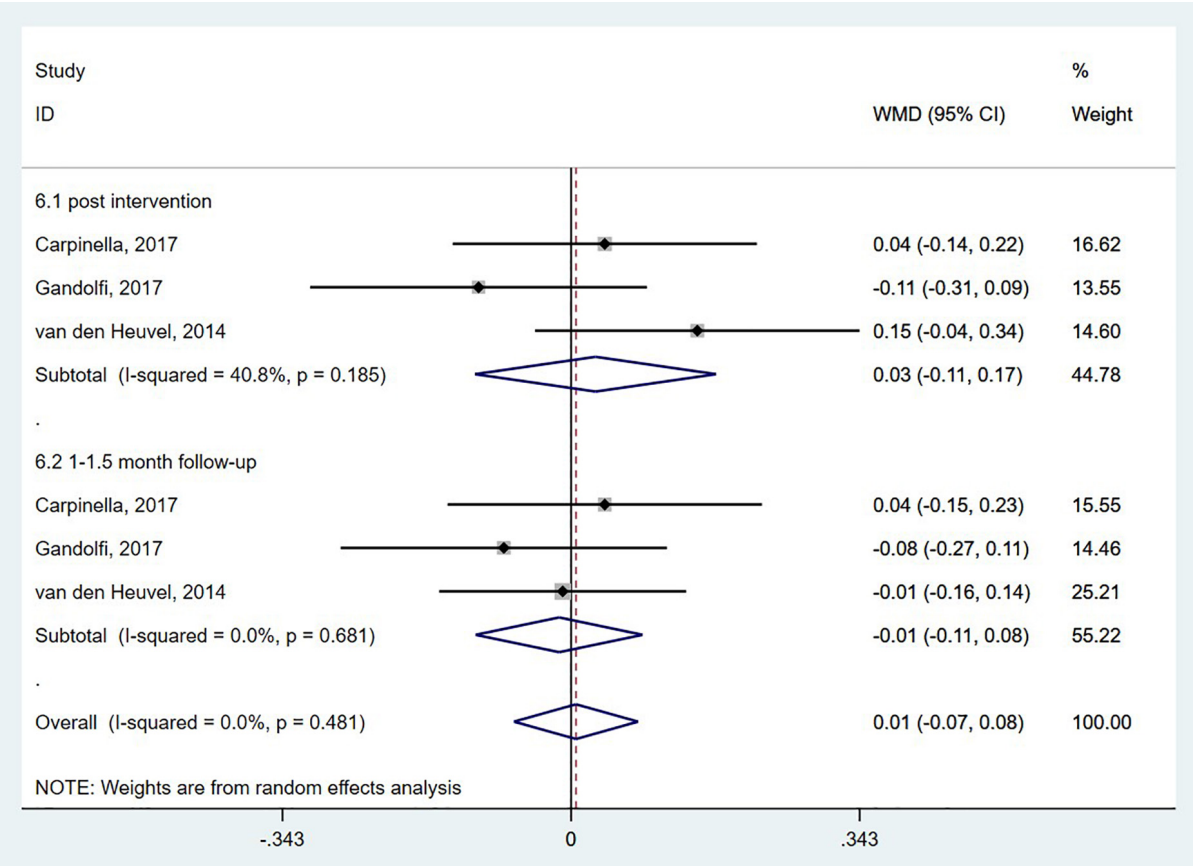


FIGURE 6 | Forest plot of pooled results for 10-meter walking test.

neurodegenerative movement disorders (Ribas et al., 2017; Ugur and Sertel, 2020; Kafle and Rizvi, 2021), such as avoiding obstacles or picking fruit.

The wearable sensors are directly attached to the patients to provide immediate and precise biofeedback on the patient's movements (Albán-Cadena et al., 2021). Optical sensors often require a bright environment, and reflective clothing will affect the accuracy of their motion capture (Warmerdam et al., 2020). Optical sensors also need a wide living room or hospital treatment room to maximize the exercise experience, which may prevent some patients from using optical sensors. Compared with the use of optical sensors, such as cameras, the application environment of wearable sensors is rarely limited. In addition, patients can be trained in a home environment under the remote guidance of professionals with the emergence of commercialized sensor devices (Garcia-Agundez et al., 2019; Milosevic et al., 2020). It can be used as a feasible solution for an exercise intervention under epidemic conditions.

Although the neurodegenerative disease is progressive and the gray matter volume changes in the left inferior parietal cortex, middle temporal gyrus and right anterior precuneus were associated with the balance capacities (Sehm et al., 2014), a significant improvement in balance was found in the wearable sensor-based exercise group at the end of the intervention, which may be due to the real-time feedback and wrong action corrections in the intensive body control training in the protocol. This systematic review showed that most movement modalities in the interventional group used a center of gravity shifting training method, requiring patients to complete the directional and quantitative shifting of the center of gravity (Liao et al., 2015a,b; Yang et al., 2016; Santos et al., 2019). The inertial sensor placed on the waist can directly reflect the change in the center of gravity, while the pressure sensor placed on the sole can indirectly reflect the change in the center of gravity through the offset of the plantar pressure, thereby providing accurate and immediate biofeedback for the patient (Padala et al., 2012; Pompeu et al., 2012; van den Heuvel et al., 2014; Liao et al., 2015a,b; Carpinella et al., 2017; Ribas et al., 2017).

Otherwise, two studies in this systematic review used the SOT and demonstrated a significantly increased score in visual domain, which might owe to the contribution of visual input significantly increased during the wearable sensor-based exercise, compared with the traditional exercises (Yen et al., 2011; Liao et al., 2015b). The increased visual gain in the SOT conditions also reflects the importance of visual input for the control of balance. As balance perturbations tend to occur in dynamic tasks and in response to environmental constraints not present during the SOT, the SOT may provide additional information for clinical

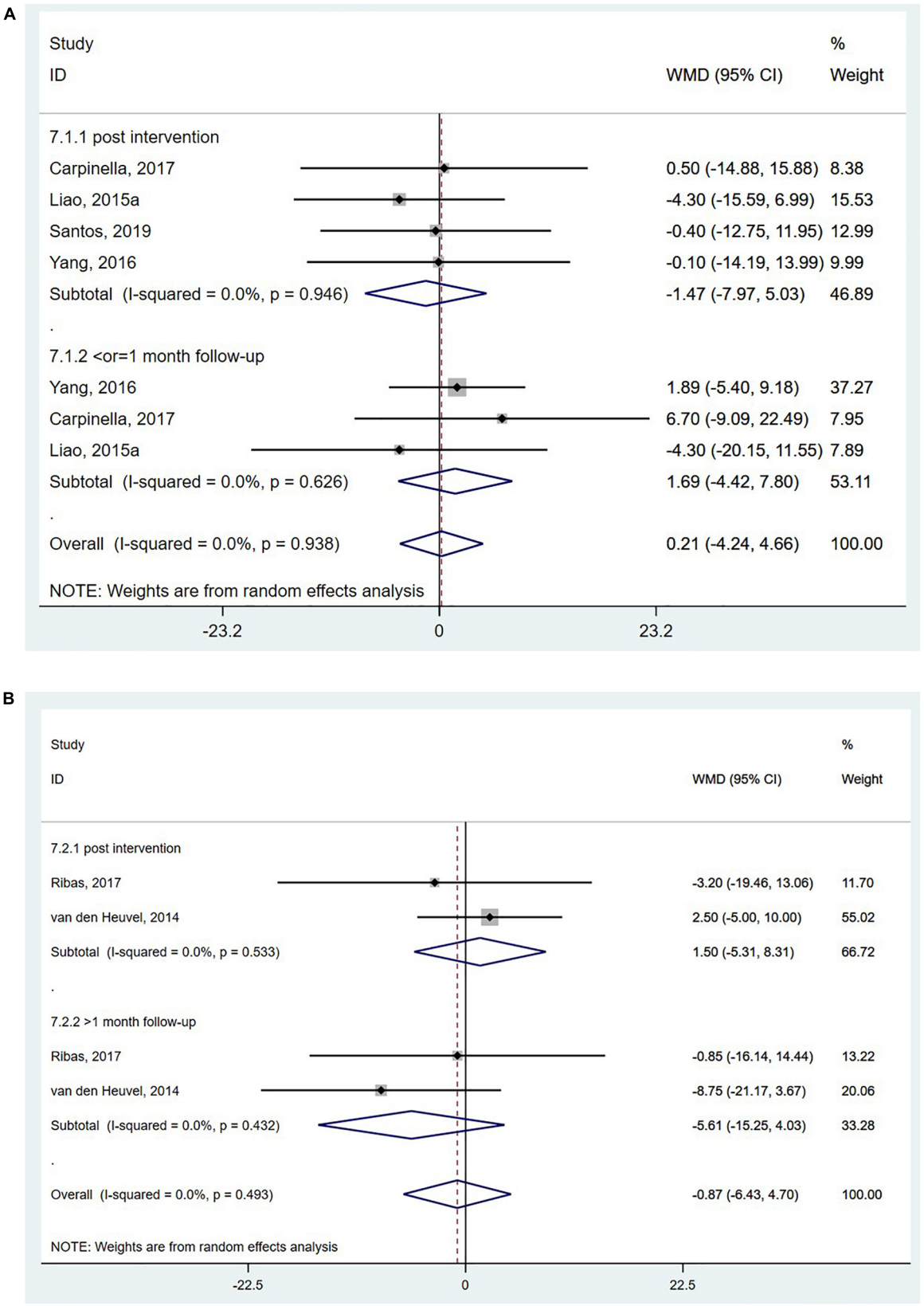


FIGURE 7 | Forest plot of pooled results for **(A)** the total score of 39-item Parkinson's disease questionnaire and **(B)** the mobility scores of the 39-item Parkinson's disease questionnaire.

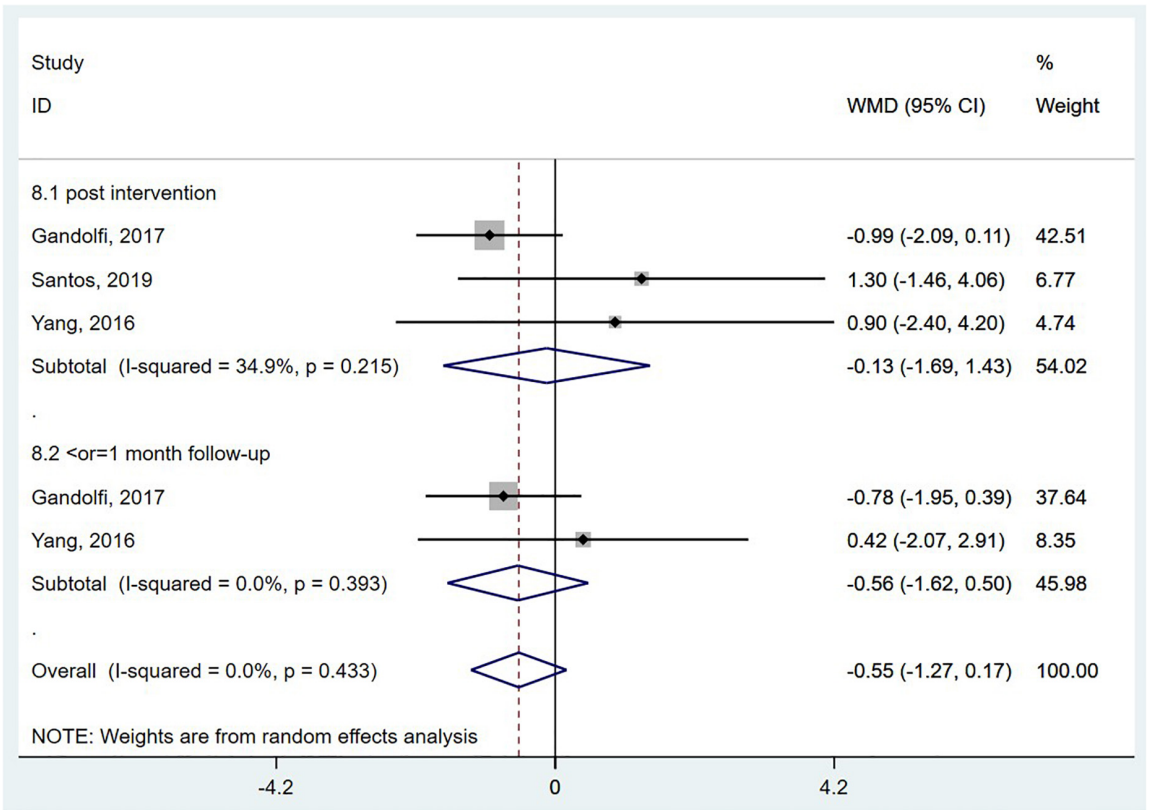


FIGURE 8 | Forest plot of pooled results for dynamic gait index.

evaluation on neurodegenerative disease and deficient sensory processing (Chien et al., 2014).

Previous meta-analysis and systematic reviews concluded promising short- and long-term benefits of exercise on various meaningful outcomes, such as balance, gait, muscle strength, motor, and functional performance (Tomlinson et al., 2012; Shen et al., 2016; Mak et al., 2017). However, compared with the traditional exercise programs, the results for the secondary outcomes showed no significance in the mobility ability, functional gait abilities, and fall-associated self-efficacy in the wearable sensor-based exercise group. Impaired flexibility and muscle weakness are two common problems that may affect postural control and mobility. As compared to neurologically normal adults, people with neurodegenerative disease had a reduced range of trunk motion, which could partially be explained by axial muscle rigidity (Schenkman et al., 2001), with a reduction in muscle strength by 30–50% (Inkster et al., 2003).

Furthermore, limited by the technical conditions of the sensor as a piece of external equipment, the training protocol in the included studies mainly consisted of the control tasks with a small range of body sway. There was a lack of activities of daily living training that simulate daily scenes, such as walking (Carpinella et al., 2017; Cikajlo and Potisk, 2019). In this meta-analysis, the intervention duration was 3–12 weeks, and the negative results may be associated with overall short treatment durations with a relatively low frequency (an average of 6–7 weeks with two–three times a week). These treatment durations would be considered short relative to multimodal physical therapy for Parkinson's disease (Tomlinson et al., 2012). On the other hand, although these measurements are the most frequently assessed in clinical practices, they might not have been sensitive enough to detect specific wearable sensor-based exercise training-related changes in dynamic postural control. Moreover, we did not find evidence that factors, such as control group (i.e., usual care vs. conventional training), sensor type, and type of training paradigm, were related to these negative findings, and the limited number of RCTs did not allow to draw definitive conclusions.

People with neurodegenerative diseases are nearly two times as likely to experience a fall as a healthy older person, often leading to debilitating effects on confidence, activity levels, and quality of life (Ashburn et al., 2019). A meta-analysis showed that performance confidence in overcoming barriers to exercise was best addressed with longer-term strategies that provided time for people to experience successfully conquering such barriers over a longer period (Higgins et al., 2014). With regard to the fall-associated self-efficacy in patients with neurodegenerative diseases, the results of our systematic review also showed that the 3–12-week wearable sensor-based exercise cannot improve fall-associated self-efficacy significantly, which might be due to the relatively short intervention duration. Moreover, people with neurodegenerative diseases may suffer from anxiety and depression, which could negatively impact

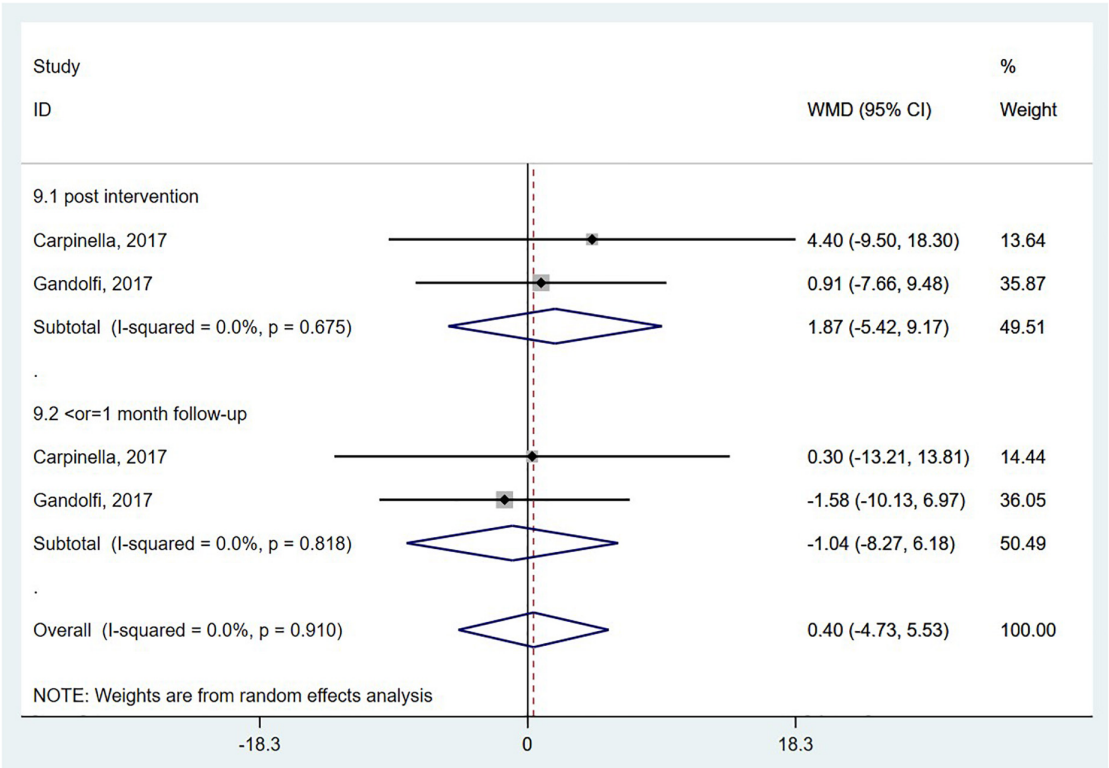


FIGURE 9 | Forest plot of pooled results for activities-specific balance confidence scale.

self-efficacy (Stevens et al., 2020), and also, the community and societal factors may account for an important proportion of the improvement in self-efficacy (Bellou et al., 2016; Lee et al., 2016; Rosa Silva et al., 2020). Multidisciplinary teams, such as exercise specialists, occupational therapists, and psychologists, should take cognitive and psychological symptoms into account when working with these patients to maximize the potential effectiveness of treatment, and social workers may be needed to help patients with neurodegenerative diseases reintegrate into the community and society (Stożek et al., 2016; Homayoun, 2018; Ritter and Bonsaksen, 2019). Future research is recommended to construct a comprehensive intervention system for fall-associated self-efficacy.

Strengths and Limitations

The strength of this meta-analysis is that only RCTs were included. Furthermore, to the best of our knowledge, this is the first meta-analysis to focus on postural control ability in patients with neurodegenerative diseases compared with traditional therapeutic exercise. However, several limitations need to be highlighted in this systematic review. First, as an indicator of postural stability, the BBS has been significantly improved, but whether the degree of postural stability improvement can lead to effective clinical improvement in movement disorders is unclear. Second, due to the insufficient number of included studies, no significant improvement was found in indicators related to social life functions, such as activities of daily living and quality of life. Finally, the quality of the evidence in this article ranged from moderate to very low (**Supplementary Table S2**). Therefore, caution should be applied, however, to avoid overestimation of findings given the several methodological weaknesses in available studies, such as short follow-up (<12 months), small sample size ($n < 100$), and missed evaluation of facilitator.

CONCLUSION

Compared with traditional exercise interventions, the wearable sensor-based exercise can significantly improve balance in patients with neurodegenerative diseases. However, there was still a lack of evidence showing the superiority of wearable sensor-based exercise technology for other indicators of dynamic postural control, such as motor symptoms, mobility ability, functional gait abilities, and fall-associated self-efficacy. In future, it is necessary to conduct more research on the effect of wearable sensor-based exercise on sensory organization and try to build a comprehensive rehabilitation treatment system to improve both postural control and quality of life.

DATA AVAILABILITY STATEMENT

All raw data included in this study are available upon request by contact with the corresponding author.

AUTHOR CONTRIBUTIONS

XL and QD had the original idea. XL, ZC, and MZ performed the literature search. QD and HG screened the studies using the eligibility criteria and undertook the data collection. XZ and JT assessed the risk of bias. XL, YY, and SG analyzed, interpreted, and discussed the results. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.934844/full#supplementary-material

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Effectiveness of aerobic and resistance training on the motor symptoms in Parkinson's disease: Systematic review and network meta-analysis

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Background/objectives: Aerobic and resistance training are common complementary therapies to improve motor symptoms in people with Parkinson's disease (PD), and there is still a lack of advice on which intensity and period of aerobic or resistance training is more appropriate for people with PD. Therefore, a network meta-analysis was conducted to assess the comparative efficacy of aerobic and resistance training of different intensities and cycles on motor symptoms in patients with Parkinson's disease.

Methods: Based on several biomedical databases, a search strategy system was conducted to retrieve randomized controlled trials (RCTs) without language restrictions. A network meta-analysis with a frequentist approach was conducted to estimate the efficacy and probability rankings of aerobic and resistance training on Parkinson's patients. What's more, a range of analyses and assessments, such as routine meta-analyses and risk of bias, were performed as well.

Results: Twenty trials with 719 patients evaluating 18 different therapies were identified. Through the Unified Parkinson's Disease Motor Rating Scale, (UPDRS III); 6-minute walk test, (6MWT); 10-meter walk test, (TWM); and time up and go (TUG) and Quality of Life Scale-39 (PDQ-39), to explore the effects of different intensity resistance and aerobic exercise on PD. As a result, short period high intensity resistance movement (standard mean difference (SMD) = −0.95, 95% confidence interval (CI) −1.68 to −0.22) had significantly decreased the Unified Parkinson's Disease Motor Rating Scale (UPDRS III). Short period high intensity resistance exercise showed similar superiority in other indices; also, aerobic and resistance training of different cycle intensities produced some efficacy in PD patients, both in direct and indirect comparisons.

Conclusion: For patients with moderate to mild Parkinson's symptoms, short periods high intensity resistance training may provide complementary therapy for PD, and aerobic or resistance training of varying intensity and periodicity may be recommended as exercise prescription for PD patients. However,

more large scale and high quality clinical trials are needed to confirm the effectiveness of this exercise therapy in the future.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42022324824.

KEYWORDS

Parkinson's disease, aerobic exercise, resistance exercise, intervention, network meta-analysis

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease whose prevalence is projected to double over the next 30 years and affect ∼611 million people worldwide (Dorsey et al., 2018; Armstrong and Okun, 2020; Bloem et al., 2021; Tolosa et al., 2021). The histopathology of PD is typically a loss of dopaminergic neurons in the substantia Nigra, and the cardinal features of PD include resting tremor, rigidity, and bradykinesia. Apart from the above symptoms, people with PD also suffer from various non-motor features such as sleep disorders, psychiatric symptoms, and cognitive dysfunction (Armstrong and Okun, 2020). Currently, no therapy can slow down or arrest the progression of PD (Bloem et al., 2021). Meanwhile, the number of patients with PD has more than doubled in the past generation due to an increase in the elderly population (2018), As a consequence, PD poses a significant challenge for the global health systems that must be resolved.

With no known cure for PD, Levodopa remains the most effective first-line treatment for motor symptoms in PD (Elkouzi et al., 2019; Armstrong and Okun, 2020; Koszła et al., 2021). Despite the effectiveness of pharmacotherapy, serious deficiencies in the long-term treatment, namely, the induction of dyskinesia and drug fade, cannot be ignored (Duncker and Bache, 2008). To avoid the negative effects of levodopa, exercise therapy, as a low-cost and universally available aid, is adopted in the current PD treatment. There is growing evidence that exercise therapy is beneficial as a complementary therapy to improve motor and non-motor symptoms such as slow movement, decreased muscle strength and reduced quality of life in PD patients when mainline medications fail to respond appropriately to the motor symptoms of PD (Speelman et al., 2011; Mak et al., 2017; Mak and Wong-Yu, 2019). Among all the common types of exercise, aerobic and strength training, recommended by the World Health Organization (WTO), play a crucial role in improving exercise performance and slowing the progression of PD (World Health Organization, 2010; Speelman et al., 2011; Carvalho et al., 2015; Mak et al., 2017; Mak and Wong-Yu, 2019). It is worth mentioning that in recent years, different evidence has emphasized the therapeutic potential of aerobic and resistance exercise for PD (Dutra et al., 2012; Churchill et al., 2017; Gamborg et al., 2022). In a major review, Petzinger et al. (2013) concluded that Aerobic exercise, regarded as important for improvement of blood flow and facilitation of neuroplasticity in elderly people, might also have a role in improvement of behavioral function in individuals with PD. In a recent systematic review of five randomized controlled trials (RCT), resistance exercise was found to have a positive effect on muscle strength, mobility, endurance and performance in functional tasks (Dibble et al., 2006, 2009b; Morris et al., 2017; de Lima et al., 2019). Furthermore, some studies have shown that resistance training can improve strength, balance and improve the quality of life of people affected by PD (Dibble et al., 2009b).

However, other research presented different results in terms of the positive effects of resistance training. In a meta-analysis including six studies and conducted by Saltychev et al. (2016). It was found that resistance training was not superior to other treatment modalities for PD. In another research, Morris et al. (2017) performed a 6-week home resistance exercise program and concluded that it did not improve falls in 133 community-dwelling PD patients. In addition to the controversial results of resistance training studies, previous reviews of meta analyses of aerobic or resistance training for PD did not classify exercise dose (e.g., exercise intensity, exercise cycle, exercise type, etc.) (Chung et al., 2016; Lavin et al., 2020), which is necessary for exercise prescription in practice. No meta-analysis has compared any types of aerobic exercise, resistance exercise, or a combination of both. With the above deficiencies in resistance training research, thus, we attempted to re-evaluate the effect of aerobic exercise and resistance training on PD through a net-work meta-analysis. By means of dividing the exercise intensity and the exercise period by the proposed ACSM (Riebe et al., 2015). we further compared the effects of different intensity and periods of aerobic and resistance training on motor symptoms in Parkinson's patients in the hope of providing a low cost and useful exercise program for PD.

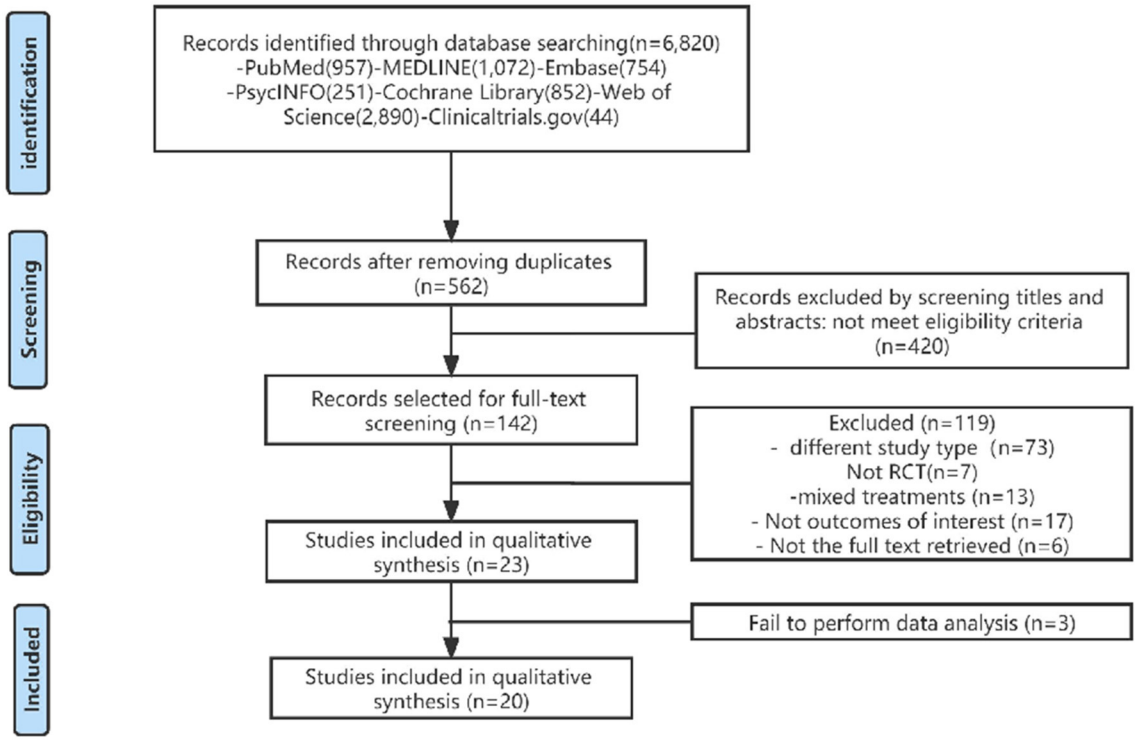


FIGURE 1
Flow chart illustrating the different phases of the search and study selection.

Materials and methods

Study registration

The systematic review protocol was developed on the strength/ basis of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-NMA) statement (Moher et al., 2015) registered in the PROSPERO database. This systematic review was registered in advance in the PROSPERO register of systematic reviews (ref: CRD42022324824). Since all the analyses were based on previously published research, there was no need for ethical approval or patient permission.

Search strategy and study selection

The following electronic databases were searched from their inception to April 2022: PubMed, EMBASE, PsycINFO, Cochrane Library, ClinicalTrials.gov, and Web of Science without language restrictions. Targeted at studies published between the start of the project and the date of the search, the retrieval was rerun shortly before the final analysis, with additional studies retrieved for inclusion (Briscoe, 2018; Cooper et al., 2018). We adopted a Boolean search strategy with the operators AND, OR, and NO as well as terms describing or relating to intervention, participants, and study design. The Medical Subject Headings (MeSH) combined with text terms followed by Boolean logical operators were used as an exhaustive search using "Parkinson's disease," "exercise," "resistance training," "aerobic exercise," "bodyweight support treadmill," "high speed resistance training," "Nordic Walking," "power training," "treadmill training," "walking," "Randomized controlled trials" and other relevant conceptual keywords. We used various combinations of medical subject headings and free terms, such as Parkinson's disease and aerobic and resistance exercise. A flowchart describing the literature selection is presented in Figure 1. In addition, reference lists were hand searched to identify further relevant articles (Supplementary material 1).

All search results were exported into EndNote and duplicates were removed. Titles and abstracts from the initial literature search were independently assessed by two reviewers (ZX and WJL). Full texts for articles were deemed eligible for inclusion from the title and abstract search by either reviewer; in addition, when opinions differed in an article in the initial screen, it would be screened independently a second time by two researchers (GXH and WRR).

TABLE 1 Selection criteria.

Category	Inclusion criteria	Exclusion criteria
Population	Aged 20–85 years;diagnosed with Idiopathic Parkinson's (IPD) and Hoehn and Yahr scale (H&Y).	Other specific diseases
Intervention	Aerobic exercise; Treadmill training; Nordic Walking and Multi component exercise program (Aerobic exercise combined with resistance exercise or multiple aerobic exercises). Resistance exercise: Power training; Strength Training; Weight Lifting Exercise Program; Multi component exercise program (Aerobic exercise combined with resistance exercise or multiple resistance exercises).	Taichi, Qigong and other physical and mental exercises; dance training; stretching, balance; flexibility training; multimodal training.
Comparator	There is only a passive control (i.e., without any regular training) that allows for normal drug taking.	Other types of active exercises (tai chi, qigong and other mind-body exercises mentioned above; dance training; balance training; flexibility training; multimodal training, etc.)
Outcome	Unified Parkinson's Disease Motor Rating Scale, UPDRS III; walking ability was evaluated by a 6-minute walk test, 6MWT; 10-meter walk test, TWM; and time up and go, TUG. Parkinson's Disease Quality of Life Scale-39 (PDQ-39)	Strength training indicators: muscle strength, muscle hypertrophy, etc.; neurological test-related indicators, etc.
Study design	Randomized controlled trials	Quasi RCTs, animal trials, clinical protocols, meeting abstracts, case reports, and systematic reviews.

Inclusion and exclusion criteria

Based on the defined inclusion and exclusion criteria (Table 1): (1) All studies were randomized controlled trials (RCTs). (2) The population of the included studies was adult patients diagnosed with PD and Hoehn and Yahr scale (H&Y): 1-3. (3) Interventions included at least one of the following exercises: Aerobic exercise; Treadmill training; Nordic Walking and Multicomponent exercise program; Resistance exercise: Power training; Strength Training; Weight Lifting Exercise Program. The control group received Usual care. (4) Outcomes: (1) Motor outcomes: Motor ability was evaluated by the Unified Parkinson's Disease Motor Rating Scale, UPDRS III; walking ability was evaluated by a 6-minute walk test, 6MWT; 10-meter walk test, TWM; and time up and go, TUG. (2) Non-motor outcomes: quality of life was evaluated by the Parkinson's Disease Quality of Life Scale-39 (PDQ-39); studies were excluded if insufficient data or in-formation about the assessment was provided. We also excluded quasi-RCTs, animal trials, clinical protocols, meeting abstracts, case reports, and systematic reviews.

Outcome measurement

Extracted from the final inclusion list of articles separately by two reviewers the data was then included into a standardized data extraction spreadsheet in Excel. At this stage, two authors extracted information on (1) relevant data regarding participant characteristics (e.g., the sample size, age, and sex); (2) the training pattern; (3) the training variables (e.g., duration, repetitions, and intensity); (4) years of diagnosis; (5) Hoehn and Yahr scale (H&Y); (6) the main result of the study. In case of incomplete raw data availability, we contacted the corresponding author of the manuscript, and studies whose authors could not be reached were left out. Our primary outcome of interest was assessed by the Unified Parkinson's Disease Motor Rating Scale, UPDRS III; other outcomes included a 6-minute walk test (6MWT), 10-meter walk test (TWM), time up and go (TUG) and Parkinson's Disease Quality of Life Scale-39 (PDQ-39).

Coding of studies

We coded RT according to the following training parameters: training period, training intensity. According to the recommendations of American College of Sports Medicine's (ACSM) (American College of Sports Medicine Position Stand, 1998; Riebe et al., 2015). We further divided aerobic exercise and resistance exercise according to the intensity of exercise and training period. For aerobic exercise, exercises with 30–40% heart rate reserve (HRR); 37–45% maximal oxygen consumption (VO_{2max}); 57–63%%Maximal heart rate (HR_{max}); 9–11 rate of perceived exertion (RPE) or 2–3 metabolic equivalent (MET) were defined as low intensity aerobic exercise. Exercises with 40–59%HRR; 46–63%VO_{2max}; 64–75%HR_{max}; RPE 12–13 or MET 3–6 were defined as moderate intensity aerobic exercise. Exercises with 60–90% HRR; 64–91% VO_{2max}; 76–95% HR_{max}; RPE 14–17 or MET 6–8.8 were defined as high intensity aerobic exercise.

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TABLE 2 The movement characteristics and classification principles.

Type / Period	Low intensity aerobic exercise (30–40% HRR; 37%-45% VO_{2max}; 57–63% % HR_{max}; 9–11 RPE; 2–3 MET)	Moderate intensity aerobic exercise (40–59%HRR; 46–63%VO_{2max}; 64–75%HRmax; RPE 12–13 or MET 3–6)	High intensity aerobic exercise (60–90% HRR; 64–91% VO_{2max}; 76–95% HRmax; RPE 14–17 or MET 6–8.8)	Low intensity resistance training (<50% 1RM or 8–12 repetitions exercise)	Moderate intensity resistance training (50–69% 1RM or 10–15 repetitions)	High intensity resistance training (>70% 1RM or 15–20 repetitions)
Short period exercises (<6 weeks)	Short period low intensity aerobic exercise	Short period moderate intensity aerobic exercise	Short period high intensity aerobic exercise	Short period low intensity resistance training	Short period moderate intensity resistance training	Short period high intensity resistance training
Moderate period exercises (6–12 weeks)	Moderate period low intensity aerobic exercise	Moderate period moderate intensity aerobic exercise	Moderate period high intensity aerobic exercise	Moderate period low intensity resistance training	Moderate period moderate intensity resistance training	Moderate period high intensity resistance training
Long period exercises (> 12 weeks)	Long period low intensity aerobic exercise	Long period moderate intensity aerobic exercise	Long period high intensity aerobic exercise	Long period low intensity resistance training	Long period moderate intensity resistance training	Long period high intensity resistance training

HRR, heart rate reserve; VO_{2max}, maximal oxygen consumption; HR_{max}, 57–63% Maximal heart rate; RPE, rate of perceived exertion; MET, metabolic equivalent; 1RM, one-repetition maximum.

For resistance training, exercises with <50% one-repetition maximum (1RM) or 8–12 repetitions exercise is defined as low intensity resistance training. 50–69% 1RM or 10–15 repetitions exercise is defined as moderate intensity resistance training. >70% 1RM or 15–20 repetitions exercise is defined as high intensity resistance training. If a study reported exercise progression over the training period, the mean number of training intensity was computed. The definition of the exercise period in the previous literature is Lacking, and based on clinical experience. Exercises with a training period greater than 12 weeks are defined as long period exercises, those with a training period of 6–12 weeks are defined as medium period exercises, and those with a training period of less than 6 weeks are defined as short period exercises.

Therefore, we coded exercise according to the following training parameters: there are the following 18 types of exercise, respectively: short period low intensity aerobic exercise (SP-LI-AE), short peri-od moderate intensity aerobic exercise (SP-MI-AE), short period high intensity aerobic exercise (SP-HI-AE), short period low intensity resistance training (SP-LI-RT), short period moderate intensity resistance training (SP-MI-RT), short period high intensity resistance training (SP-HI-RT), moderate period low intensity aerobic exercise (MP-LI-AE), moderate period moderate intensity aerobic exercise (MP-MI-AE), moderate period high intensity aerobic exercise (MP-HI-AE), moderate period low intensity resistance training (MP-LI-RT), moderate period moderate intensity resistance training (MP-MI-RT), moderate period high intensity resistance training (MP-HI-RT), long period low intensity aerobic exercise (LP-LI-AE), long period moderate intensity aerobic exercise (LP-MI-AE), long period high intensity aerobic exercise (LP-HI-AE), long period low intensity resistance training (LP-LI-RT), long period moderate intensity resistance training (LP-MI-RT), long period high intensity resistance training (LP-HI-RT) (Table 2).

Risk of bias (quality) assessment

We assessed and classified each individual's risk of bias (ROB). Studies were first selected according to the Cochrane Risk of Bias tool (Tarsilla, 2010) and then classified according to priority criteria Seven. ROB domains were evaluated independently. Two authors categorized all the eligible studies as high, low, or indifferent uncertain bias risk, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The evaluation of ROB was carried out in Review Manager (Version 5.3). In the selective outcome data, we accounted for a broader assessment considering also the selective non reporting ROB due to the missing results in index meta analyses (e.g., missing or unavailable outcome results crosschecked from method plans) according to published criteria by Page et al. For

TABLE 3 The specific movement characteristics and classification principles.

Publication	Inclusion criteria	N (E/C)	Mean age ± SD ALL	Intervention (E/C)	Intensity (E/C)	Exercise intensity and period categories	Frequency (days/wk/month)	Main outcome assessments			Pharmacological treatments
Ferreira et al. (2018)	Hoehn-Yahr 1–3	35 (18/17)	65.9 ± 7.95	Resistance training	IN: 8–12 repetitions	Long period high intensity resistance training)	2/wk/6M	UPDRS	PDQ-39		"on" state of medication
				Usual care	Usual care						Customary medication
Vieira de Moraes Filho et al. (2020)	Hoehn-Yahr 1–3	40 (25/15)	64.6 ± 5.5	Resistance training	IN: 2 sets of 10–12 repetitions until fatigue	Short period high intensity resistance exercise	2/9 wk	TMW	TUG	UPDRS-III	NA
				Disease lectures	Usual care						NA
Santos et al. (2017)	Hoehn-Yahr 1–2	28 (13/15)	73.6 ± 15.86	PRE training	IN: 1 set of 15–20 repetitions at 40–50% of 1RM/1–2 W 2 sets of 7–10 repetitions at 70–75% 1RM/3–6 W 2 sets of 4–7 repetitions at 80-85% of the 1RM/7–8 W	Short period high intensity resistance exercise	2/8 wk	MDS-UPDRS	PDQ-39	TMM	"on" state of medication
				Usual care	Usual care						Customary medication
Schenkman et al. (2018)	Hoehn-Yahr 1–2	128 (43/45/40)	63.7 ± 9.67	Intensity treadmill exercise	IN: 80–85% MHR	Long period high intensity aerobic exercise	4/26 wk	UPDRS	MDS-UPDRS		"on" state of medication
				Moderate intensity treadmill exercise	IN: 60–65% MHR	Long period moderate intensity aerobic exercise					"on" state of medication
				Usual care	Usual care						Customary medication
Ni et al. (2016)	Hoehn-Yahr 1–3	26 (14/10)	73.3 ± 7.45	power resistance training	IN: 3 circuits of 10–12 repetitions	Long period high intensity aerobic exercise	2/12 wk	PDQ-39			"on" state of medication
				Normal group	Usual care						Customary medication
Dibble et al. (2009b)	Hoehn-Yahr 2–3	20 (10/10)	65.7 ± 9.9	Eccentric training	IN: high-force Weight was increased as tolerated	Long period high intensity resistance exercise	3/12 wk	6 MW	UPDRS-III		1–1.5 h after taking their PD medications
				Standard exercises	Usual care						1–1.5 h after taking their PD medications

(Continued)

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TABLE 3 Continued

Publication	Inclusion criteria	N (E/C)	Mean age ± SD ALL	Intervention (E/C)	Intensity (E/C)	Exercise intensity and period categories	Frequency (days/wk/month)	Main outcome assessments			Pharmacological treatments
Dibble et al. (2006)	Hoehn-Yahr 2–3	20 (10/10)	65.7 ± 9.9	Eccentric training	IN: high-force Weight was increased as tolerated	Long period high intensity resistance exercise	3/12 wk	6 MW			1–1.5 h after taking their PD medications
				Standard exercises	Usual care						1–1.5 h after taking their PD medications
Demonceau et al. (2017)	Hoehn-Yahr 1–3	52(20/17/15)	66 ± 9	Aerobic training	IN: High intensity cycling at 70% to 80% 30 s to three min of high intensity cycling at 70% to 80% of PWL	Long period high intensity resistance exercise		TUG	PDQ-39		NA
				Strength training	IN:10–15 repetitions at 50–60% /1RM/1–6W; 5-8 repetitions at 80–90% of the 1RM/7–12 W	Long period high intensity aerobic exercise	2–3/12 wk				NA
				Care, control group,	Usual care						Customary medication
Frazzitta et al. (2014)	Hoehn-Yahr 1–1.5	25 (15/10)	NR	Aerobic training	IN: MHR ≤60% and a maximum speed of treadmill scrolling of 3.5 km/h. 30 min/20 sessions	Short period low intensity aerobic exercise	20/4 wk	UPDRS-III	6 MWT		NA
				Normal group	Usual care						Customary medication
Canning et al. (2012)	Hoehn-Yahr 1-2	20 (10/10)	61.8 ± 7.9	Home-based treadmill training	IN:60% of the average speed	Short period moderate intensity aerobic exercise	4/6 wk	6 MWT	PDQ-39	TMW	"on" state of medication
				Usual care	Usual care						Customary medication
Shulman et al. (2013)	Hoehn-Yahr 1–3	67 (23/22/22)	65.7 ± 10.83	Higher-Intensity Treadmill Training	IN: 70–80% of HRR (30 min)	Long period high intensity aerobic exercise	3/12 wk	6 MW	TMW	UPDRS -III	"on" or within 3 h of medication
				Lower-Intensity Treadmill Training	IN:15 min 0% incline (start) increased 5 min every 2 weeks at 40–50% of MHR (50 min)	Long period low intensity aerobic exercise					"on" or within 3 h of medication
				Stretching	IN: Weight was increased as tolerated						"on" or within 3 h of medication

(Continued)

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TABLE 3 Continued

Publication	Inclusion criteria	N (E/C)	Mean age ± SD ALL	Intervention (E/C)	Intensity (E/C)	Exercise intensity and period categories	Frequency (days/wk/month)	Main outcome assessments		Pharmacological treatments
Paul et al. (2014)	IPD	40 (20/20)	NR	Power training	IN: 60% of the one repetition maximum.	Long period medium strength resistance exercise	2/12 wk	TUG		NA
				Usual care	Usual care					NA
Cugusi et al. (2015)	Hoehn-Yahr 1–3	20 (10/10)	67.4 ± 8	Nordic walking	IN: 60–80% HRR	Long period high intensity aerobic exercise	2/12 wk	UPDRS-III	6 MWT	Customary medication
				Usual care	Usual care					Customary medication
Fisher et al. (2008)	Hoehn-Yahr 1–2	30 (10/10/10)	62.3 ± 10.65	High-intensity group	IN: 3.0 METS and/or 75% of an AAMHR	Short period high intensity aerobic exercise	3/8 wk	UPDRS-III		Customary medication
				Low-intensity group	IN: 3.0 or fewer METS/50%HRR or less of their AAMHR for 45 min	Short period low intensity resistance exercise				Customary medication
				Zero-intensity group.	Usual care					Customary medication
Kurtais et al. (2008)	Hoehn-Yahr 1–3	24 (12/12)	64.8 ± 7.95	Training program on a treadmill	IN: 70–80% MHH either speed or inclination was gradually increased over time.	Short period high intensity aerobic exercise	3/6 wk	TUG		"on" state of medication
				No intervention	Usual care					Customary medication
Qutubuddin et al. (2013)	UPDRS-III >30	23 (13/10)	NR	Cycling program	IN: 61–80% of the individual's aerobic maximum.Weight was increased as tolerated	Short period high intensity aerobic exercise	2/8 wk	UPDRS-III	PDQ-39	"on" state (within 3 h)
				No intervention	Usual care					Customary medication
Schilling et al. (2010)	Hoehn-Yahr 1–2.5	15 (8/7)	59.2 ± 7.85	Hammer Strength	IN: Two sets for 8 repetitions, and the final set between 5 and 8 repetitions.	Short period high intensity resistance exercise	2/8 wk	6 MWT		"on" state of medication
				Standard care	Usual care					"on" state of medication

(Continued)

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TABLE 3 Continued

Publication	Inclusion criteria	N (E/C)	Mean age ± SD ALL	Intervention (E/C)	Intensity (E/C)	Exercise intensity and period categories	Frequency (days/wk/month)	Main outcome assessments			Pharmacological treatments
Dibble et al. (2015)	IPD	41(20/21)	68.4 ± 11.95	Resistance Exercise	IN: RPE was 13	Long period high intensity resistance exercise	12 wk	UPDRS-III	TUG	6 MWT	"on" medication state (1–1.5 h after medication intake).
				Standard care	Usual care						Customary medication
van der Kolk et al. (2018)	Hoehn-Yahr 1–2	37 (15/22)	NR	Aerobic exercise	IN: virtual reality software within their prescribed heart rate zone.	Long period low intensity aerobic exercise	3/6 M	UPDRS III	TWM	PDQ-39	OFF state
				No intervention	Usual care						OFF state
Carvalho et al. (2015)	Hoehn-Yahr 1–3	22 (5/8/9)	64.4 ± 11.7	Aerobic training	IN: 60% of the maximum VO_{2max} or 70% MHR	Long period high intensity aerobic exercise	2/12 wk	UPDRS III			NA
				Strength training	IN: 8–12 1RM	Long period high intensity resistance exercise					NA
				Physiotherapy	Usual care						NA

N, number of participants; E, experimental group; C, control group; WK, week; M, month; NA, not applicable; IN, intensity; 1RM, of 1 repetition maximum; MHR, Maximal Heart Rate; VO_{2max}, maximal oxygen consumption; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ39, Parkinson's Disease Questionnaire 39; TUG, Timed Up and Go; TMW, 10-meter walk test; MDS-UPDRS, MDS-Unified Parkinson's Disease Rating Scale;6WMT, 6-min walk test.

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each study, the items were scored as high, low or unclear (not enough information reported) ROB. Two reviewers scored the studies according to the proposed scale. In case of disagreements on the scores, a consensus was adopted; if necessary, a third reviewer evaluated the article (WRR).

Data synthesis and analysis

The network meta-analysis has a categorical advantage over traditional meta-analysis due to its ability to summarize comparisons between multifarious treatments concurrently, which allows greater flexibility to use complex models and produces relatively scientific interpretation in terms of causal relationships (Stroup et al., 2000). Based on the random effect statistical model, the prior minimally informative distributions were implemented to compare 18 exercise therapies simultaneously by forming a connected network integrating direct and indirect evidence. We first carried out a conventional pairwise meta-analysis in comparisons available for each contrast. In terms of statistical heterogeneity, I^2 statistic whose values were 25%, 50%, and 75% indicated mild, moderate, and high heterogeneity, respectively, and was provided to measure whether there was a substantial heterogeneity generation (Melsen et al., 2014). A comparison adjusted funnel plot was drawn for detecting the presence of any dominant types of bias, such as publication bias, selective reporting, and the like.

A network plot was generated as a simple/ brief summary description for revealing all the available evidence of each treatment evidence. The above analyses were conducted in STATA, version 16.0 (Stata, Corp, College Station, TX). As the presence of effect sizes refers to the continuous outcome, standard mean differences (SMDs) were calculated for each comparison using group (relevant) means and standard deviations (SDs) from individual studies (Hirschtritt et al., 2017). The flowing 95% Confidence Interval (CI) and pooled SMDs were calculated as a measurement of estimated uncertainty and pooled effect sizes, respectively. If the data we were to extract for our analysis (such as mean, SD, or sample size) were not provided in the included literature, we would present them in another form by calculating other available values such as standard errors, confidence intervals, or other statistical indices as described elsewhere which may clarify SD accordingly (Egger et al., 2003).

Network transitivity is the most important assumption underlying NMA, whose assessment would directly affect our further analysis (Salanti, 2012). Therefore, to ensure the similarity of various treatment comparisons so as to provide valid indirect inferences, we apprised the transitivity assumption by comparing the clinical and methodological characteristics such as patients and experimental designs in all the included studies (Tarsilla, 2010). As an estimated probability used for ranking the different exercise types of intervention, the surface under the cumulative ranking curve (SUCRA) was presented as a simple numerical statistic cumulative ranking probability

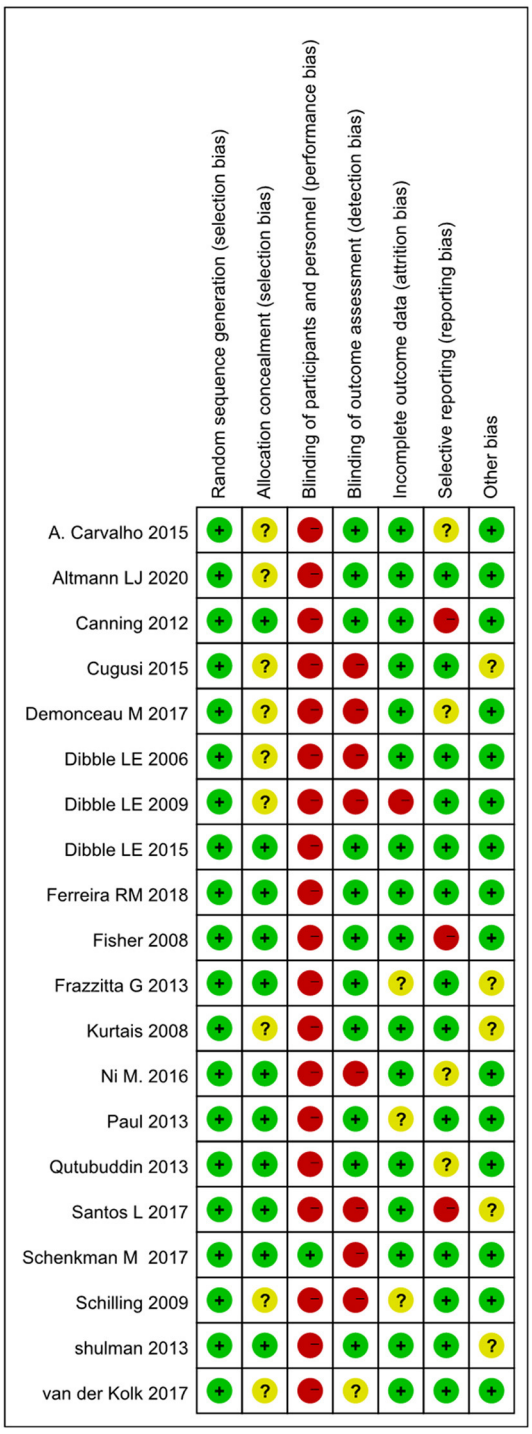


FIGURE 2
Combined percentage risk of bias in each risk domain for all included trials.

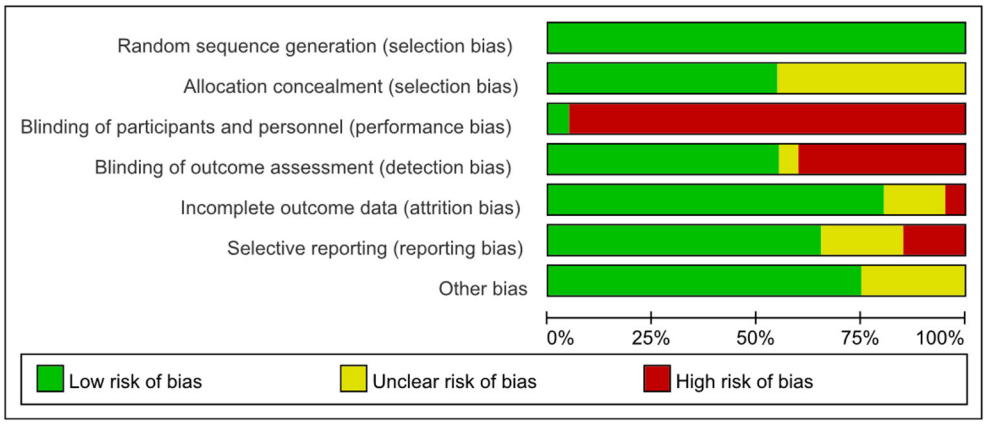


FIGURE 3
Risk of bias summaries for all exercise trials.

plot summarized for each treatment. SUCRA with a higher value denotes a greater likelihood of a given treatment being in the top rank or highly effective, while zero indicates that the treatment is definitely the worst (Page et al., 2016). To make sure whether a potential source inconsistency will be generated in our network or not, we used the "node-splitting" technique (van Valkenhoef et al., 2016), by comparing the direct evidence to the indirect from the entire network (with a *p*-value higher than 0.05 indicating a consistency generation) (Stang, 2010). The above analyses were per-formed using the "network "and "meta" packages (version 0.8-2) in R language (X64 3.32 version).

Results

Study selection

All included trials were published between 2006 and 2022, 20 eligible RCTs with 811 patients diagnosed with PD were included in this network meta-analysis (Dibble et al., 2006, 2009b, 2015; Fisher et al., 2008; Kurtais et al., 2008; Schilling et al., 2010; Canning et al., 2012; Qutubuddin et al., 2013; Shulman et al., 2013; Frazzitta et al., 2014; Paul et al., 2014; Carvalho et al., 2015; Cugusi et al., 2015; Ni et al., 2016; Demonceau et al., 2017; Santos et al., 2017; Ferreira et al., 2018; Schenkman et al., 2018; van der Kolk et al., 2018; Vieira de Moraes Filho et al., 2020) (Supplementary material 2). Four hundred and sixteen participants (49%) were in the control group, and 395 (51%) in the exercise group, most of whom' were diagnosed with mild-moderate PD (Hoehn and Yahr scale I–III), two studies described as IPD (Paul et al., 2014; Dibble et al., 2015). In terms of medication taking, five studies did not mention their medication use (Frazzitta et al., 2014; Paul et al., 2014; Carvalho et al., 2015; Demonceau et al., 2017; Vieira de Moraes Filho et al., 2020), one study (van der Kolk et al., 2018) was tested in the "OFF" phase and the rest of the studies were assessed and tested in the "ON" phase of the patients, the specific literature screening results characteristics of the different types of studies are shown in Table 3.

Quality assessments of the selected literature

The individual and overall study level quality were presented in Figures 2, 3. All the 20 included trials reported adequate random sequence generation. Eleven RCTs described their approach of allocation concealment. Because the included articles are based on human research, it is difficult to apply blinding to the participants. One RCTs with low bias concerned blinding of performance bias, 11 RCTs with low bias with detection bias. Three RCTs with a high risk of allover bias originated from reporting bias and other bias, respectively.

Results of direct meta-analysis

We performed a direct meta-analysis to investigate the efficacy of aerobic and resistance training of different intensity and period in PD. 14 direct studies were included in UPDRS III, 5 direct studies in TUG, 5 direct studies in 6MWT, 8 direct studies in TWM; and 5 direct studies in PDQ-39; as shown in Table 4. Based on strong heterogeneity ($p > 0.05$ or $I^2 \leq 50\%$), fixed-effects models were selected to estimate the combined results of different comparisons for the following indicators: UPDRS III indicators: long period high intensity aerobic exercise vs. control, long period high intensity resistance training vs. control, short period high intensity aerobic exercise vs. control. TWM indicators: long period high intensity aerobic exercise vs. control, long period low intensity aerobic exercise

TABLE 4 Results of Direct meta-analysis.

Variable	Group	k	SMD (95%CI)	Direct Evidence	I^2 (%)	Model
UPDRS III	LP-HI-AE VS. CON	4	−0.36 [−0.90; 0.17]	0.76	0	Fixed
	LP-HI-RT VS. CON	3	−0.20 [−0.79; 0.038]	0.87	0	Fixed
	LP-MI-AE VS. CON	1	−0.26 [−1.09; 0.57]	0.58		
	SP-HI-AE VS. CON	2	−0.31 [−1.10; 0.47]	0.8	0	Fixed
	SP-LI-RT VS. CON	1	0.21 [−0.91; 1.34]	0.6		
	LP-HI-AE VS. LP-HI-RT	1	−1.28 [−2.74; 0.18]	0.21		
	LP-HI-AE VS. LP-MI-AE	1	0.21 [−0.62; 1.04]	0.58		
	SP-HI-AE VS. SP-LI-RT	1	−0.22 [−1.35; 0.91]	0.6		
TUG	LP-HI-AE VS. CON	3	−0.39 [−0.82; 0.04]	0.85	0	Fixed
	LP-HI-RT VS. CON	1	−0.00 [−0.72; 0.72]	0.58		
	LP-HI-AE VS. LP-HI-RT	1	−0.44 [−1.16; 0.27]	0.58		
6MWT	LP-HI-AE VS. CON	3	0.21 [−0.68; 1.10]	0.84	0.81	Random
	LP-LI-AE VS. CON	1	1.06 [−0.40; 2.51]	0.59		
	LP-HI-AE VS. LP-LI-AE	1	−1.71 [−3.19;−0.23]	0.57		
TWM	LP-HI-AE VS. CON	3	−0.20 [−0.64; 0.34]	0.69	0	Fixed
	LP-HI-RT VS. CON	1	0.04 [−1.05; 1.14]	0.54		
	LP-LI-AE VS. CON	2	0.17 [−0.27; 0.61]	0.73	0	Fixed
	LP-HI-AE VS. LP-HI-RT	1	0.05 [−1.06; 1.17]	0.52		
	LP-HI-AE VS. LP-LI-AE	1	−0.20 [−0.78; 0.39]	0.52		
PDQ-39	LP-HI-AE VS. CON	3	0.18 [−0.28; 0.64]	0.83	0.05	Fixed
	LP-HI-RT VS. CON	1	−0.00 [−0.72; 0.72]	0.59		
	LP-HI-AE VS. LP-HI-RT	1	0.66 [−0.77; 1.38]	0.58		

K, Number of studies; LP-HI-AE, long period high intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-MI-AE, long period moderate intensity aerobic exercise; SP-HI-AE, short period high intensity aerobic exercise; SP-LI-RT, short period low intensity resistance training; LP-HI-AE, long period high intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-LI-AE, long period low intensity aerobic exercise; UPDRSIII, Unified Parkinson's Disease Rating Scale; PDQ39, Parkinson's Disease Questionnaire 39; TUG, Timed Up and Go; TMW, 10-meter walk test; 6MWT, 6-min walk test.

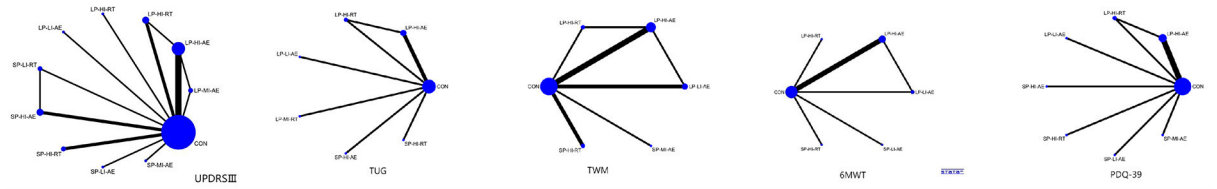


FIGURE 4
Network of evidence UPDRS-III outcome. SP-MI-AE, short period moderate intensity aerobic exercise; SP-LI-AE, short period low intensity aerobic exercise; SP-HI-RT, short period high intensity resistance training; SP-HI-AE, short period high intensity aerobic exercise; SP-LI-RT, short period low intensity resistance training; LP-LI-AE, long period low intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-HI-AE, long period high intensity aerobic exercise; LP-MI-AE, long period moderate intensity aerobic exercise; CON, control group.

vs. control; TUG indicator: long period high intensity aerobic exercise vs. control as TUG indicator. PDQ-39: long period high intensity aerobic exercise vs. control; but 6MWT: long period high intensity aerobic exercise vs. con comparison using random effects model. Thus, the results of the meta-analysis indicating that the differences between these long period high intensity aerobic exercise and long period low intensity aerobic exercise (95% CI < 0) comparisons were significant and that different exercises had a therapeutic effect on PD, but none of the other differences between comparisons were statistically significant.

Results of network meta-analysis

Unified Parkinson's Disease Rating Scale Motor (UPDRS III). Network meta-analysis (12/20) studies (Dibble et al., 2006,

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TABLE 5A Network meta-analysis of the efficacy of UPDRSIII.

SP-HI-RT	NA	NA	NA	NA	NA	NA	−0.95 (−1.68; −0.22)	NA	
−0.51 (−1.48; 0.45)	**LP-MI-AE**	−0.21 (−1.04; 0.62)	NA	NA	NA	NA	−0.26 (−1.09; 0.57)	NA	
−0.54 (−1.41; 0.32)	−0.03 (−0.66; 0.60)	**LP-HI-AE**	NA	NA	−1.28 (−2.74; 0.18)	NA	−0.36 (−0.90; 0.17)	NA	
−0.54 (−1.94; 0.86)	−0.03 (−1.38; 1.32)	−0.00 (−1.28; 1.28)	**SP-MI-AE**	NA	NA	NA	−0.41 (−1.60; 0.78)	NA	
−0.70 (−1.71; 0.32)	−0.18 (−1.13; 0.76)	−0.16 (−1.00; 0.69)	−0.16 (−1.54; 1.23)	**SP-HI-AE**	NA	NA	−0.31 (−1.10; 0.47)	−0.22 (−1.35; 0.91)	
−0.90 (−1.81; 0.01)	−0.39 (−1.20; 0.43)	−0.36 (−1.03; 0.32)	−0.36 (−1.67; 0.96)	−0.20 (−1.09; 0.69)	**LP-HI-RT**	NA	−0.20 (−0.79; 0.38)	NA	
−0.99 (−2.20; 0.21)	−0.48 (−1.63; 0.67)	−0.45 (−1.52; 0.62)	−0.45 (−1.98; 1.08)	−0.30 (−1.49; 0.90)	−0.09 (−1.20; 1.01)	**LP-LI-AE**	0.04 (−0.92; 1.00)	NA	
−0.95 (−1.68; −0.22)	−0.44 (−1.07; 0.19)	−0.41 (−0.87; 0.05)	−0.41 (−1.60; 0.78)	−0.25 (−0.96; 0.45)	−0.05 (−0.60; 0.49)	0.04 (−0.92; 1.00)	**CON**	−0.21 (−1.34; 0.91)	
−1.04 (−2.18; 0.10)	−0.53 (−1.60; 0.55)	−0.50 (−1.49; 0.49)	−0.50 (−1.98; 0.98)	−0.34 (−1.21; 0.53)	−0.14 (−1.17; 0.89)	−0.05 (−1.34; 1.25)	−0.09 (−0.96; 0.78)	**SP-LI-RT**	

2015; Fisher et al., 2008; Canning et al., 2012; Qutubuddin et al., 2013; Frazzitta et al., 2014; Carvalho et al., 2015; Cugusi et al., 2015; Ferreira et al., 2018; Schenkman et al., 2018; van der Kolk et al., 2018; Vieira de Moraes Filho et al., 2020) involving 574 subjects with data provided between 11 different treatment nodes assessed motor function using UPDRS III measurements (Figure 4). The NMA of UPDRS III showed that short period high intensity resistance movement (SMD = −0.95; 95% CI −1.68 to −0.22) was significantly reduced compared with the control group. The pairwise meta-analysis showed that in comparison with the control group, short period high intensity resistance movement significantly decreased the UPDRS III score (Table 5A). Other comparisons were found to be statistically insignificant. The ranking of treatments based on cumulative probability plots and SUCRAs reveals that all exercises showed better results than the control group, except for short periods of low intensity resistance exercise. Short period high intensity resistance movement (SUCRA = 87%) was the most effective treatment and short period low intensity resistance exercise (27%) the least (Figures 5A, 6A). No evidence of publication bias was presented in Figure 7A. Quantification of the inconsistencies between direct and indirect comparisons using node-splitting methods and the design-by-treatment interaction model showed that all *p*-values exceeded 0.05 (*p*-value = 0.58), which indicated satisfactory consistency.

Timed-Up-and-Go Test (TUG). We conducted a network meta-analysis of the TUG results, which showed that short period high intensity resistance movement (SMD = −4.80, 95% CI −6.08 to −3.52) and long period high intensity aerobic exercise (SMD = −0.40, 95% CI −0.79 to 0.00) were more conducive to lower TUG scores than controls Table 5B. We assessed the ranking of the various treatments according to TUG scores and found that short period high intensity resistance movement ranked highest (SUCRA = 92.6%) Figures 5B, 6B. All other treatments were better than the control group, but there was no significant difference. Quantification of inconsistency between direct and indirect comparisons using a node-splitting approach and a design-treatment interaction model showed that all p-values exceeded 0.05, which indicates satisfactory agreement. Figure 7B shows no evidence of publication bias.

10-meter walk test (TWM). The results of the network meta-analysis showed that short period high intensity resistance movement (SMD = −1.10; 95% CI −1.62 to −0.57) was greatly different from the control group Table 5C. The SUCRA (Figures 5C, 6C) showed that all the results were better than the control group except for the long period low intensity aerobic exercise treatment and short period high intensity resistance movement scored the highest in the TWM (SUCRA = 98 %). Figure 7C shows no evidence of publication bias. All other exercises were better than the control group, but there was no significant difference. All p-values exceeded 0.05, which indicates satisfactory agreement.

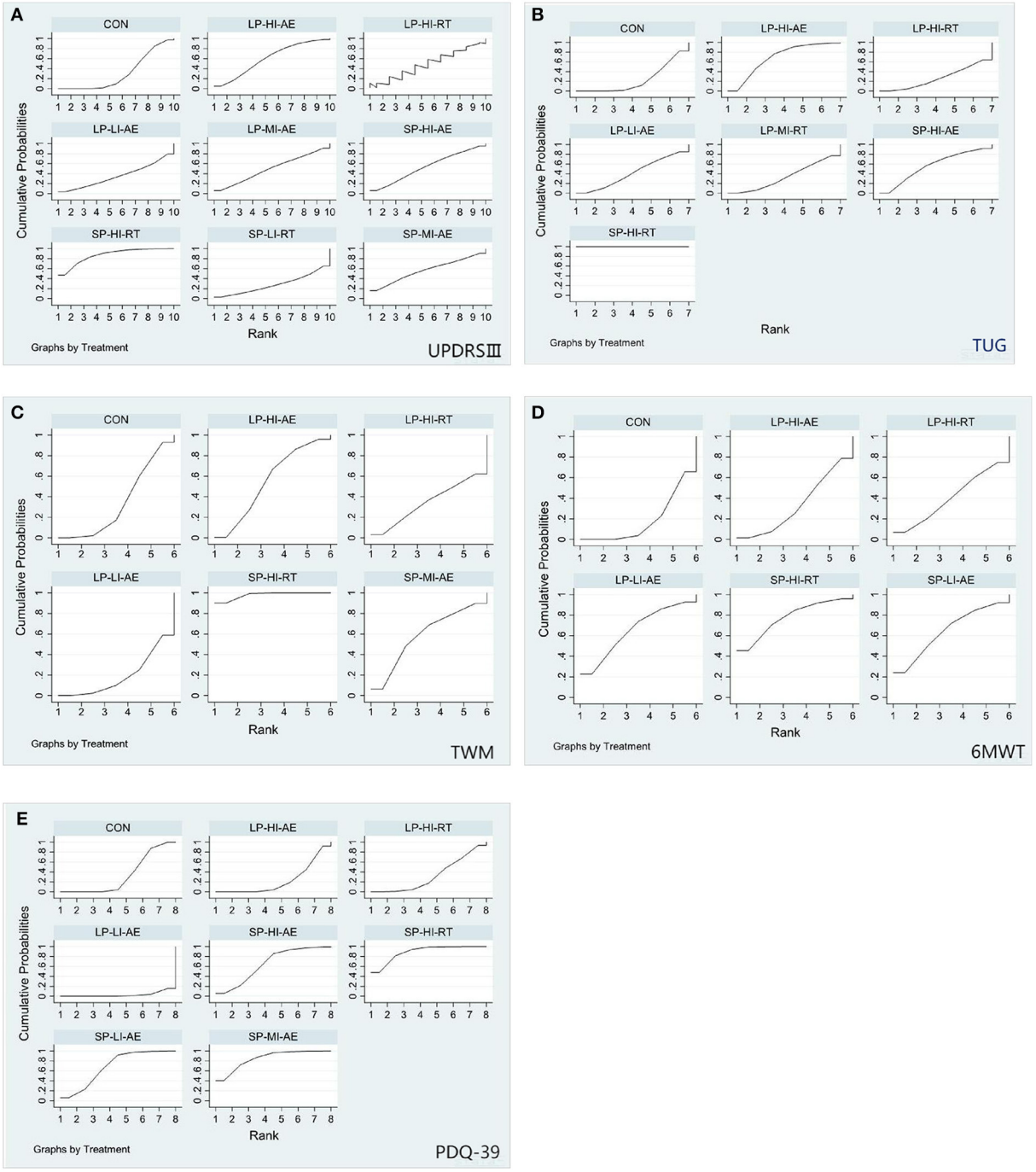


FIGURE 5
The rank probability of various interventions based on the SUCRA [**(A)** UPDRS-III outcome; **(B)** TUG outcome; **(C)** TWM outcome; **(D)** 6MWT outcome; **(E)** PDQ-39 outcome; SP-LI-AE, short period low intensity aerobic exercise; SP-HI-RT, short period high intensity resistance training; SP-HI-AE, short period high intensity aerobic exercise; SP-LI-RT, short period low intensity resistance training; LP-LI-AE, long period low intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-HI-AE, long period high intensity aerobic exercise; LP-MI-AE, long period moderate intensity aerobic exercise; CON, control group].

6 Minute Walk Test (6MWT). Paired mesh meta-analysis showed a significant difference between short periods high intensity resistance exercise (SMD = 1.06; 95% CI −0.63 to 2.75) and control group Table 5D. There was a significant difference in the long period low intensity of aerobic exercise (SMD = −0.58; 95% CI 0.28 to 2.55) compared to the control group

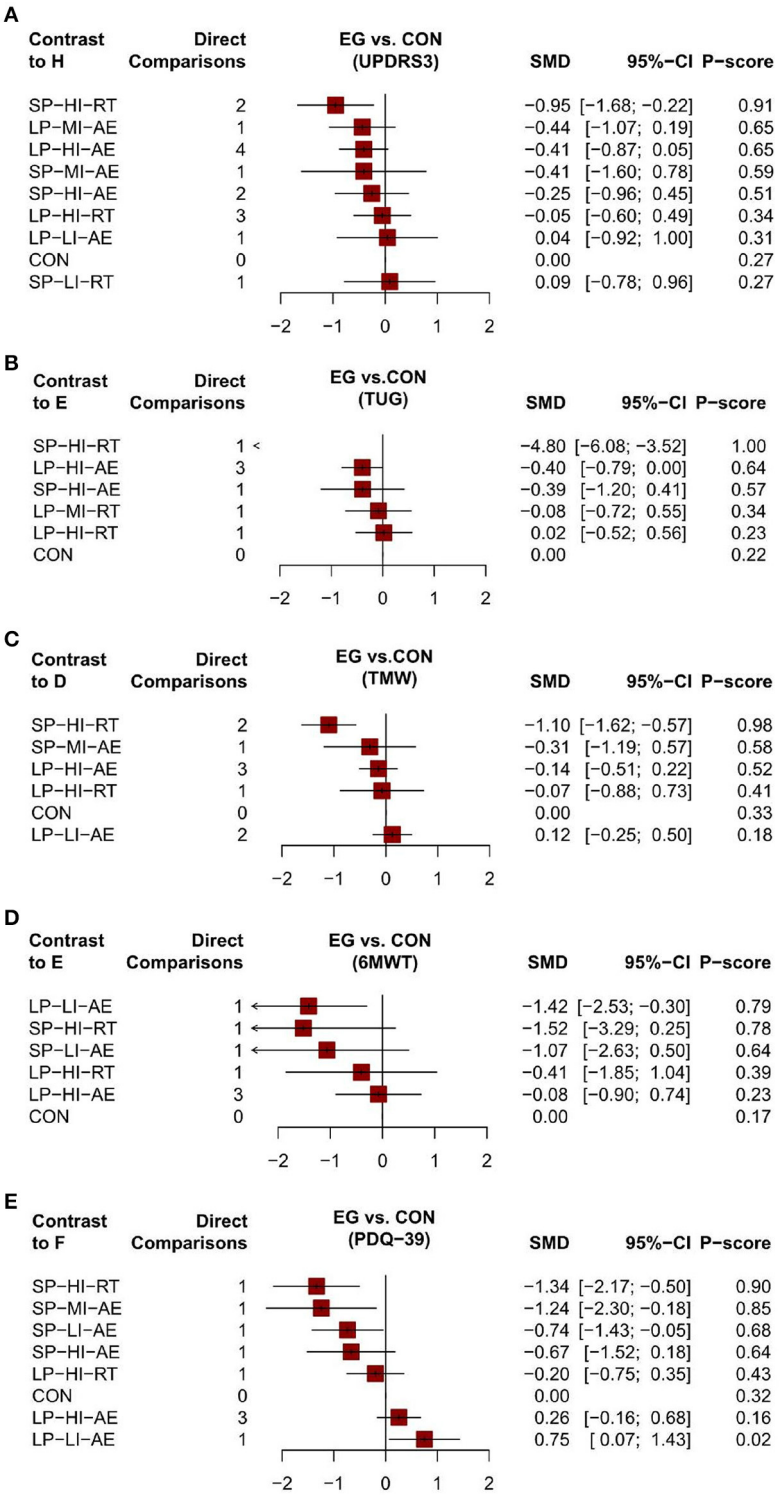


FIGURE 6
The forest plot of aerobic and resistance exercise outcomes [**(A)** UPDRS-III outcome; **(B)** TUG outcome; **(C)** TWM outcome; **(D)** 6MWT outcome; **(E)** PDQ-39 outcome; SP-MI-AE, short period moderate intensity aerobic exercise; SP-LI-AE, short period low intensity aerobic exercise; SP-HI-RT, short period high intensity resistance training; SP-HI-AE, short period high intensity aerobic exercise; SP-LI-RT, short period low intensity resistance training; LP-LI-AE, long period low intensity aerobic exercise; LP-HI-RT, long pe-riod high intensity resistance training; LP-HI-AE, long period high intensity aerobic exercise; LP-MI-AE, long period moderate intensity aerobic exercise; CON, control group; EG, experimental group; SMD, Mean Difference; 95%CI, confidence interval].

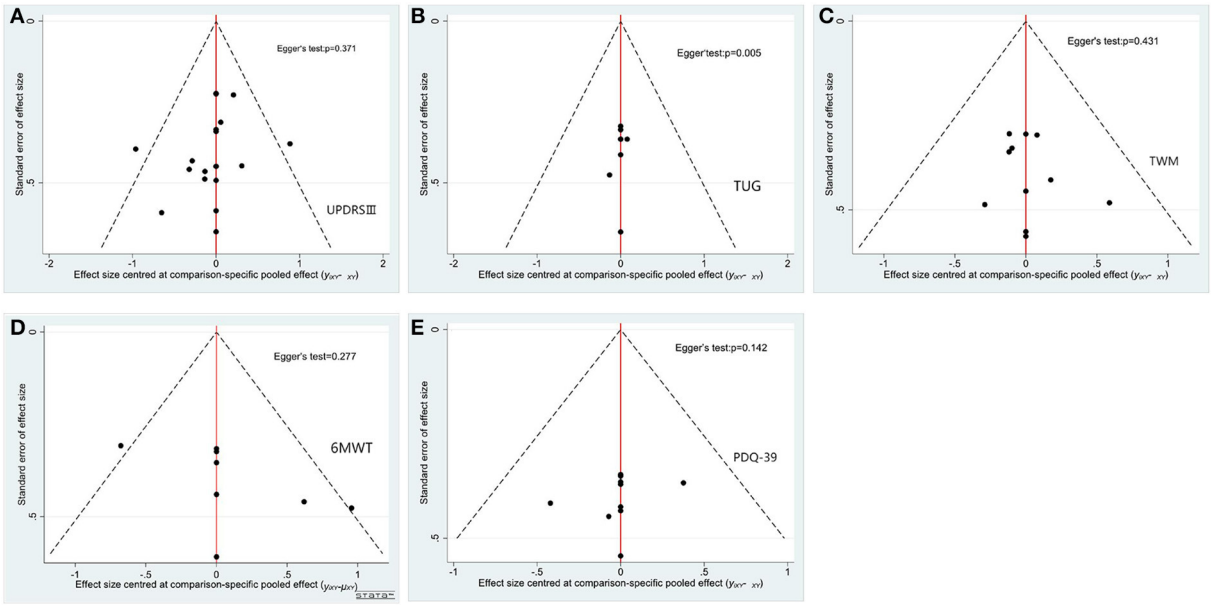


FIGURE 7
Funnel plots and bias of aerobic and resistance exercise outcomes [**(A)** UPDRS-III outcome; **(B)** TUG outcome; **(C)** TWM outcome; **(D)** 6MWT outcome; **(E)** PDQ-39 outcome; SP-MI-AE, short period moderate intensity aerobic exercise; SP-LI-AE, short period low intensity aerobic exercise; SP-HI-RT, short period high intensity resistance training; SP-HI-AE, short period high intensity aerobic exercise; SP-LI-RT, short period low intensity resistance training; LP-LI-AE, long period low intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-HI-AE, long period high intensity aerobic exercise; LP-MI-AE, long period moderate intensity aerobic exercise].

(Figures 5D, 6D). all other exercises were better than the control group, but there was no significant difference. No evidence of publication bias Figure 7D.

The 39-item Parkinson's Disease Questionnaire (PDQ-39). The NMA for the PDQ-39 showed that compared to the control group, there were significant differences in short period high intensity resistance exercise (SMD = −1.34; 95% CI −2.17 to 0.50), short periods of moderate-intensity aerobic training (SMD = −1.24; 95% CI −2.3 to −0.18); and short periods of low-intensity aerobic training (SMD = −0.74; 95% CI −1.43 to −0.05) Table 5E. The ranking of treatments based on cumulative probability plots and SUCRA (Figures 5E, 6E) showed that the most effective treatment was short period high intensity resistance movement exercise (SUCRA = 90%). Figure 7E shows no evidence of publication bias.

Discussion

The aim of this study was to perform a network meta-analysis of aerobic and resistance exercise therapy in patients with PD. To our knowledge, to date, no other review has performed a network meta-analysis of aerobic and resistance training with different outcomes on motor function in PD, as well as no further classification of exercise doses for aerobic and resistance training. Our results show that different aerobic and resistance training showed effects in PD patients, reflecting the complementary efficacy of aerobic and resistance training in the non-pharmacological treatment of PD, as well as the prominent role of high intensity training based on different doses of exercise modalities. In difference to the previous network meta-analysis of multiple exercise modalities by Tang et al. (2019), the focus of this paper is that since aerobic and resistance are the most common training modalities, studies of specific intensity cycles can provide a broader range of dose recommendations for future studies, rather than being limited to one specific study.

In particular, the studies in this paper show the effectiveness of short periods high intensity exercise, and many studies in recent years have highlighted the value of high intensity resistance training, with previous studies confirming muscle atrophy, weakness, low muscle strength, and fatigability associated with aging in PD, and demonstrating the role of resistance exercise training at high intensity in PD patients (Leek et al., 2001; Bickel et al., 2011; Chalé et al., 2013). Kelly et al. (2018) concluded that PD patients perform exercise training at sufficient intensity to achieve robust adaptation of skeletal muscle, that preferential hypertrophy of type II muscle fibers is a hallmark adaptation of resistance training, and that resistance training can counteract aging type II atrophy by promoting regeneration.

In comparison with controls, from pooled analysis, short period high intensity resistance movement (SMD = −0.95;

TABLE 5B Network meta-analysis of the efficacy of TUG.

SP-HI-RT	NA	NA	NA	NA	NA	−4.80 (−6.08; −3.52)
−4.29 (−5.65; −2.92)	**LP-HI-AE**	NA	NA	NA	−0.44 (−1.16; 0.27)	−0.54 (−1.11; 0.03)
−4.41 (−5.92; −2.90)	−0.12 (−1.07; 0.83)	**SP-HI-AE**	NA	NA	NA	−0.39 (−1.20; 0.41)
−4.61 (−6.05; −3.18)	−0.33 (−1.15; 0.50)	−0.21 (−1.25; 0.84)	**LP-HI-AE**	NA	NA	−0.19 (−0.85; 0.47)
−4.72 (−6.14; −3.29)	−0.43 (−1.24; 0.37)	−0.31 (−1.34; 0.72)	−0.10 (−1.02; 0.81)	**LP-MI-RT**	NA	−0.08 (−0.72; 0.55)
−4.76 (−6.16; −3.37)	−0.48 (−1.04; 0.08)	−0.36 (−1.34; 0.63)	−0.15 (−1.02; 0.71)	−0.05 (−0.90; 0.80)	**LP-HI-RT**	0.00 (−0.72; 0.72)
−4.80 (−6.08; −3.52)	−0.52 (−1.01; −0.02)	−0.39 (−1.20; 0.41)	−0.19 (−0.85; 0.47)	−0.08 (−0.72; 0.55)	−0.04 (−0.60; 0.52)	**CON**

TABLE 5C Network meta-analysis of the efficacy of TWM.

SP-HI-RT	NA	NA	NA	−1.10 (−1.62; −0.57)	NA
−0.79 (−1.82; 0.24)	**SP-MI-AE**	NA	NA	−0.31 (−1.19; 0.57)	NA
−0.95 (−1.59; −0.31)	−0.16 (−1.12; 0.79)	**LP-HI-AE**	0.05 (−1.06; 1.17)	−0.20 (−0.64; 0.24)	−0.20 (−0.78; 0.39)
−1.02 (−1.98; −0.07)	−0.23 (−1.43; 0.96)	−0.07 (−0.87; 0.73)	**LP-HI-RT**	0.04 (−1.05; 1.14)	NA
−1.10 (−1.62; −0.57)	−0.31 (−1.19; 0.57)	−0.14 (−0.51; 0.22)	−0.07 (−0.88; 0.73)	**CON**	−0.17 (−0.61; 0.27)
−1.22 (−1.87; −0.58)	−0.43 (−1.39; 0.53)	−0.27 (−0.69; 0.15)	−0.20 (−1.06; 0.66)	−0.12 (−0.50; 0.25)	**LP-LI-AE**

TABLE 5D Network meta-analysis of the efficacy of 6MWT.

SP-HI-RT	−0.46 (−3.06, 2.13)	−0.45 (−3.11, 2.20)	−1.11 (−3.70, 1.47)	−1.29 (−3.51, 0.93)	−1.06 (−2.75, 0.63)
0.46 (−2.13, 3.06)	**LP-LI-AE**	0.01 (−2.45, 2.47)	−0.65 (−3.03, 1.73)	−0.83 (−2.80, 1.15)	−0.88 (−3.49, 1.73)
0.45 (−2.20, 3.11)	−0.01 (−2.47, 2.45)	**SP-LI-AE**	−0.66 (−3.11, 1.79)	−0.84 (−2.90, 1.22)	−1.52 (−3.49, 0.45)
1.11 (−1.47, 3.70)	0.65 (−1.73, 3.03)	0.66 (−1.79, 3.11)	**LP-HI-RT**	−0.18 (−2.15, 1.79)	−0.41 (−2.09, 1.28)
1.29 (−0.93, 3.51)	0.83 (−1.15, 2.80)	0.84 (−1.22, 2.90)	0.18 (−1.79, 2.15)	**LP-HI-AE**	−0.23 (−1.25, 0.79)
1.06 (−0.63,−2.75)	0.88 (−1.73, 3.49)	1.52 (−0.45, 3.49)	0.41 (−1.28, 2.09)	0.23 (−0.79, 1.25)	**CON**

95% CI −1.68 to −0.22) was much more effective than other aerobic and resistance training in reducing UPDRS-III motor symptoms. Our results complement previous studies (Egger et al., 2003), expand on existing treatments, and are consistent with the recommendations in the ACSM (Riebe et al., 2015) for providing regular moderate to high intensity resistance training advice for PD. By contrast, the score of short period low intensity resistance movement (SMD = 0.09; 95% CI 0.78 to 0.96) lags behind in UPDRS III scores. Appropriate intensity has been identified as a key determinant of neuromuscular adaptations to strength training, since the exercise needs to reach a certain intensity to achieve neuromuscular changes, and high intensity leads to greater neuromuscular adaptations (Petzinger et al., 2013; Sallis et al., 2015). Furthermore, several studies have confirmed that potential mechanisms for high intensity resistance training induced neuromuscular remodeling and improved motor function may be related to the up regulation of genes that enhance muscle development, and that central motor path-ways still exhibit altered neuroplasticity following resistance training despite the advanced age and neurological dysfunction of PD (Lötzke et al., 2015; Saltychev et al., 2016). At the same time, we observed that other intensities and periods of both aerobic and resistance training showed advantages over the control group, which further confirms the improvement of aerobic and resistance training on motor aspects in PD. Similar results were obtained with resistance training conducted by Corcos et al. (2013), who carried out progressive resistance training in PD for two years and showed statistically and clinically significant reductions in UPDRS-III scores, suggesting resistance training as a useful adjunct treatment to improve motor signs in PD. Interestingly, animal studies in PD models have also shown that locomotor training can reduce α-synuclein aggregation and improve both motor and cognitive function (Zhou et al., 2017) and exercise increases neuronal activation and dopamine increases in the basal ganglia (Lau et al., 2011), which may have an impact on UPDRS scores, and regular exercise therapy may reverse or attenuate the underlying neurodegenerative process in PD, ultimately leading to improved UPDRS scores.

As common indicators of motor performance and gait, the results of TUG, 6MWT, and TWM suggest that short period low intensity resistance movement can be used as an adjunct to improve motor symptoms and prevent falls in Parkinson's patients. This is consistent with the results of a previous meta-analysis (Santos et al., 2017; Tang et al., 2019). A study by Santos et al. (2017) found that resistance training improved freezing gait in PD patients. The strength improvement brought by resistance training may facilitate the activation of balance related

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TABLE 5E Network meta-analysis of the efficacy of PDQ-39.

SP-HI-RT	NA	NA	NA	NA	−1.34 (−2.17; −0.50)	NA	NA
−0.10 (−1.45; 1.25)	SP-MI-AE	NA	NA	NA	−1.24 (−2.30; −0.18)	NA	NA
−0.60 (−1.68; 0.48)	−0.50 (−1.77; 0.76)	SP-LI-AE	NA	NA	−0.74 (−1.43; −0.05)	NA	NA
−0.67 (−1.86; 0.52)	−0.57 (−1.93; 0.79)	−0.07 (−1.17; 1.02)	SP-HI-AE	NA	−0.67 (−1.52; 0.18)	NA	NA
−1.14 (−2.14; −0.14)	−1.04 (−2.24; 0.15)	−0.54 (−1.42; 0.34)	−0.47 (−1.48; 0.54)	LP-HI-RT	0.00 (−0.72; 0.72)	−0.66 (−1.38; 0.07)	NA
−1.34 (−2.17; −0.50)	−1.24 (−2.30; −0.18)	−0.74 (−1.43; −0.05)	−0.67 (−1.52; 0.18)	−0.20 (−0.75; 0.35)	CON	−0.18 (−0.64; 0.28)	−0.75 (−1.43; −0.07)
−1.59 (−2.53; −0.66)	−1.50 (−2.64; −0.36)	−1.00 (−1.80; −0.19)	−0.93 (−1.87; 0.02)	−0.45 (−1.01; 0.10)	−0.26 (−0.68; 0.16)	LP-HI-AE	NA
−2.09 (−3.16; −1.01)	−1.99 (−3.25; −0.73)	−1.49 (−2.46; −0.52)	−1.42 (−2.51; −0.33)	−0.95 (−1.82; −0.07)	−0.49 (−1.29; 0.31)	LP-LI-AE

Relative effect sizes of efficacy at post-treatment according to network meta-analysis. Treatments are orders in the rank of their chance of being the best treatment. Numbers in bule boxes are SUCRA (the surface under the cumulative ranking curve) values and their CrIs (credible intervals). Significant pairwise comparisons are highlighted in red. For efficacy in post-treatment, standardized mean differences (SMDs) less than 0 favor the column-defining treatment. UPDRS, Unified Parkinson's Disease Rating Scale; PDQ39, Parkinson's Disease Questionnaire 39; TUG, Timed Up and Go; TMW, 10-meter walk test; MDS-UPDRS, MDS-Unified Parkinson's Disease Rating Scale; 6WMT, 6-min walk test; LP-HI-AE, long period high intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-MI-AE, long period moderate intensity aerobic exercise; SP-HI-AE, short period high intensity aerobic exercise; SP-LI-RT, short period low intensity resistance training; LP-HI-AE, long period high intensity aerobic exercise; LP-HI-RT, long period high intensity resistance training; LP-LI-AE, long period low intensity aerobic exercise.

muscle groups. This mechanism may be related to the fact that high intensity resistance training improves cardiovascular conditioning and increases the level of skeletal muscle force production (Dibble et al., 2015). In addition, high intensity resistance training may help to enhance neural drive (Dibble et al., 2009b), leading to better postural control and thus improved gait. Also, long period high intensity aerobic exercise (SMD = 0.40; 95%CI 0.78 to 0.96) showed significant differences from controls in TUG, which is consistent with the conclusion of a previous meta-analysis that both aerobic and resistance training were effective in improving patients' gait (Tomlinson et al., 2012). Previous studies emphasizing high intensity aerobic exercise show promise for improving PD symptoms (Alberts et al., 2011; Schenkman et al., 2018). For example, Fisher et al. (2008) used treadmill training to have patients with Parkinson's disease perform gait training at a faster pace than they would have chosen for themselves, and over an 8-week period, the patients improved gait and balance parameters as the training was progressively improved, while showing a decrease in cortical motor excitability *via* transcranial magnetic stimulation.

For the quality of life, the PDQ-39 results show that short cycles of high intensity resistance exercise improve the quality of life in PD patients with mild or moderate symptoms. This is consistent with the previous observation (Dibble et al., 2009a) in which eccentric training was found to have significantly improved patients' quality of life and after resistance training patients experienced some positive changes in habitual behaviors that could be attributed to the training. Participants in this research enjoyed an improved quality of life who felt less fatigued, had a better appetite, and slept and rested well. In conclusion, we recommend that people with Parkinson's disease incorporate resistance movement into their physical activity routine to improve motor symptoms and enhance their quality of life (Wu et al., 2017). However, the above benefits may arise from the design of the research, the sample size and the measurement problems of the research, or the fidelity of implementation in other issues.

Advantages

To our knowledge, this network meta-analysis is the first study to compare the effects of aerobic and resistance training on Parkinson's patients and to further divide them according to exercise periods and intensity when determining the beneficial guidance of different exercise doses for PD. It also explores the ranking of various PD treatments based on a comprehensive ranking that identifies the best option for improving movement and quality of life for Parkinson's patients. A variety of physiotherapy methods are applied to treat people with Parkinson's disease, but previous reviews have focused on simply one type of physiotherapy (Shu et al., 2014; Lamotte et al., 2015).

Limitations

Following are the limitations of our study. In terms of exercise outcomes, the number of studies is small and direct comparisons of exercise assessments are lacking the studies included in our NMA used the results as continuous variables as a basis. At the same time, the more restrictive classification of exercise intensity and exercise period resulted in many mixed-mode exercises not being included, which may have led to incomplete results. Future studies need to further refine the way exercise doses are studied. The classification of motion periods is a gap in current research, and despite our efforts to try to find more objective criteria, unfortunately there are no relevant studies, which is the limitation of this paper and requires further investigation in the future. In the analysis section, we extracted the mean, SD, and sample size values at the last observation for analysis. However, some studies lost the above data, which made the number of available studies even smaller. Also, the participant was blinding at the time of inclusion in some of the literature, and it was difficult to ensure participant blinding in exercise therapy, which may lead to bias. The quality of several studies potentially threatened the validity of our study. Future studies should explore a wider range of metrics for evaluating different types of exercise doses, include more types of studies, and increase the credibility of the studies. Therefore, based on the complexity of the Network meta, the results of this study should be interpreted with caution due to the small number of studies.

Conclusion

In conclusion, our network meta-analysis showed that short period high intensity resistance training, as a complement to pharmacotherapy, improved motor symptoms in PD better compared to aerobic and resistance exercise of other period and intensity. However, both aerobic and resistance training of different intensities and cycles showed some effects, and aerobic and resistance training can be recommended as types of exercise for PD. In the future, we need more high quality multicentre randomized controlled trials to confirm our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

XZ served as principal author and had full access to all the data in the study, takes responsibility for the accuracy of the data analysis, and the integrity of the data. RW and JW contributed to the conception and design. XZ, RW, and JW contributed to data acquisition and interpretation. XZ and JW contributed to draft of the manuscript. XZ, JW, and XG contributed to revise of the article and final approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.935176/full#supplementary-material

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Association between walking speed and cognitive domain functions in Chinese suburban-dwelling older adults

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Objective: To examine the relationship among walking speed, cognitive impairment, and cognitive domain functions in older men and women living in a Chinese suburban community.

Methods: In total, 625 elderly (72.54 ± 5.80 years old) men (n = 258) and women (n = 367) from the Chongming district of Shanghai participated in this study. All participants had Mini-Mental State Examination (MMSE), 4-m walking test, medical history questionnaire, and physical examination. They were grouped according to walking speed (>0.8 vs. ≤0.8 m/s) with the stratification of sex. The odds ratio (*OR*) and the 95% confidence interval (*CI*) were assessed using the chi-square test and logistic regression analysis.

Results: Around 11.6% of men and 14.2% of women had slow walking speeds. After adjusting for age, body mass index (BMI), education level, spouse, faller, the Geriatric Depression Scale (GDS) score, heart disease, stroke, arthritis, and low back pain, walking speed was negatively related to cognitive impairment in men (*OR* 0.11 [95% *CI*: 0.01, 0.94]; $p = 0.043$). In addition, the relationship between walking speed and impaired orientation was significant in both men (*OR* 0.003 [95% *CI*: 0.001, 0.05]; $p < 0.001$) and women (*OR* 0.15 [95% *CI*: 0.03, 0.75]; $p = 0.021$).

Conclusion: The relationship between walking speed and cognitive impairment was only significant in men, but the association with impaired orientation was found in both men and women. Assessing the walking speed of the elderly is beneficial, which may help with early detection and early therapeutic prevention of cognitive impairment.

KEYWORDS

cognitive impairment, sex-difference, orientation, slow walking speed, cognitive domain functions

Introduction

Cognitive impairment, such as mild cognitive impairment (MCI) and dementia, is associated with age-related neurodegenerative disease. Impairment of different cognitive domain functions, such as memory, orientation, executive function, and language, may affect daily life to varying degrees (Morley, 2018). In China, the incidence of cognitive

impairment among the elderly aged 60 years and above is 12.6–30.0% (Giri et al., 2016; Wu et al., 2019). When the decline in cognitive function progresses to the stage of dementia, neurodegeneration and cognitive impairment will be irreparable. Until then, non-pharmacological interventions, such as exercise, diet, and chronic disease management can help delay or prevent the decline of cognitive function to a certain extent (Rosenberg et al., 2018). Walking has been recognized as one of the most convenient and economical ways of engaging in physical activity. Previous reports have shown links between cognitive function and walking speed in the elderly (Hackett et al., 2018; Liu et al., 2021), but it is unclear whether any specific cognitive domain functions are more strongly associated with walking speed.

Usual walking speeds are chosen by most people for their least energy expenditure and greatest walking efficiency. However, for the elderly, especially those with chronic diseases, walking speed is relatively slow due to limited aerobic capacity and additional demand for energy expenditure associated with physical activity (Schrack et al., 2016). Brain imaging studies have shown that reduced walking speed is associated with smaller hippocampal volume and cerebrocortical mass (Lee et al., 2019). The predictive power of slow walking speed for cognitive impairment has also been demonstrated in older adults (Hackett et al., 2018; Chou et al., 2019; Knapstad et al., 2019). However, studies on the relationship between walking speed and cognitive function in different domains are limited and inconsistent. Some studies reported that walking speed is significantly correlated with all cognitive domain functions (Toots et al., 2019a; Liu et al., 2021). However, other studies have indicated that walking speed is significantly related to the decline of orientation, executive function, and visuospatial function (Zhang et al., 2019; Zuo et al., 2019). Furthermore, walking speed and cognitive function are both reported to decline with age, but sex differences in these declines are still unclear.

Older adults in the suburban community have less opportunity to receive health information and services compared with the urban areas and are more likely to ignore the physical and cognitive problems associated with aging (Liu et al., 2020). The purpose of the present study was to examine the relationship among walking speed, cognitive impairment, and cognitive domain functions in men and women living in a Chinese suburban community to provide a reference for predicting cognitive decline and identifying cognitive impairment early among the population at high risk.

Abbreviations: MMSE, Mini-Mental State Examination; OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; IPAQ-SF, International Physical Activity Questionnaire Short Form; BMI, body mass index.

Methods

Study design and participants

This was a cross-sectional study conducted from August to November 2018 in the Chongming district of Shanghai, China. The participants of this study were volunteers from the Screening and Rehabilitation Nursing Intervention Study of Cognitive Impairment in the Elderly. All participants were ≥60 years old and lived independently in the community. The exclusion criteria are as follows: (1) those walking with an assistive walking device, such as a cane, walker, or crutch(es); (2) those suffering from serious somatic and/or psychiatric illness, or treatment that may significantly affect walking speed (such as unhealed fractures and tumors); (3) those unable to perform the study required tests (such as 4-m walking test); and (4) those with mental illness, dementia, visual impairment, deafness, or inability to speak that could cause communication difficulties. Finally, 625 participants (258 men (73.16 ± 5.82 years old) and 367 women (72.15 ± 5.73 years old) signed informed consent and were enrolled in the study. The study protocol was approved by the Ethics Committee of the Shanghai University of Medicine and Health Sciences (2020-E4-6200-20-201032-03-210302197009090947). There were training sessions to emphasize the details of the testing and to address the questions for all research associates involved in the study.

Assessment of cognitive function

Cognitive function was assessed by the Chinese version Mini-Mental State Examination (MMSE), which contains 12 test items to assess several different cognitive domains, such as orientation (0–10), immediate recall (0–3), delayed recall—short-term memory (0–3), attention or concentration ability (0–5), and verbal ability (0–9) (Wu et al., 2019). Higher scores indicate better cognitive function (with a perfect score = 30). Considering the fact that cognitive performance correlates with educational level, the cut-off value of cognitive impairment was adjusted according to the education level, ≤17 for illiterate, ≤20 for primary school, and ≤24 for junior high school and above (Wu et al., 2019; Zhang et al., 2021). The scores for each cognitive domain of the MMSE were transformed into an age-specific *Z*-score for the participants in their 60, 70, and 80s and above, utilizing the data for all participants included in this study. Impairment in each domain of the MMSE was defined as a

score >1.0 SDs below the age-specific means (Kondo et al., 2021).

Assessment of walking speed

Walking speed was measured by a 4-m walking test on a flat, straight corridor. The beginning and end points of the corridor are prominently marked with yellow tape and both points have a 1-m buffer distance (Bohannon and Wang, 2019). The participants were told to walk at their usual pace along the corridor, recording the time in meters per second. They performed the test two times and the mean walking speed (m/s) was calculated and documented (Hooghiemstra et al., 2017). Canes or walkers were allowed to be used. According to walking speed, the participants in this study were divided into two groups: slow walking speed (≤0.8 m/s) or normal walking speed (>0.8 m/s) as previously described (Ke et al., 2021).

Covariates

Face-to-face epidemiological questionnaire interviews were performed by trained interviewers. The questionnaire included questions about age, sex, spouse, living alone, education level (0, 1–6, and >6 years), smoking habits, and drinking habits. According to the history of previous falls, participants were divided into the "non-faller" or "faller" groups. When asked the question: "Have you had any falls in the last year?" Participants offering an affirmative answer were assigned to the "faller" group, and others were assigned to the "non-faller" group (Lavedan et al., 2018). In addition, body mass index (BMI) was calculated by dividing weight (kg) by height (m^2). Physical activity was assessed by the International Physical Activity Questionnaire Short Form (IPAQ-SF) based on the amount of heavy physical activity, moderate physical activity, and walking activity (Zhang et al., 2021). Depressive symptomatology was measured by the 30-item Geriatric Depression Scale (GDS-30), which has a high sensitivity (70.6%) and specificity (70.1%) in a Chinese population sample aged 60 years and over (Rong et al., 2019). Medical or health history was evaluated based on participants' responses (yes or no) to questions about their history, past diagnoses made by physicians, and current or historical medication regimens. Diseases of interest include diabetes mellitus, hypertension, hyperlipidemia, stroke, heart disease, arthritis, and low back pain.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), continuous non-normal distribution variables, such as IPAQ, were expressed by median and quartile, and classification variables were expressed by percentage (%). Differences in baseline characteristics according to walking speed were analyzed using an independent sample *t*-test, Pearson's chi-square test, and the Mann–Whitney *U*-test. Binary logistic regression models were used to examine the relationship between walking speed and cognitive impairment and impaired cognitive domain function. Adjusted variables in Model 1 included age, BMI, education level, and those in Model 2 included age, BMI, education level, spouse, faller, the GDS score, heart disease, stroke, arthritis, and low back pain. A *p*-value of <0.05 was considered statistically significant. SPSS 25.0 statistical software was used for the analysis.

Results

A total of 625 participants (258 men and 367 women; average: 72.54 ± 5.80 years old) were included in the analysis. The characteristics of the participants according to sex and categories of walking speed are shown in Table 1. The proportion of slow walking speed was 11.6 and 14.2% in men and women, respectively. Men with slower walking speed were older, had higher GDS scores, lower IPAQ, were more likely to be spouseless, living alone, fallers, and had a higher prevalence of heart disease and cognitive impairment. Women with slower walking speed were older, less educated, had higher GDS scores, lower IPAQ, were more likely to be spouseless, and had a higher prevalence of stroke and cognitive impairment.

Table 2 shows the association between walking speed and cognitive function in men. In Model 1, walking speed was negatively correlated to cognitive impairment (odds ratio [*OR*] 0.12 [95% *CI* 0.02, 0.79]; $p = 0.024$), impaired orientation (*OR* 0.02 [95% *CI* 0.002, 0.15]; $p < 0.001$), and impaired immediate recall (*OR* 0.11 [95% CI 0.02, 0.88]; $p = 0.031$), impaired delayed recall (*OR* 0.27 [95% *CI* 0.07, 0.96]; $p = 0.045$). In Model 2, walking speed remained significantly associated with cognitive impairment (*OR* 0.11 [95% *CI* 0.01, 0.94]; $p = 0.043$) and impaired orientation (*OR* 0.003 [95% *CI* 0.001, 0.05]; $p < 0.001$), while impaired immediate recall (*OR* 0.10 [95% *CI* 0.007, 1.09]; $p = 0.060$), impaired attention, (*OR* 0.43 [95% *CI* 0.06, 3.18]; $p = 0.400$), impaired delayed recall (*OR* 0.33 [95% *CI* 0.08, 1.38]; $p = 0.130$), and impaired language function (*OR* 2.13 [95% *CI* 0.82, 10.78]; $p = 0.091$) were not.

Table 3 shows the association between walking speed and cognitive function in women. After adjusting for age, BMI, education level, spouse, faller, GDS scores, heart disease, stroke, arthritis, and low back pain, walking speed was only negatively related to impaired orientation (*OR* 0.15 [95% *CI* 0.03, 0.75]; $p = 0.021$), while impaired immediate recall (*OR* 0.85 [95% *CI* 0.16, 4.48]; $p = 0.843$), impaired attention, (*OR* 2.00 [95% *CI* 0.45, 4.18]; $p = 0.362$), impaired delayed recall (*OR* 1.33 [95% *CI* 0.35, 5.14]; $p = 0.672$), and impaired language function (*OR* 0.79 [95% *CI* 0.13, 4.76]; $p = 0.798$) were not.

TABLE 1 Participant characteristics.

Variables	Men ($n = 258$)		*P*-value	Women ($n = 367$)		*P*-value
	Normal walking speed ($n = 228$)	Slow walking speed ($n = 30$)		Normal walking speed ($n = 315$)	Slow walking speed ($n = 52$)	
Age, yrs	72.75 ± 5.39	76.20 ± 7.85	0.002	71.27 ± 4.80	77.44 ± 7.76	<0.001
BMI, kg/m^2	25.09 ± 3.37	25.10 ± 4.94	0.995	25.00 ± 3.57	25.73 ± 4.08	0.192
Education, *n* (%), yrs			0.092			<0.001
0	10 (4.4)	4 (13.3)		48 (15.3)	21 (40.3)	
≤6	106 (46.5)	15 (50.0)		162 (51.4)	21 (40.3)	
>6	112 (49.1)	11 (36.7)		105 (33.3)	10 (19.2)	
Spouse (%)	214 (94.3)	21 (70.0)	<0.001	241 (76.5)	27 (51.9)	0.001
Living alone (%)	18 (7.9)	5 (16.7)	0.001	49 (15.5)	10 (19.2)	0.419
Smoker (%)	75 (33.0)	7 (23.3)	0.284	3 (1.0)	0 (0)	0.490
Drinker (%)	123 (53.9)	15 (50.0)	0.632	43 (13.7)	7 (13.5)	0.938
Faller (%)	26 (11.4)	9 (30.0)	0.006	54 (17.1)	12 (23.1)	0.262
IPAQ, Met/wk	3,612 (1,017, 9,043)	1,212 (591, 5,662)	0.027	6,132 (2,358, 11,760)	1,593 (486, 6,252)	<0.001
GDS,score	6.11 ± 4.01	7.80 ± 5.32	0.040	7.64 ± 4.80	11.55 ± 6.97	<0.001
Disease (%)						
Diabetes	31 (13.7)	6 (20.0)	0.352	40 (12.7)	6 (12.2)	0.898
Hypertension	151 (66.5)	22 (73.3)	0.455	176 (56.8)	31 (63.3)	0.393
Hyperlipidemia	34 (15.0)	7 (23.3)	0.240	49 (15.5)	8 (15.3)	0.926
Stroke	23 (10.1)	4 (13.3)	0.591	42 (13.3)	14 (28.6)	0.007
Heart disease	27 (11.8)	10 (33.3)	0.002	56 (17.8)	13 (25.0)	0.162
Arthritis	40 (17.5)	3 (10.3)	0.265	53 (16.8)	14 (26.9)	0.064
Low pack pain	31 (13.7)	6 (20.0)	0.352	70 (22.2)	14 (26.9)	0.357
Cognitive impairment	19 (8.3)	6 (20.0)	0.049	46 (14.6)	15 (28.8)	0.003

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; GDS, geriatric depression scale.

TABLE 2 Associations between walking speed and cognitive impairment and impaired cognitive domain function in men by binary logistic regression analysis.

Variables	Model 1 OR (95%CI)	*P*	Model 2 OR (95%CI)	*P*
Cognitive impairment	0.12 (0.02, 0.79)	0.024*	0.11 (0.01, 0.94)	0.043*
Orientation, impaired	0.02 (0.002, 0.15)	<0.001**	0.003 (0.001, 0.05)	<0.001**
Immediate recall, impaired	0.11 (0.02, 0.88)	0.031*	0.10 (0.007, 1.09)	0.060
Attention, impaired	0.8 (0.16, 4.61)	0.808	0.43 (0.06, 3.18)	0.400
Delayed recall, impaired	0.27 (0.07, 0.96)	0.045*	0.33 (0.08, 1.38)	0.130
Language function, impaired	1.72 (0.70, 5.73)	0.124	2.13 (0.82, 10.78)	0.091

Model 1: adjusted for age, BMI, education level.
Model 2: adjusted for age, BMI, education level, spouse, faller, GDS score, heart disease, stroke, arthritis, low back pain.
*$p < 0.05$, **$p < 0.001$.

Discussion

This study explored the relationship between cognitive performance and cognitive domain functions and walking speed in Chinese suburban-dwelling older adults. After adjusting for BMI, educational level, spouse, faller, GDS score and heart disease, stroke, arthritis, and low back pain, we found that slower walking speed was associated with cognitive impairment

TABLE 3 Associations between walking speed and cognitive impairment and impaired cognitive domain function in women by binary logistic regression analysis.

Variables	Model 1 OR (95%CI)	*P*	Model 2 OR (95%CI)	*P*
Cognitive impairment	0.94 (0.20, 4.55)	0.939	1.42 (0.26, 8.11)	0.689
Orientation, impaired	0.09 (0.02, 0.39)	0.001**	0.15 (0.03, 0.75)	0.021*
Immediate recall, impaired	0.60 (0.13, 2.68)	0.496	0.85 (0.16, 4.48)	0.843
Attention, impaired	1.49 (0.39, 5.79)	0.556	2.00 (0.45, 4.18)	0.362
Delayed recall, impaired	0.69 (0.21, 2.34)	0.551	1.33 (0.35, 5.14)	0.672
Language function, impaired	0.45 (0.09, 2.26)	0.325	0.79 (0.13, 4.76)	0.798

Model 1: adjusted for age, BMI, education level.
Model 2: adjusted for age, BMI, education level, spouse, faller, GDS score, heart disease, stroke, arthritis, low back pain.
*$p < 0.05$, **$p < 0.001$.

in men, while the negative association between walking speed and orientation was significant in both women and men.

Prevalence of cognitive impairment

Previous studies have reported that the prevalence of cognitive impairment ranged from 12.6 to 30% in Chinese community-dwelling older adults with adjusted education-specific cutoffs (Giri et al., 2016; Wu et al., 2019), which was similar to this study (13.8%). In addition, we also observed that the prevalence of cognitive impairment was higher in the elderly with slow walking speed than in those with normal walking speed (25.6 vs. 11.9%, $p < 0.001$), and the prevalence rate was higher in women than in men (16.6 vs. 9.7%, $p = 0.008$).

Walking speed and cognitive impairment

Walking is the most common exercise method for the elderly living in a suburban setting in China, as it does not require special venues and equipment and is suitable for most of the elderly. Walking speed is a recognized indicator of physical function that gradually decreases with age and can predict a variety of adverse health outcomes, such as physical function, cognitive function, disability, and all-cause death in the elderly (Toots et al., 2019b; Grande et al., 2020). The loss of hippocampal integrity is an important cause of cognitive impairment. Hippocampal atrophy exists in both patients with MCI and Alzheimer's disease (AD), and decreased hippocampal volume can predict a deterioration in cognitive function (Su et al., 2018). Rosso et al. suggested that the relationship between walking speed and cognitive function is supported by a shared neural substrate that includes a smaller right hippocampus (Rosso et al., 2017; Lee et al., 2019).

This study found a negative correlation between walking speed and cognitive impairment, which was in agreement with previous reports that slow walking speed was an independent risk factor for cognitive impairment (Hackett et al., 2018). Compared with the healthy elderly, the elderly with symptoms of cognitive impairment walk slower (Knapstad et al., 2019), which also indicated that the change in walking speed is closely related to the slight decline of cognitive function. Liu et al. reported a significant negative correlation between walking speed and mild cognitive impairment among community elderly people (*OR* 0.25 [95% *CI* 0.10, 0.64]; $p = 0.004$) (Liu et al., 2021). Walking speed is sensitive to changes in cognitive function, so we hypothesized that interventions that increase walking speed may be beneficial to the improvement of cognitive function.

Notably, the decline in physical performance, especially usual walking speed, which decreases with age, also showed sex differences. In this study, the proportion of men who walked slowly was lower than that of women (11.6 vs. 14.2%). Coelho-Junior et al. also reported that the usual walking speed for women rather than men showed an age-dependent decline (Coelho-Junior et al., 2021). Similarly, there are sex differences in the trajectory of cognitive decline, and longitudinal studies show that men perform worse on most cognitive tests adjusted for education level and decline faster than women in terms of episodic memory, language fluency, and verbal ability (Morley, 2018). The results of this study showed that the slower men walked, the more likely they were to have cognitive impairment (*OR* 0.11 [95% *CI* 0.01, 0.94]; $p = 0.043$), however, Tirkkonen et al. reported that the relationship between walking speed and cognitive function did not differ between the sexes among elderly people in the community (Tirkkonen et al., 2021). We speculate that poorer physical performance is likely to indicate worse health, including cognitive function, and more research is needed in the future to investigate whether there are sex differences in the relationship between physical performance and cognitive function.

Previously, it has been reported that exercise intervention improves both physical function and cognitive function (Saez De Asteasu et al., 2019). Both low- and high-intensity physical

exercise could significantly improve physical functions, such as balance, walking speed, and endurance in older adults, but the improvement effect of exercise on cognitive function is more obvious in the elderly with better functional ability. For the elderly with dementia, exercise intervention has little effect on cognitive function (Saez De Asteasu et al., 2019; Sanders et al., 2020). Therefore, early diagnosis and early intervention of cognitive impairment are particularly important, the close correlation between cognitive impairment and walking speed can also provide a reference for clinical intervention and public health screening.

Walking speed and orientation

The detailed division of MMSE domains is important for the evaluation of cognitive impairment. In the process of neuropsychological evaluation, a single cognitive domain function test cannot simultaneously evaluate multiple cognitive domain functions, while the MMSE scale can evaluate multiple cognitive domain functions, such as orientation, immediate recall, and attention, and the results are often applied to the prediction model (Xie et al., 2011).

Although cognitive function gradually declines with age, the function of different cognitive domains may not decline equally at the same time. The decline of MMSE orientation appears in the early stage of cognitive impairment (Xie et al., 2011). In this study, the relationship between walking speed and orientation was significant in both men and women after adjusting for covariates. The brain regions associated with directional force or spatial orientation are concentrated in the retrosplenial cortex (Peer et al., 2015). The retrosplenial cortex is interconnected with the hippocampus and various parahippocampal cortical regions involved in navigation and spatial cognition (Todd and Bucci, 2015), and the cortical loop connects the retrosplenial cortex to M2, the secondary motor cortex (Yamawaki et al., 2016). This may explain the close connection between walking speed and orientation. Liu et al. investigated the correlation between walking speed and cognitive domain function among elderly people living in Chinese communities, and the relationship between walking speed and orientation was also significant, which is consistent with the results of this study (Liu et al., 2021).

Study limitations and perspectives

This research is the first to focus on the association of walking speed and cognitive impairment in different cognitive domains in men and women in suburban communities in China. In addition, the 4-m walking speed test was easy to practice, suitable for the elderly, and had a good retest reliability (Bohannon and Wang, 2019). The cognitive screening and walking speed tests are also easy to be applied in the community departments of public health.

However, this study also has certain limitations. First, as this study is a cross-sectional study, the impact of changes in walking speed on cognitive function needs to be verified in the elderly with senescence in further studies. Second, the population in this study is the elderly from the Chongming District of Shanghai, and the outcomes and interpretations of the study may not be representative enough of people in other regions or different age groups. The sample size and the number of related areas need to be increased in the future.

Conclusion

In conclusion, walking speed is an important risk factor for cognitive impairment, independent of certain variables. We observed that the relationship between walking speed and cognitive impairment was only significant in men, but the association with impaired orientation was found in both men and women. This study added to evidence that walking speed may be important to consider when assessing the risk of cognitive impairment and impaired cognitive domain functions in older adults, and we can speculate that exercise intervention may serve as a means of primary prevention of cognitive decline. Future studies should explore a causal relationship between walking speed and cognitive impairment and impaired cognitive domain functions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The study protocol was approved by the Ethics Committee of the Shanghai University of Medicine and Health Sciences (2020-E4-6200-20-201032-03-210302197009090947). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HW and HZ performed the literature search, conceived and designed the study, analyzed the data, and drafted the manuscript. PC analyzed the data and critically revised the

manuscript. YC, CG, and MC performed the literature search. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of vibration training on motor and non-motor symptoms for patients with multiple sclerosis: A systematic review and meta-analysis

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Background: Vibration therapy is one of the rehabilitation programs that may be effective in treating both motor and non-motor symptoms in Multiple Sclerosis patients. We conducted a comprehensive systematic review and meta-analysis to assess the effects of vibration therapy on motor and non-motor symptoms (functional mobility, balance, walking endurance, gait speed, fatigue, and quality of life) of this population.

Methods: A systematic search of PubMed, Embase, the Cochrane Library, Web of Science, Physiotherapy Evidence Database, Scopus, Google Search Engine, and the China National Knowledge Infrastructure (CNKI). Two reviewers independently assessed the study quality.

Results: Fourteen studies with 393 participants were finally included in the meta-analysis. The pooled results showed that vibration therapy had a significant advantage over the control intervention in improving balance function [mean difference (MD) = 2.04, 95% confidence interval (CI): 0.24–3.84, $P = 0.03$], and walking endurance (SMD = 0.34, 95% CI: 0.07–0.61, $P = 0.01$). Meanwhile, the degree of disability subgroup analysis revealed that the Expanded Disability Status Scale (EDSS) score (3.5–6) significantly improved functional mobility (MD: −1.18, 95% CI: −2.09 to 0.28, $P = 0.01$) and balance function (MD: 3.04, 95% CI: 0.49–5.59, $P = 0.02$) compared with the control group, and the EDSS (0–3.5) were more beneficial in walking endurance. The duration subgroup analysis indicated a significant difference in the effect of the duration (<4 weeks) on enhancing walking endurance (SMD: 0.46, 95% CI: 0.04–0.87, $P = 0.03$). However, no significant improvement was found in functional mobility, gait speed, fatigue, and quality of life.

Conclusion: Vibration therapy may improve balance function and walking endurance, and the degree of disability and duration of intervention may affect outcomes. The evidence for the effects of vibration therapy on functional mobility, gait speed, fatigue, and quality of life remains unclear. More trials with rigorous study designs and a larger sample size are necessary to provide this evidence.

Systematic Review Registration: PROSPERO, https://www.crd.york.ac.uk/prospero/#recordDetails, identifier: CRD42022326852.

KEYWORDS

vibration therapy, multiple sclerosis, motor and non-motor symptoms, meta-analysis, physical therapy

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS), with neurodegeneration being most prominent in progressive phenotypes (Benedict et al., 2020). In 2016, about 2.2 million people were affected globally, with rates varying widely in different regions and among different populations (Wallin et al., 2019). The disease usually begins between the ages of 20 and 50 and is twice as common in women as in men (Milo and Kahana, 2010). The symptoms and dysfunction of MS include muscle weakness, sensory, balance, and mobility problems, spasticity, tremor, rapidly growing fatigue, or cognitive difficulties, which significantly influence the quality of life among MS patients (Compston and Coles, 2008; Benedict et al., 2020; Zielinska-Nowak et al., 2020). Despite disease-modifying therapies (DMTs) reducing the rate of disease progression (Hauser and Cree, 2020), the development of effective rehabilitation programs remain essential in managing the disease (Zuber et al., 2020).

Vibration therapy is one of the rehabilitation programs that have potential benefits on muscle performance, mobility, postural control, and proprioception in healthy and neurological populations (Alashram et al., 2019a; Moggio et al., 2021). It takes advantage of sinusoidal mechanical oscillation to stimulate muscles, characterized by amplitude, frequency, and phase angle, that might be used in the rehabilitation field as whole-body vibration (WBV) and focal muscle vibration (FMV) (Alashram et al., 2019b; Moggio et al., 2021). Numerous mechanisms have been proposed to explain the vibration phenomenon (Cochrane, 2011). The transmission of vibrations and oscillations to the biological system can produce physiological changes on several levels by stimulating skin receptors (Sonza et al., 2013), muscle spindles (Barrera-Curiel et al., 2019), and vestibular system (Ardic et al., 2021). The most common hypothesis is that vibration can affect the muscle spindle and lead to increased α-motor neurons and enhance muscle contraction (Cardinale and Bosco, 2003; Abercromby et al., 2007; Rittweger, 2010).

In the past decades, several studies used different parameters and treatment protocols of vibration therapy have reported improvements in muscle strength, functional mobility, balance, spasticity, fatigue, and participation in activities of daily living in subjects with MS (Schuhfried et al., 2005; Broekmans et al., 2010; Claerbout et al., 2012; Paoloni et al., 2013; Uszynski et al., 2014; Ebrahimi et al., 2015; Spina et al., 2016). However, other studies did not show improvements (Wolfsegger et al., 2014; Freitas et al., 2018; Ayvat et al., 2021). Six review articles (Santos-Filho et al., 2012; Sitja Rabert et al., 2012; Kantele et al., 2015; Kang et al., 2016; Castillo-Bueno et al., 2018; Alam et al., 2020) examine the impact of WBV on patients with MS have been published. A 2012 Cochrane Review found no evidence of a short-term or long-term effect of WBV on any functional outcomes (body balance, gait, muscle performance) or QoL, compared with other active physical therapy or passive intervention (Sitja Rabert et al., 2012). The authors recommended further investigation given the limitations of the review, with only four low-quality trials included. More recently, a systematic review and meta-analysis included 8 RCTs that showed an overall effect of WBV on strength and some measures of balance and mobility, but its impact remains inconclusive (Alam et al., 2020). Furthermore, all review articles included studies that were published in 2015 or earlier, and only focused on the WBV. Meanwhile, no reviews have been established to focus on the impacts of vibration therapy on non-motor impairments such as quality of life, disability level, or fatigue after MS, and the influence of stimulation parameters, including frequency and duration, was not evaluated.

In light of the limitations of these prior reviews, the clinical conclusion to date was that there was insufficient high-level evidence to support the routine use of vibration therapy for improving both motor and non-motor impairments, and the potential for vibration therapy to improve access to, and quality of, rehabilitation services while reducing costs, an update of the previous review was warranted. Besides, more studies have been carried out in recent years due to the further development and appliance of vibration therapy (Paoloni et al., 2013; Ebrahimi et al., 2015; Spina et al., 2016; Uszynski et al., 2016; Ayvat et al., 2021). Hence, the purposes of this review were to examine the effects of vibration therapy on motor and on-motor impairments–focused outcomes in individuals with MS and to investigate which vibration exposure parameters (i.e., frequency, EDSS, duration) induced improvement in motor and non-motor symptoms.

Materials and methods

This systematic review and meta-analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and by use of applying research protocol (Moher et al., 2009).

Search strategy

Data were collected from PubMed, Embase, the Cochrane Library, Web of Science, Physiotherapy Evidence Database, Scopus, Google Search Engine, and the China National Knowledge Infrastructure (CNKI). These databases were searched systematically from inception to December 2021. In addition, reference lists of identified studies were also screened to identify additional relevant articles. The keywords were entered using a standard search and included "whole-body vibration," "WBV," "vibration," "focal vibration," "focal vibration therapy," "focal muscle vibration," "localized vibration," "FVT," "FMV," and "multiple sclerosis." There was no restriction on language. Two reviewers initially evaluated the obtained studies by reading the title and abstract to exclude studies that did not meet the criteria. They then read the full text to determine eligibility. The detailed search strategy is described in Appendix 1 in Supplementary material.

Inclusion and exclusion criteria

Studies were selected based on the following inclusion criteria: (1) Study design: Randomized controlled trials (RCTs); (2) Patients: patients diagnosed with MS, without age or level of disability restrictions; (3) Intervention: vibration therapy, WBV or FMV; (4) Control: placebo, sham treatment, exercise alone or conventional rehabilitation; (5) Outcomes: at least one outcome related to either motor and non-motor performance was provided. The motor performance index includes Timed Up and Go (TUG), Berg Balance Scale (BBS), 6-minute walk test (6MWT), 2-minute walk test (2MWT); 3MWT: 3-minute walk test (3MWT), 10-m walk test (10MWT), and Timed 25-foot Walk (T25FW). The TUG is an excellent tool used to assess mobility capabilities in MS, with good reliability (ICC = 0.98) (Kalron et al., 2017; Valet et al., 2019). The minimal detectable change (MDC95) was 1.3 s (Valet et al., 2019). The BBS has been confirmed, test-retest and inter-rater reliability were excellent in MS (ICC > 0.95) (Cattaneo et al., 2007), and there is strong first-level evidence to support its use to assess changes in static and dynamic sitting balance (Moore et al., 2018; Mehta et al., 2019).

The 6MWT and 2MWT have high reliability (ICC: 0.95–0.99) in persons with MS and are responsive to changes in deteriorating status in persons with MS (Fry and Pfalzer, 2006; Bennett et al., 2017). The 10MWT and 25FWT provide a performance-based measure of walking dysfunction based on walking speed over a short distance, with greater disability of MS with a very high correlation (0.96–0.97) (Kieseier and Pozzilli, 2012). The non-motor performance index includes the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Quality of Life-54 (MSQOL-54), and Multiple Sclerosis Impact Scale (MSIS-29). The FSS and MFIS can be regarded as feasible measures of self-reported fatigue in MS. The data quality of the FSS was excellent, with 99.6% of computable scale scores and floor and ceiling effects were minimal (Rosti-Otajarvi et al., 2017). The reported internal consistency of all the MFIS scores was "excellent," with the following Cronbach α values: total, 0.81; cognitive, 0.95; physical, 0.91; and psychosocial, 0.81 and a change in score of 10 or more to be clinically relevant (Kos et al., 2007). The MSQOL-54 is a structured, self-report questionnaire that the patient can generally complete with little or no assistance with the alpha coefficient calculated for the whole instrument was 0.84 (Heiskanen et al., 2007).

The MSIS-29 is a new patient-based rating scale for multiple sclerosis (MS) that was predominantly developed from a community-based sample derived from the MS Society. Floor and ceiling effects were small and were considerably less than the recommended maximum of 15% (Riazi et al., 2002). The lowest score was 3.8 and the Cronbach's α exceeded the standard criteria of 0.80 (Riazi et al., 2002).

Exclusion criteria were as follows: (1) retrospective studies, animal studies, single-case reports, protocols, reviews, meta-analyses, poster presentations, or conference abstracts; (2) study objective or intervention measures failed to meet the inclusion criteria; (3) duplicate or multiple publications of the same study; and (4) studies without usable data.

Data extraction

The abstracts of retrieved studies were independently reviewed by two authors (YD and PX), and full articles were examined when necessary. The data were extracted independently by these two authors, and any disagreements were resolved by discussion with at least one more author until a consensus was reached. If more than one article was published from the same cohort, the study with the most comprehensive data was selected for inclusion. The following information was extracted from all qualifying articles: general information (name of the first author, publication year, the region where the population resided, study type, sample size, mean ages, sex), EDSS, interventions characteristics (frequency, amplitude, duration, device) and outcomes (as defined above).

Assessment of risk of bias of included studies

The risk of bias in included trials was evaluated by two reviewers (MW and WXD) using the Cochrane Risk of Bias Tool, and another author (JCC) resolved any disagreement. The tool consists of seven elements: (1) random sequence generation; (2) allocation concealment; (3) blinding of participant and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. Every section had a high risk of bias, low risk of bias, and unclear risk of bias depending on the actual content of the included study (Higgins et al., 2022). Each of these factors was classified as high risk, low risk, or unclear risk.

Statistical analysis

The extracted data were statistically analyzed using Review Manager software 5.3 (Cochrane Collaboration, Oxford, United Kingdom). For all the outcome measures we used, that were continuous variables, the mean difference (MD) or standardized mean difference (SMD) with a 95% confidence interval (CI) was determined. The SMD and standard error (SE) for each outcome before and after treatment were determined by Morris' formula (Morris, 2007). If the data were reported as mean and 95% CI, SD was calculated by Rev Man software. If the data were reported as the median interquartile range (IQR), we calculated the mean and standard deviation utilizing the Wan and Luo formulae (Wan et al., 2014; Luo et al., 2018). The SMD statistic was selected to evaluate the results of different scales. Cochran's Q test and Higgins I^2 statistic were used to measure the heterogeneity of the included studies and to choose the effect model. If $I^2 < 50\%$ and $P > 0.05$, the included studies were considered homogeneous, and a fixed-effects model was selected. Otherwise, if $I^2 > 50\%$ and $P < 0.05$, indicating that statistical heterogeneity existed among studies, a random-effects model was selected. In this meta-analysis, $P < 0.05$ was defined as statistically significant for all tests.

If clinical heterogeneity was present in the combined results, a subgroup analysis was performed to identify the source of heterogeneity. Meanwhile, we conducted subgroup analyses to explore the effect of different categories of vibration therapy. For the motor symptoms, subgroup analyses were performed for the EDSS scores, frequency, and duration.

We also performed a sensitivity analysis by sequentially eliminating each study to test the stability of the results. Before calculating the effect size, we deleted each of the included studies and excluded those that resulted in high heterogeneity or altered the pooled effect of the results (Jin et al., 2019). For the functional mobility and balance function, we used funnel plots and Egger's test to evaluate the publication bias of the included studies.

Results

Study identification and selection

Utilizing the search strategy, a total of 955 relevant records were initially identified from the eight electronic databases. After excluding duplicates and irrelevant studies by screening titles and abstracts, 541 records were excluded. After reading the full text to identify available data, 21 were excluded. Finally, we included 14 studies (Schuhfried et al., 2005; Schyns et al., 2009; Broekmans et al., 2010; Alguacil Diego et al., 2012; Claerbout et al., 2012; Hilgers et al., 2013; Paoloni et al., 2013; Uszynski et al., 2014, 2016; Wolfsegger et al., 2014; Ebrahimi et al., 2015; Spina et al., 2016; Freitas et al., 2018; Ayvat et al., 2021) that met the criteria for data extraction and meta-analysis. The PRISMA flow diagram of identification and selection is shown in Figure 1.

Study characteristics

The characteristics of the included studies are summarized in Table 1. A total of 14 RCTs involving 393 participants (146 males and 247 females, mean age ranged from 33.86 to 54 years) were included in the review.

The studies were published between 2005 and 2021, four (28.57%) studies were published after 2015. The countries of the publications were the Austria ($n = 2$,14.29%), Belgium ($n = 2$, 14.29%), Iran ($n = 1$, 7.14%), Italy ($n = 2$, 14.29%), Ireland ($n = 2$,14.29%), Germany ($n = 1$, 7.14%), Spain ($n = 1$, 7.14%), Britain ($n = 1$, 7.14%), United States ($n = 1$, 7.14%), and Turkey ($n = 1$, 7.14%).

The mean score of the EDSS in included studies ranged from 2.4 to 5.50. The intervention investigated in the trials included WBV ($n = 11$, 78.57%) and FMV ($n = 3$, 21.43%). The duration of the intervention in the included studies ranged from 5 days to 20 weeks. The vibration frequency of VB in the included studies ranged from 2 to 100 Hz. Twelve (85.71%) studies mentioned treatment frequency which three times weekly ($n = 7$, 50%), five times weekly ($n = 1$, 7.14%), one time weekly ($n = 1$, 7.14%), 5 consecutive days ($n = 1$, 7.14%), 5 training sessions per 2 week cycle ($n = 1$,7.14%), and 10 sessions of over a period of 3 weeks ($n = 1$,7.14%). Four (28.57%) of the control groups were treated with routine excise alone, 5 (35.71%) with placebo, 3 (21.42%) with no intervention, 1 (7.14%) with conventional therapy (multi-disciplinary), and 1 (7.14%) with botulinum toxin.

Ten (71.43%) trials selected the TUG to functional mobility. Seven (50%) trials used the BBS to assess balance. Six trials used the 6MWT ($n = 4$, 28.57%), the 2MWT ($n = 1$, 7.14%), or the 3MWT ($n = 1$) (7.14%) to assess walking endurance. Six trials used the 10MWT ($n = 4$, 28.57%) or the T25FW ($n = 2$, 14.29%) to assess gait speed. Five trials used the FSS (n

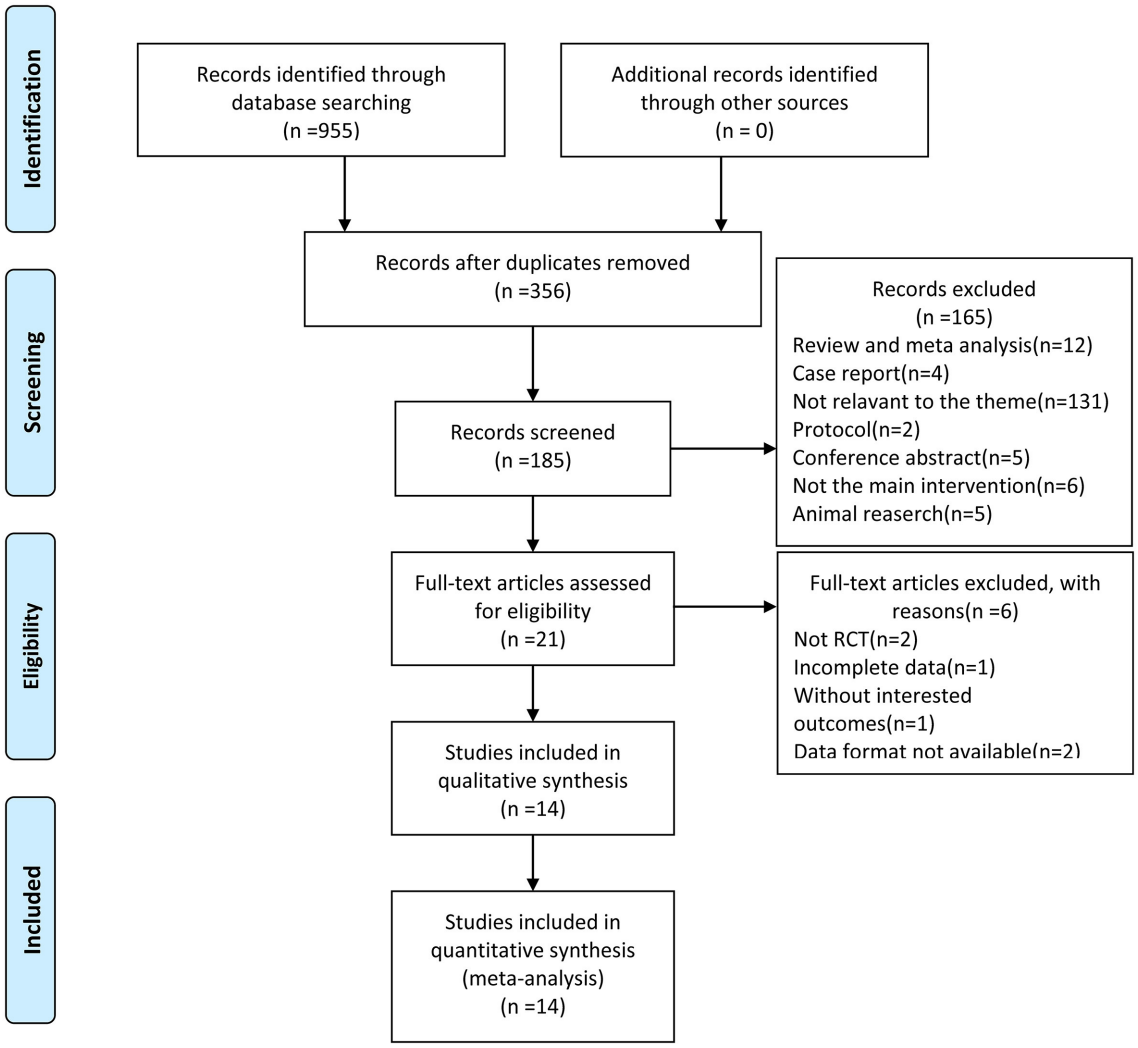


FIGURE 1
Flow of the trial selection process.

= 2, 14.29%) or the MFIS (n = 3, 21.43%) to assess fatigue. Three trials used the MSQOL-54 (n = 1, 7.14%) or the MSIS-29 (n = 2, 14.29%) to assess the health-related quality of life (HRQoL).

Risk of bias assessment

The risk of bias assessment of the included studies is presented in Figures 2, 3. All of the included articles reported randomized group allocation, twelve studies (85.71%) reported the methods of random sequence generation, three studies (21.43%) used computer-generated random numbers, four studies (28.57%) used a random number table, three (21.43%) used envelope to allocate, one study (7.14%) used block randomization, and one study (7.14%) used gender randomization. Eight studies (57.14%) reported the use of allocation concealment. All of the included studies demonstrated a high risk of performance bias, as participants and personnel were not blind to the intervention. Only one study (7.14%) succeeded in blinding the participants and personnel. Elven studies (78.57%) were assessed as having a low risk of bias considering the blinding of assessors. Thirteen studies (92.86%) reported a low risk of attrition bias. Regarding reporting bias, we judged that all the studies reported the expected results. The risk of other bias in the included studies was judged as "unclear" due to insufficient information to judge whether there is a significant risk of bias, even if the sample size and follow-up time limitations are described.

TABLE 1 The characteristics of the included studies.

References, country	Mean age, year	Duration of disease, year	EDSS	NO. T/C	Sex, M/F	Intervention group	Control group	Vibration amplitude	Vibration frequency	Duration	Times	Outcome assessments	Devices
Alguacil Diego et al. (2012), Spain	T:43 (17) C:44 (20)	None	T:3.99 (0.80) C:4.58 (0.36)	17/15	16/16	WBV	None	3 mm	6 hz	5 days	5 consecutive days	BBS, TUG, 10MWT	Zeptoring® vibrating platform
Ayvat et al. (2021), Turkey	T1:37.7 (9.7) T2:38.4 (11.07) C:33.86 (6.74)	T1:11.3 (6.43) T2:7 (4.74) C:10.58 (7.03)	T1:3 (1.08) T2:2.75 (1) C:3 (0.81)	11/11/11	10/23	T1:FMV (50Hz) + exercise T2:FMV (100Hz)+ exercise	Exercise	None	50 hz, 100 hz	8 weeks	3 times/week	FSS	Vibrasens©
Broekmans et al. (2010), Belgium	T:46.1 (6.96) C:49.7 (12.35)	None	T:4.5 (1.32) C:4.1 (1.12)	11/14	18/7	WBV	None	2.5 mm	25–45 hz	20 weeks	5 training sessions per 2 week cycle	BBS, TUG, 2MWT, T25FW	Alpha Vibe® Nijverdal
Claerbout et al. (2012), Belgium	Tf:67.2 (14.3) Tl:43.8 (12.6) C:47.6 (8.3)	T1:12.1 (9.2) T2:12.5 (9.1) C:10.3 (8.4)	T1:5.3 (1.3) T2:5.1 (1.2) C:5.2 (1.1)	20/28/17	34/21	T1: WBV (standing on a standard mat of 2 cm thickness) + conventional therapy T2: WBV (standing on a standard mat of 10 cm thickness) + conventional therapy	Conventional therapy	1.6 mm	30–40 hz	3 weeks	10 sessions over a period of 3 weeks	BBS, TUG, 3MWT	Fysiomed NV-SA
Ebrahimi et al. (2015), Iran	T:37.06 (8.42) C:40.75 (10.56)	T:6.5 (4.17) C:10.5 (6.4)	T:3.12 (1.19) C:3.10 (0.76)	16/14	7/23	WBV	None	2 mm	2–20 hz	10 weeks	3 times/week	MFIS, BBS, 10MWT, TUG, 6MWT, MSQOL-54	None
Freitas et al. (2018), United States	46.6 (9.6)	None	None	12/9	0/21	WBV	Placebo	3 mm	30 hz	1 week	1 time/week	BBS, TUG	PowerPlate; Next Generation, Northbrook, Illinois
Hilgers et al. (2013), Germany	T:43.5 (10) C:43.9 (7.5)	None	T:3.5 (1.2) C:3.3 (1.3)	30/30	15/45	WBV	Placebo	1-2mm	30 hz	3 weeks	3 times/week	TUG, 6MWT, 10MWT	Power Plate pro

(Continued)

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TABLE 1 Continued

References, country	Mean age, year	Duration of disease, year	EDSS	NO. T/C	Sex, M/F	Intervention group	Control group	Vibration amplitude	Vibration frequency	Duration	Times	Outcome assessments	Devices
Paoloni et al. (2013), Italy	T:47.4 (5.6) C:50.6 (8.9)	None	T:4.74 (1.48) C:5.50 (1.48)	14/14	9/19	FMV and BTX	BTX	None	120 hz	4 weeks	3 times/week	FSS	Horus
Schuhfried et al. (2005), Austria	T:49.3 (13.3) C:46 (12.7)	None	T:3.9 (0.8) C:3.7 (0.8)	6/6	3/ 9	WBV	Placebo	3mm	2.0-4.4 hz	2 weeks	None	TUG	Zeptor-Med system
Schyns et al. (2009), Britain	T:45.8 (8.4) C:49.5 (6.14)	T:6.7 (5.54) C:11.8 (3.62)	None	8/8	4/12	WBV + exercise	Exercise	2mm	40hz	4 weeks	3 times/week	TUG,10 MWT, MSIS-29	VibroGym International BV
Spina et al. (2016), Italy	T:47 (12.7) C:48 (12.34)	T:7.55 (5.76) C:6.4 (8.88)	T:3.88 (1.31) C:3.7 (1.13)	10/10	8/12	FMV	Placebo	None	None	3 weeks	5 times/week	BBS, T25FW, FSS	Equistasi® devices
Uszynski et al. (2014), Ireland	T:44.4 (10.4) C:52.7 (10.5)	None	None	8/9	3/14	WBV + exercise	Exercise	None	40 hz	8 weeks	3 times/week	MFIS, BBS, TUG, 6MWT, MSIS-29	Crazy Fit 1000 W 70 Speed Vibroplate
Uszynski et al. (2016), Ireland	T:45.5 (10.22) C:54 (12.22)	None	None	14/13	4/ 23	WBV + exercise	Exercise	None	40 hz	12 weeks	3 times/week	MFIS-29, 6MWT	Crazy Fit 1000W 70 Speed Vibroplate
Wolfsegger et al. (2014), Austria	T:43 (13.4) C:39.3 (10.6)	None	T:2.5 (1.0) C:2.4 (0.8)	9/8	15/2	WBV	Placebo	None	2.5–5.0 hz	3 weeks	None	TUG	Zeptor-Med system

WBV, whole-body vibration; FMV, focal muscle vibration; TUG, Timed Up and Go; BBS, Berg Balance Scale; 6MWT, 6-minute walk test; 2MWT, 2-minute walk test; 3MWT, 3-minute walk test; 10MWT, 10-m walk test; T25FW, Timed 25-foot Walk; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MSQOL-54, Multiple Sclerosis Quality of Life-54; MSIS-29, Multiple Sclerosis Impact Scale.

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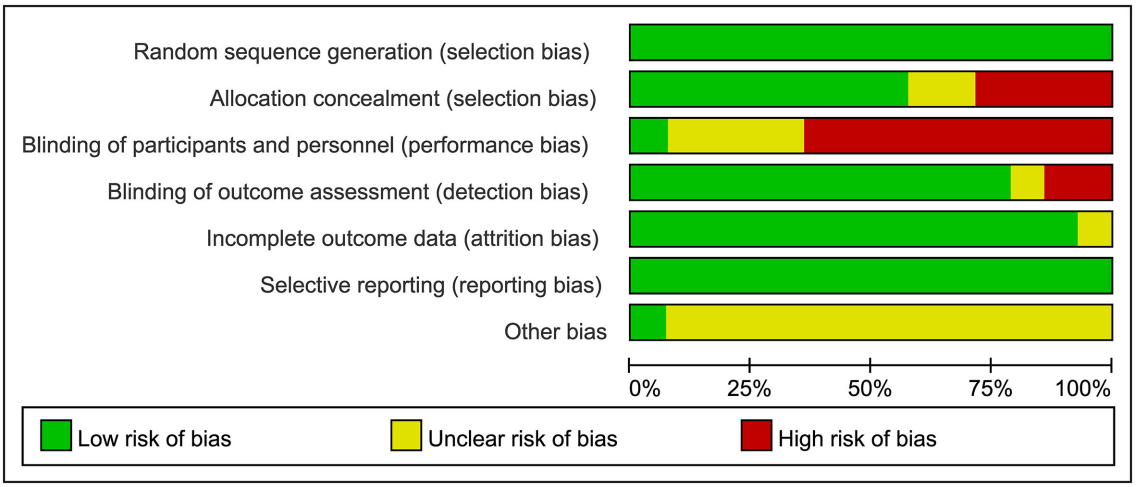


FIGURE 2
Risk of bias graph review authors' judgements about each risk of bias item presented as percentages across all included studies.

Effects of the intervention

Motor impairments outcomes assessment

Functional mobility

Ten studies with 290 patients using TUG as the measurement were included in the meta-analysis to evaluate functional mobility. Ten studies examined the effects of WBV interventions on TUGT. A fixed-effects model was used, as low heterogeneity existed ($P = 0.52$, $I^2 = 0\%$). The combined results demonstrated that WBV had no significant advantage over the control group in improving functional mobility (MD: −0.39, 95% CI: −0.93 to 0.16, $P = 0.16$) (Figure 4A).

Taking into account whether the vibration exposure parameters and degree of disability affect functional mobility, subgroup analyses were performed based on EDSS, duration of the intervention, and frequency.

Subgroup analysis based on the degree of disability: only one study did not report an EDSS score, and the rest of the studies reported an EDSS score between 0-6.5. We classified the EDSS into 0–3.5, 3.5–6, and unreported. No significant differences were observed among the subgroups ($P = 0.99$, $I^2 = 0\%$). The EDSS score (0–3.5) showed no improvement in TUG (MD: 0.25, 95% CI: −0.64 to 1.15, $P = 0.58$) (Figure 4B). However, the EDSS score (3.5–6) of MS in three articles resulted in a significant difference in improving functional mobility compared with the control group (MD: −1.20, 95% CI: −2.09 to −0.31, $P = 0.008$).

Subgroup analysis based on vibration frequency: the vibration frequency of the nine studies ranged from 2 to 45 Hz and was classified into low frequency (<20 Hz) and high frequency (≥20 Hz). No significant differences were observed among the subgroups ($P = 0.48$, $I^2 = 0\%$). The subgroup analysis revealed that both the low frequency (MD: −0.59, 95% CI: −1.39–0.20, $P = 0.14$) and high frequency had no significant advantage over the control group in improving functional mobility (MD: −0.21, 95% CI: −0.95–0.53, $P = 0.59$) (Figure 4C).

Subgroup analysis based on different durations of the intervention: the intervention period of nine studies ranged from 5 days to 20 weeks. We classified the duration of the intervention into 0–4, 4–8, and >8 weeks. No significant differences were observed among the subgroups ($P = 0.96$, $I^2 = 0\%$). The subgroup analysis revealed that none of the three subgroups improved significantly in the WBV group compared to the control (MD: −0.35, 95% CI: −0.95 to 0.25, $P = 0.25$, $0 < \text{duration} < 4$; MD: −0.52, 95% CI: −1.92 to 0.88, $P = 0.47$, $4 \leq \text{duration} \leq 8$; MD: −0.71, 95% CI: −4.21 to 2.80, $P = 0.69$, duration > 8) (Figure 4D).

Sensitivity analysis

To assess the robustness of the results, we performed sensitivity analyses by eliminating each study and rerunning the analysis, the result of sensitivity analyses found that the combined results were stable and not affected by a single dataset (Supplementary Figure 1).

Balance

Seven studies with 208 patients using BBS as the measurement were included in the meta-analysis to evaluate balance. Six studies examined the effects of WBV interventions on BBS scores, and only one study examined the effects of FV interventions. A fixed-effects model was used, as low heterogeneity existed ($P = 0.59$, $I^2 = 0\%$). The combined results demonstrated that these two types of vibration therapy had a significant advantage over the control group in improving balance function (MD: 2.04, 95% CI: 0.24–3.84, $P = 0.03$) (Figure 5). Six studies examining WBV showed advantages in BBS scores compared with the control group (MD: 2.20,

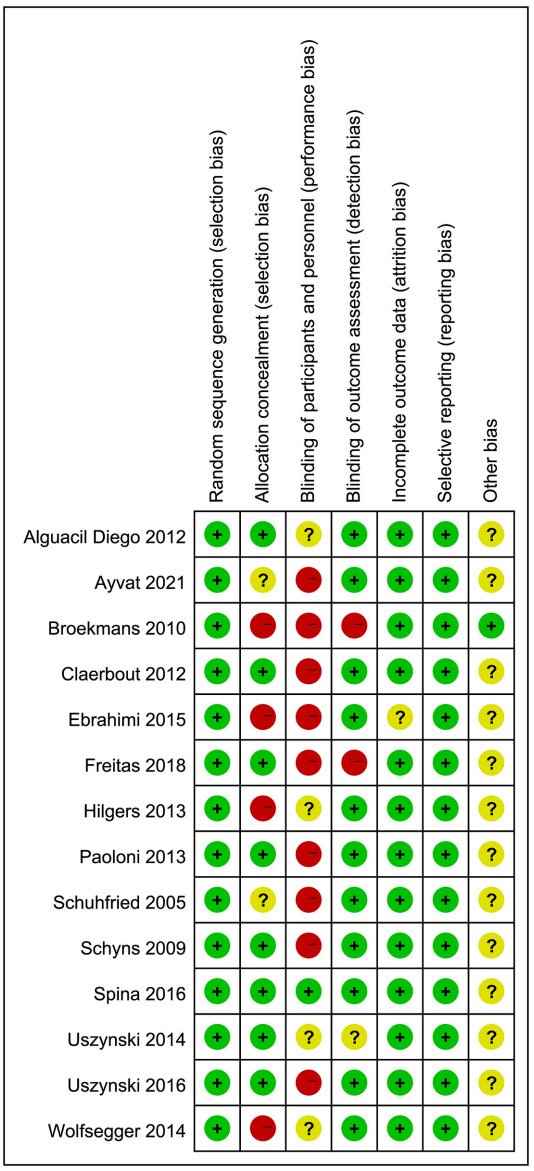


FIGURE 3
Risk of bias summary review authors' judgements about each risk of bias item for each included study.

95% CI: 0.33–4.07, $P = 0.02$) (Figure 5). However, only one study examining FMV did not show a significant difference in improving balance function (MD: 0.04, 95% CI: −6.65 to 6.73, $P = 0.99$) (Figure 5). We also performed subgroup analyses of BBS based on the degree of disability, duration of the intervention, and frequency. No significant differences were observed among the subgroups ($P = 0.37$, $I^2 = 0\%$, EDSS; $P = 0.80$, $I^2 = 0\%$, duration; $P = 0.62$, $I^2 = 0\%$, frequency). The subgroup analysis only indicated that the WBV group was more sensitive to improving BBS scores than the control group when the EDSS scores ranged from 3.5 to 6 (MD: 3.04, 95% CI: 0.49–5.59, $P = 0.02$) (Figure 6). Other subgroup analysis results were not significant (Supplementary Figures 2, 3).

Walking endurance

Six studies with 216 patients used 6MWT, 2MWT, or 3MWT to assess the walking endurance. We calculated the SMD to eliminate the difference. All studies examined the effects of WBV interventions on walking endurance. A fixed-effect model was used since no heterogeneity existed ($P = 0.8$, $I^2 = 0\%$). The pooled result showed that WBV had a significant effect on improving the walking endurance with MS (SMD: 0.34, 95% CI: 0.07–0.61, $P = 0.01$) (Figure 7). We performed subgroup analyses of walking endurance based on the degree of disability (0–3.5; 3.5–6; unreported) and durations of the intervention (<4 weeks; ≥4 weeks). No significant differences were observed among the subgroups ($P = 0.43$, $I^2 = 0\%$, EDSS; $P = 0.45$, $I^2 = 0\%$, duration). The subgroup analysis indicated that the WBV group was more sensitive to improving walking endurance than the control group when the EDSS score ranged from 0 to 3.5 (SMD: 0.55, 95% CI: 0.13–0.98, $P = 0.01$) (Figure 8) and the duration of the intervention was less than 4 weeks (SMD: 0.46, 95% CI: 0.04–0.87, $P = 0.03$) (Figure 9). Other subgroup analysis results were not significant (Supplementary Figure 4).

Gait speed

Six included RCTs with 184 patients used 10 mWT or 25FWT to assess the gait speed. We calculated the SMD to eliminate the difference. One study examined the effects of FV interventions on gait speed, other studies examined the effects of WBV interventions. A fixed-effect model was used since no heterogeneity existed ($P = 0.96$, $I^2 = 0\%$). The combined results demonstrated that these two types of vibration therapy had no significant advantage over the control group in improving gait speed (SMD: −0.21, 95% CI: −0.50 to 0.08, $P = 0.15$) (Figure 10). We performed subgroup analyses of gait speed based on the degree of disability (0–3.5; 3.5–6), frequency (<20 Hz, ≥20 Hz), and duration of the intervention (<4 weeks; ≥4 weeks). No significant differences were observed among the subgroups ($P = 0.44$, $I^2 = 0\%$, EDSS; $P = 0.43$, $I^2 = 0\%$, frequency; $P = 0.70$, $I^2 = 0\%$, duration). All subgroup analysis results were not significant (Supplementary Figures 5–7).

Non-motor impairments outcomes assessment

Fatigue

Two studies with 45 patients selected FSS as an outcome measure to assess the fatigue, and this meta-analysis found a non-significant pooled effect size (SMD: −0.15; 95% CI:−0.73–0.42, $P = 0.60$; $I^2 = 0\%$) (Figure 11). Three studies with 69 patients used the MFIS to assess the fatigue, and this meta-analysis showed a non-significant pooled effect size (SMD:0.02; 95% CI:−0.46–0.50, $P = 0.93$; $I^2 = 0\%$) (Figure 11). One study with two frequencies of intervention used VAS to assess the fatigue, and this meta-analysis showed a non-significant pooled effect size (SMD:0.00; 95% CI:−0.68-0.68, P=1; $I^2 = 0\%$) (Figure 11).

Health-related quality of life

The health-related quality of life consists of physical and mental components. One study selected MSQOL-54 and two studies used MSIS-29 as an outcome measure. The results demonstrated that vibration therapy had no significant advantage over the control group in improving physical and mental health (Supplementary Figures 8, 9).

Publication bias

Publication bias assessments are presented based on funnel plots and Egger's test. From the roughly symmetrical shapes of these funnel plots and Egger's test result, no significant publication bias was observed in studies evaluating functional mobility and balance (Supplementary Figures 10, 11; Supplementary Tables 1, 2).

Discussion

Multiple sclerosis is a chronic neuroinflammatory disease, which has an early disease onset, a progressive course, and a very long duration with a median survival time of about 40 years from diagnosis (Weinshenker, 1994; Kesselring and

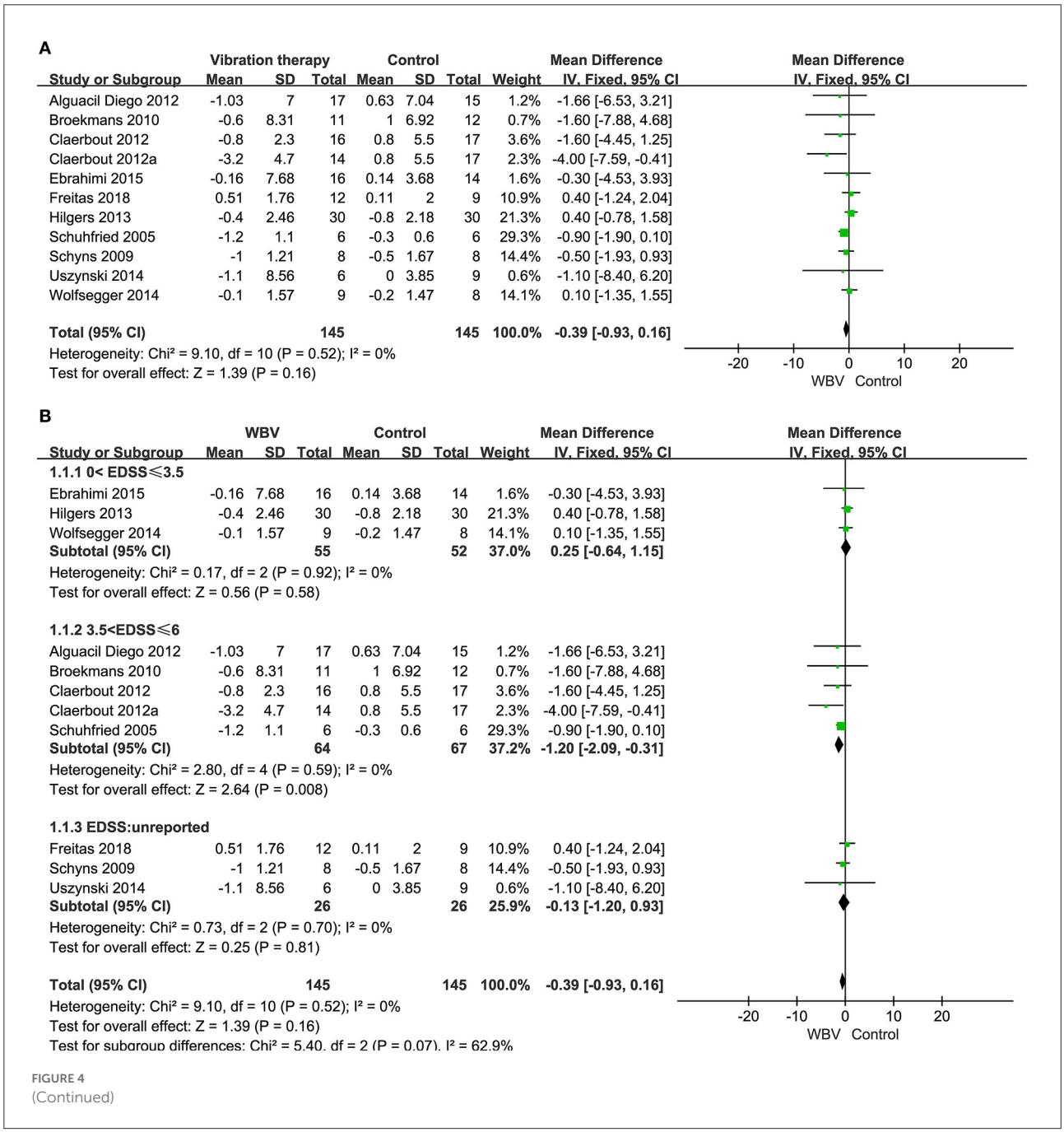


FIGURE 4
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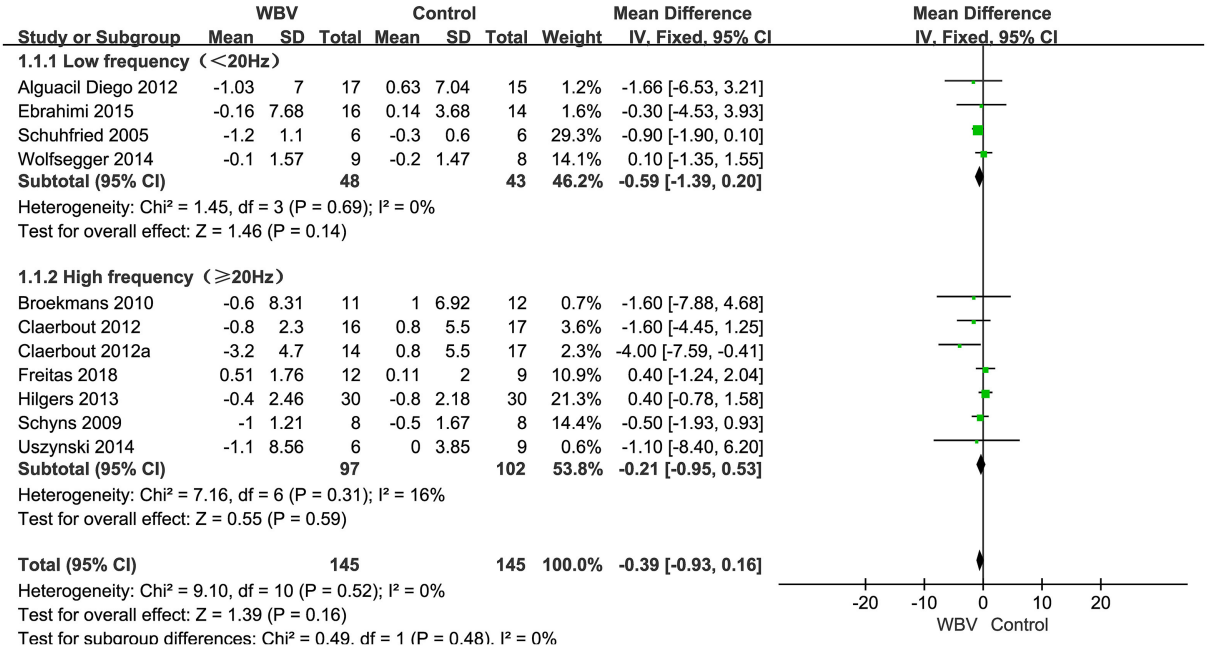


FIGURE 4
(A) Forest plot showing the effects of WBV on functional mobility. **(B)** Forest plot showing the effects of WBV on functional mobility in subgroups stratified according to the EDSS score. **(C)** Forest plot showing the effects of WBV on functional mobility in subgroups stratified according to the frequency. **(D)** Forest plot showing the effects of WBV on functional mobility in subgroups stratified according to the different durations of the intervention.

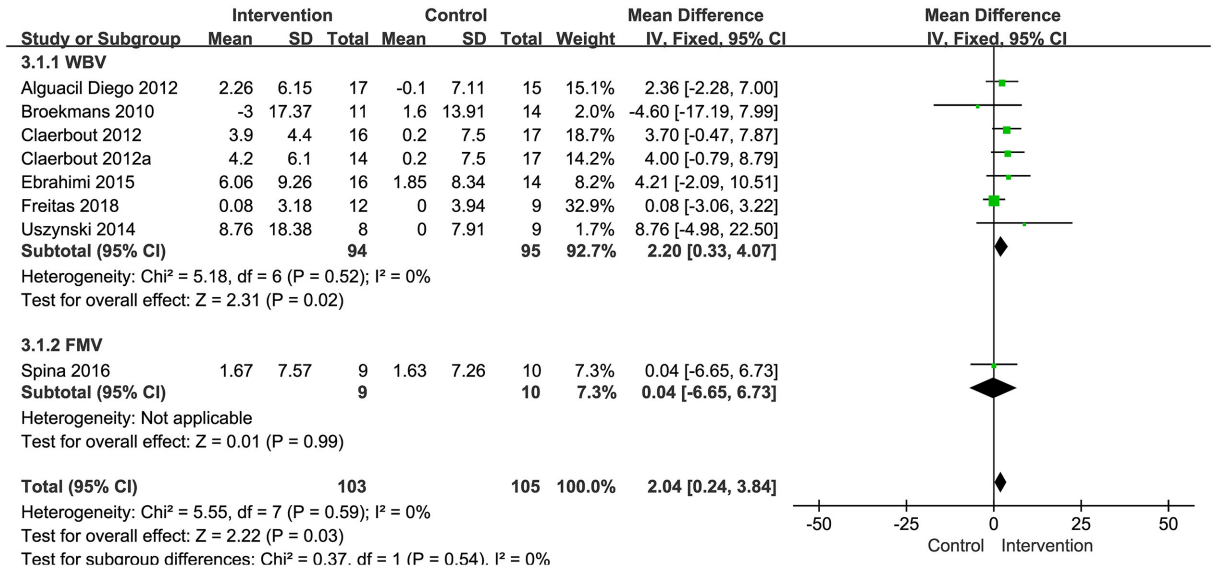


FIGURE 5
Forest plot showing the effects of vibration therapy on balance.

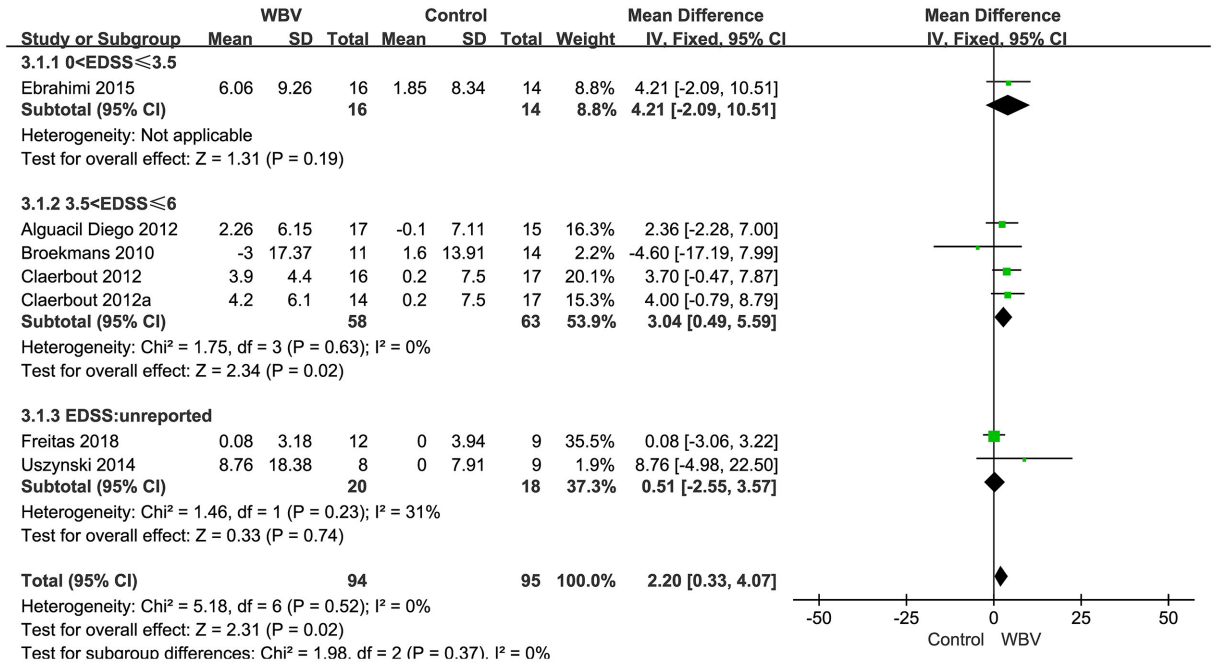


FIGURE 6
Forest plot showing the effects of WBV on balance in subgroups stratified according to the EDSS score.

Beer, 2005). Multiple symptoms can appear with fatigue and walking disability is reported to be among the most debilitating (Zhang et al., 2021). The natural history study found that around 50% use walking aids, 29% need a wheelchair, and 50–80% become unable to work (Weinshenker, 1994). Therefore, reducing the progression of disability is of interest.

Rehabilitation can be a beneficial treatment strategy for people with MS to ease the burden of these symptoms by managing symptoms, restoring function, optimizing the quality

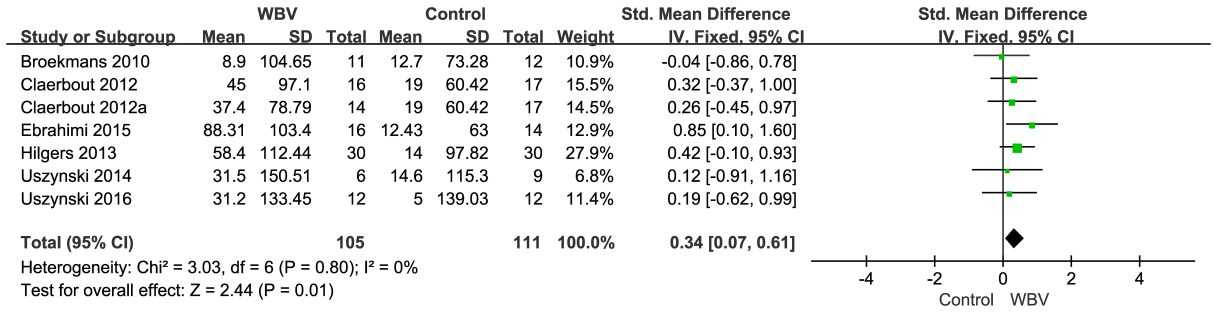


FIGURE 7
Forest plot showing the effects of WBV on walking endurance.

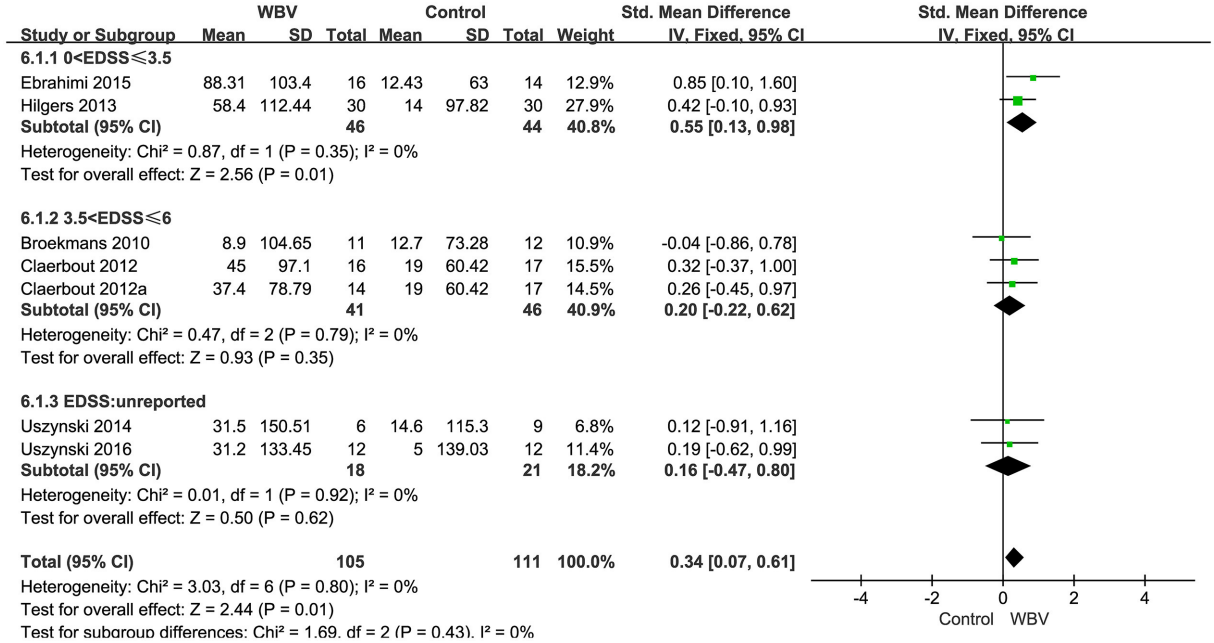


FIGURE 8
Forest plot showing the effects of WBV on walking endurance in subgroups stratified according to the EDSS score.

of life, promoting wellness, and boosting participation in activities of daily living (Kesselring and Beer, 2005; Khan and Amatya, 2017; Motl et al., 2017). This systematic review and meta-analysis sought to evaluate the relationship between vibration therapy in patients with MS. We performed a meta-analysis of 14 RCTs with 393 participants. The results demonstrate that vibration therapy has a positive effect on improving balance function and walking endurance. In addition, the subgroup analysis results showed that WBV might be more sensitive to improving functional mobility, balance, and walking endurance when the EDSS scores ranged from 3.5 to 6. We also concluded that WBV with a duration of <4 weeks potentially improved walking endurance. However, some subgroup analyses were performed only including a few articles, so the results need to be treated with caution. Certainly, We did not find any other meta-analysis that discussed the effect of EDSS, duration of the intervention, and frequency of vibration on improving motor symptoms in patients with MS. Our findings might add new insights to the current literature.

Concerning the possible mechanisms as regard to the overall results of our study. We speculate that neurogenic adaptations and post-activation potentiation mechanisms might explain the balance function and walking endurance after vibration therapy (Bazett-Jones et al., 2008; Rittweger, 2010). Vibration therapy improves balance through activating the Ia and II afferents of muscle groups and inducing sensory stimulation of foot-sole

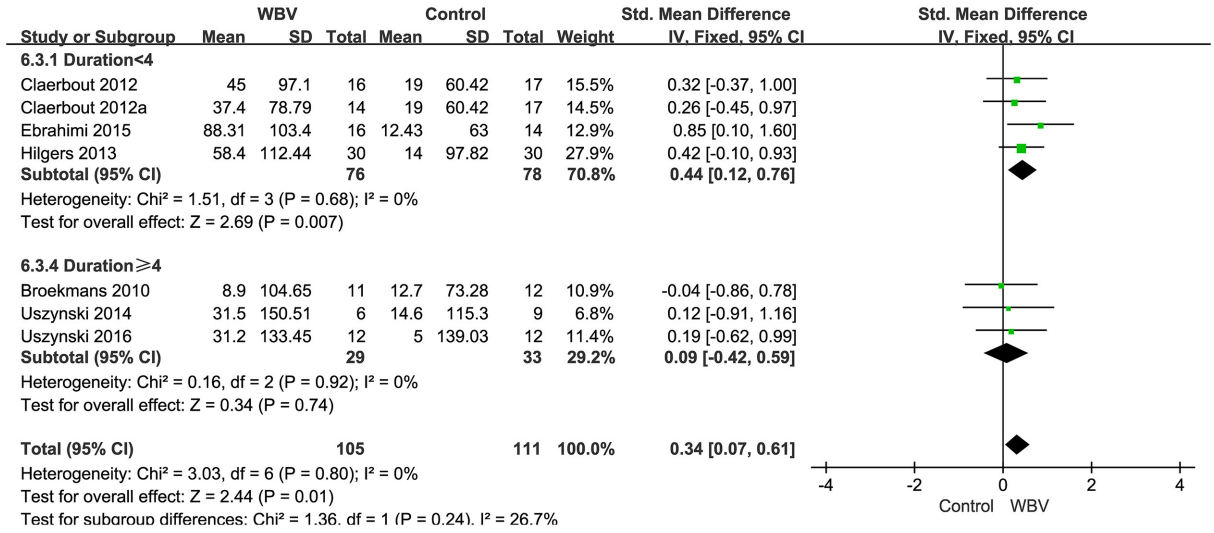


FIGURE 9
Forest plot showing the effects of WBV on walking endurance in subgroups stratified according to the different durations of the intervention.

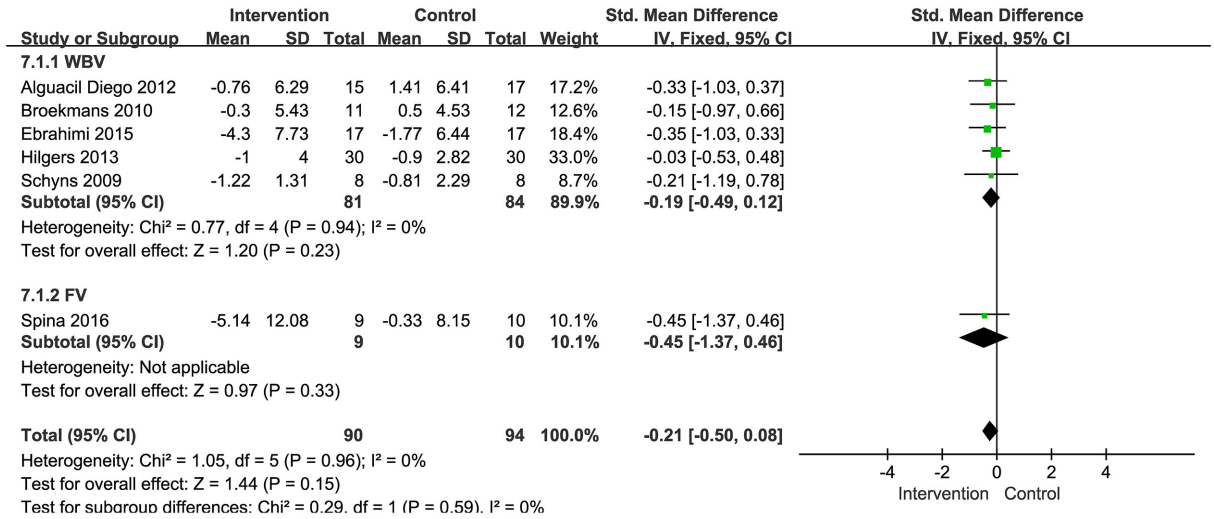


FIGURE 10
Forest plot showing the effects of vibration therapy on gait speed.

afferents, increasing the sensitivity of muscle mechanoreceptors (i.e. Golgi tendon organs and muscle spindle) and changing joint stiffness (Kavounoudias et al., 1999; Fontana et al., 2005; Siu et al., 2010; Ritzmann et al., 2014; Abdel-Aal et al., 2021).

In addition, the improvement in walking endurance after vibration is attributed to enhanced capacity for transporting and utilizing oxygen in the muscle (e.g. increased blood flow to the active skeletal muscle) (Bogaerts et al., 2009; Games et al., 2015; Betik et al., 2021), improvements in skeletal muscle function and morphology (e.g. hypertrophy, increase in capillary density) and increase VO_{2peak} (Aoyama et al., 2019).

Reduced mobility is probably the commonest impairment compromising daily living activities of subjects affected by MS with moderate to severe walking disability (Gijbels et al., 2010; Gianni et al., 2014). In our study, the outcome of the TUG test measurements is described as functional mobility-a formulation of combining balance, gait, and mobility, which is an excellent tool used to assess mobility capabilities in MS, monitor disease progression, and identify potential MS fallers (Kalron et al., 2017). Our results demonstrated that

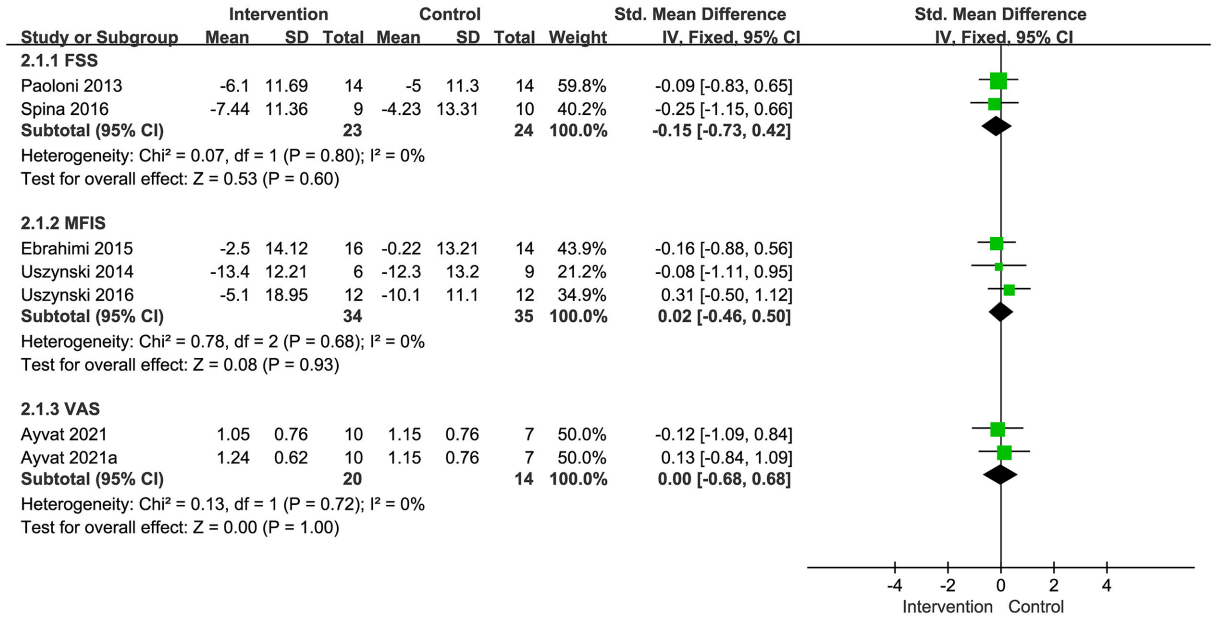


FIGURE 11
Forest plot showing the effects of vibration therapy on fatigue.

vibration therapy was not a significant improvement for functional mobility similar to other studies (Schyns et al., 2009; Broekmans et al., 2010; Uszynski et al., 2014; Wolfsegger et al., 2014; Ebrahimi et al., 2015; Freitas et al., 2018; Alam et al., 2020). The results were persistent and stable when sensitivity analyses were conducted. On the other hand, the whole-body vibration exercise also did not improve functional mobility in a randomized, multi-center, parallel, clinical study in older people (Sitja-Rabert et al., 2015), which is consistent with our results. However, from an intervention perspective, these findings may be related to significant differences between patients, interventions (e.g. frequency, duration, equipment, etc.), and control (e.g. exercise alone and placebo). Thus, we did subgroup analysis based on EDSS scores, duration of the intervention, and frequency. The results showed that the effect of WBV was superior to the conventional therapy paradigm with the EDSS score ranging 3.5 from to 6, but the duration and frequency did not show an ideal effect on functional mobility. One hypothesis may be that EDSS may affect the effectiveness of therapy (Haselkorn et al., 2015). The mild disability (EDSS $\leq$3.5) may already have been performing at their individual maximal physical activity level with less potential to improve (Claerbout et al., 2012). Meanwhile, the transfers on/off the floor and into/out of chairs are increasingly challenging with moderate to severe disability (EDSS, range, 3.5-6) (Kalb et al., 2020), which have great potential for improvement.

Balance impairment is one of the most disabling symptoms in people with MS that affects about 50–80% of patients during the disease (Molhemi et al., 2021). These impairments have recently been proposed as a key mechanism of frequent falls in MS with more than 50% of MS reporting one fall or more over a 3 to 12-month period (Mohamed Suhaimy et al., 2020). In our study, we used BBS to evaluate the balance with MS. The BBS has been confirmed, test-retest and inter-rater reliability were excellent in MS (Cattaneo et al., 2007), and there is strong first-level evidence to support its use to assess changes in static and dynamic sitting balance (Moore et al., 2018; Mehta et al., 2019). Many studies have shown that vibration therapy can improve the balance function of MS (Uszynski et al., 2014; Ebrahimi et al., 2015). A meta-analysis of four RCT studies by Alam et al. (2020) showed significant improvement with WBV intervention to improve balance, which is consistent with the findings of our study. Another meta-analysis of the effects of WBV did not significantly raise the BBS score for patients with MS, but the included studies of that review are not rigorous and the sample size is small, Our study has better homogeneity and stronger conclusions. In addition, the results demonstrated no significant changes in BBS (Broekmans et al., 2010; Alguacil Diego et al., 2012; Freitas et al., 2018), and found a significant improvement within the WBV group only (Claerbout et al., 2012; Spina et al., 2016). This may be related to the higher baseline levels of BBS in these studies and the limited number of studies. Our subgroup analysis showed that the effect of WBV was more sensitive

to improving balance function with the EDSS scores ranging from 3.5 to 6, similar to the functional mobility. In addition to the reasons explained above, the possible reason is that BBS captures mostly static balance and transfers without considering other facets such as dynamic balance skills that are important in situations nearer to activities of daily living (Gervasoni et al., 2017).

Walking endurance compromise is a common, life-altering feature of MS (Motl and Learmonth, 2014). The 6MWT and 2MWT have been the most commonly applied performance-based measure of endurance walking capacity in MS (Motl et al., 2012; Learmonth et al., 2013; Carpinella et al., 2021). They highlight motor fatigue resulting from extended task execution, thus, effectively assessing the physical efforts and level of autonomy of MS (Moore et al., 2018). It is important to note that the one of included studies used 3MWT to assess walking endurance (Claerbout et al., 2012). The reason was that the patients were unable to complete 6MWT due to fatigue and the walking endurance data can only be obtained by reducing walking time. However, the validity and reliability of the 3 min walk for MS remain unconfirmed to date. Considering the completeness of the data, this study was also included in our analysis. As revealed by our meta-analysis, overall heterogeneity did not change after adding this study (Claerbout et al., 2012). Previous studies have provided some evidence that WBV is beneficial for improving walking endurance in individuals with MS (Hilgers et al., 2013; Ebrahimi et al., 2015; Alam et al., 2020). Our analysis outcomes showed that WBV had a significant effect on improving the walking endurance with MS. In contrast, other studies (Broekmans et al., 2010; Uszynski et al., 2014, 2016) have not conclusively shown that WBV provides a significant advantage over the control group among MS populations due to the limited number of studies. However, these studies showed WBV improved significantly before and after treatment with values equal or greater than 21.6 m which can be considered clinically meaningful in MS (Baert et al., 2014). Our subgroup analysis showed that the effect of WBV was more sensitive to improved walking endurance when the EDSS scores ranged from 0 to 3.5 and durations of the intervention was less than 4 weeks similar to Hilgers et al. (2013). The study indicated the walking distance was found to be inversely related to the EDSS scores. MS is classified as having a mild disability when the EDSS scores <3.5, and its overall function is good, while MS requires assistive devices when the EDSS scores above 3.5 and may be accompanied by a reduction of muscle strength and cardiorespiratory endurance (Chetta et al., 2004). The effect of WBV alone on improving walking endurance may be more pronounced at lower disability levels. However, the duration (>4 weeks) did not show an ideal effect on walking endurance, it might be due to the patients reaching a plateau where no significant clinical benefit was observed. In summary, the optimal WBV training parameters for improving walking endurance was recommended to be per week with a duration of less than 4 weeks for MS of EDSS scores less than 3.5.

A deterioration in gait speed occurs very early following diagnosis of MS when people report no or minimal limitations in function (Martin et al., 2006; Cattaneo et al., 2022). The 10MWT and 25FWT provide a performance-based measure of walking dysfunction based on walking speed over a short distance, which are the common objective measure for characterizing walking dysfunction among persons with MS (Feys et al., 2014; Amatachaya et al., 2020; Sikes et al., 2020; Kalinowski et al., 2022). The studies found that the 10MWT and 25FWT demonstrated more significant changes in those with greater disability of MS with a very high correlation (Feys et al., 2014; Williams et al., 2016). Two of included studies used 25FWT (Broekmans et al., 2010; Spina et al., 2016), and four of included studies used 10MWT (Schyns et al., 2009; Alguacil Diego et al., 2012; Hilgers et al., 2013; Ebrahimi et al., 2015). Many studies have shown that vibration therapy is not beneficial for improving gait speed in individuals with MS (Schyns et al., 2009; Broekmans et al., 2010; Alguacil Diego et al., 2012; Hilgers et al., 2013; Ebrahimi et al., 2015; Spina et al., 2016). A meta-analysis of 3 studies reported WBV was no significant improvement in 10MWT (Alam et al., 2020). Another meta-analysis of 3 studies revealed that the WBV was not significantly associated with the walking speed (Kang et al., 2016). Our meta-analysis showed that vibration therapy did not significantly improve gait speed, consistent with the above studies. Of course, our subgroup analysis results were also negative. Gait speed is a valid, reliable, sensitive measure appropriate for assessing and monitoring functional status and overall health in a wide range of populations (Middleton et al., 2015). The improvement of gait speed is affected by many factors, and the dysfunctional features of MS are multidimensional (e.g., balance and mobility impairments, weakness, reduced cardiovascular fitness, ataxia, fatigue, pain, cognitive deficits, depression, etc.) (Feinstein et al., 2015). Vibration therapy alone may not be effective, which is also found in stroke patients (Brogardh et al., 2012; Moggio et al., 2021).

Additional studies have strong evidence that WBV can be increased to improve gait speed in older adults by assessing 10MWT (Fischer et al., 2019; Wadsworth and Lark, 2020). The above evidence shows that WBV is affected by the type of disease in improving gait speed. In addition, numerous factors can affect the results of the program (e.g., the duration of the intervention, the frequency or volume of the sessions; the type, frequency, and amplitude of the vibrations, and the exercises performed on the platform) (Wadsworth and Lark, 2020). Therefore, a standardized vibration therapy regimen needs to be developed.

Fatigue is the most common and debilitating symptom of MS and has a significant impact on virtually all aspects of an individual's daily functioning (Latimer-Cheung et al., 2013). It typically is measured through self-report questionnaires (Krupp, 2004). Measures included in our study are the FSS, MFIS, and

VAS. A few studies have reported that WBV is not a significant reduction in MFSI (Uszynski et al., 2014, 2016; Ebrahimi et al., 2015). The results reported by Paoloni et al. (2013) and Spina et al. (2016) found FMV was significantly improved in FSS, whereas there was no difference between the FMV and control groups. Only one study used VAS to evaluate the fatigue, which increased in all groups. Our meta-analysis showed that vibration did not result in a significant improvement in fatigue compared with the control group. One possible reason is that patients in included studies had different baseline fatigue levels, which may have affected the results. Furthermore, the self-report questionnaires are entirely subjective and confounded by other symptoms of MS (Schwid et al., 2002). Considering the importance of improving fatigue in MS patients, recent studies have suggested that a multimodal approach should be used to address fatigue in persons with MS, combining psychological and physical aspects (Carter et al., 2014).

MS patients report lower HRQoL as compared to general and other chronic disease populations (Berrigan et al., 2016). Restricted walking prevents MS patients from participating in family and social activities and is a major determinant of overall impairment (Schwid et al., 1997). Currently, few studies have examined the impact of vibration training on the health-related quality of life in MS patients. The studies we included mainly used the MSQL-54 and the MSIS-29 to assess the health-related quality of life. However, there was insufficient evidence of added benefit from the whole body vibration. Both intervention programs facilitate the patient's socialization, which in itself may have contributed to some of the beneficial effects (Ebrahimi et al., 2015). This finding corroborates previous results suggesting that exercise, regardless of the type, has a strong positive effect on the physical and psychological impact of multiple sclerosis (Heine et al., 2015). The quality of life is affected by multiple factors, including interpersonal relations, life environment, psychological and physical state, as well as individual life satisfaction (Gil-Gonzalez et al., 2020). Therefore, recent studies have suggested that a multimodal approach should be used to address health-related quality of life in persons with MS, combining psychological and physical aspects (Carter et al., 2014).

Strengths and limitations

Our systematic review comprehensively explored the effects of Vibration therapy as a treatment on patients with MS. Although there are currently systematic reviews and meta-analyses of the effects of whole-body vibration therapy on motor function in patients with MS, our systematic review and meta-analysis may be the first to explore the effects of vibration therapy on non-motor symptoms, and to perform subgroup analyses on the motor function to illustrate the effects of disability, vibration frequency, and duration of intervention. However, there are several limitations to this review. First, 14 studies were included, but the overall sample size was small; Second, the strength and accuracy of the conclusions of NMS are limited by the small number of eligible studies available; Third, the subgroup analyses were performed only included a few articles, which might increase the deviation of results; Fourth, the studies reported were inconsistent about vibration exposure. Finally, the long-term effectiveness of vibration therapy should be investigated, because it holds significant value in clinical practice.

Conclusion

In conclusion, the present systematic review and meta-analysis suggested that vibration therapy may be more beneficial to improve balance function and walking endurance. Nevertheless, the degree of disability and duration of intervention may affect outcomes. However, there is insufficient evidence to demonstrate that vibration therapy is effective in the treatment of functional mobility, gait speed, fatigue, and quality of life of patients with MS. Further multi-center research with larger sample sizes is needed. Meanwhile, future research should focus on determining the vibration parameters that are most beneficial to the functional recovery of patients with MS.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

YZ and PX put forward this review and designed the protocol and performed the statistical analysis. PX, YD, JC, and WD conducted the literature search and extracted and interpreted data. YZ wrote the first draft of the manuscript. MW and CN provided suggestions on writing and revised the article. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.960328/full#supplementary-material

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Exploration of combined physical activity and music for patients with Alzheimer's disease: A systematic review

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Objective: Alzheimer's disease (AD) can be treated in different ways, one of which is combined physical activity and music intervention, which is a non-pharmacological one. This study provided a thorough systematic review on the application of combined physical activity and music intervention in patients with AD.

Method: Online sources, such as PubMed, Web of Science, SAGE Premier, EBSCO, and Cochrane, published from January 2002 to March 2022 were searched for articles. Reviewer screened articles on inclusion criteria and identified relevant studies. 200 studies were selected as potentially relevant; of these, eight met all the inclusion criteria.

Results: The systemic review looked at eight studies, two of which had high methodological quality and six were of moderate quality. Various types of research were included: randomized controlled tails, single-subject study, crossover study, and case report. Music intervention was conducted during an exercise program in six studies. A cognitive stimulation was applied with music therapy and physical activities among two studies. The physical activities or movements included balance training, stretching, strengthening, and different sports activities. Outcome assessment, including the Barthel index in two studies and the functional independence measure, was conducted to evaluate the daily functional score. Mental health was evaluated by Mini-Mental State Examination in three studies.

Conclusion: Combined physical activity and music intervention are beneficial and improve the cognition, function and well-being of patients with AD. Supporting combined physical and music intervention will play a key role in helping clinical guidelines for both physical therapists and music therapists.

KEYWORDS

physical activity, music therapy, Alzheimer's disease, rehabilitation, non-pharmacological

Introduction

Alzheimer's disease (AD) is the major cause of dementia worldwide, partly because its prevalence continues to grow as the world's population ages (Qiu et al., 2009; Arvanitakis et al., 2019; Soria Lopez et al., 2019). AD is a common neurological disease that begins with memory loss and gradual loss of abilities to call and respond to the surroundings (CDC, 2020). In addition, according to the report of Centers for Disease Control and Prevention, there are more than 5.8 million Americans living with AD at the end of 2020 (CDC, 2020). The annual cost per patient was approximately 19,144 dollars in 2015, and it is expected to be 507.49 billion in 2040 (Jia et al., 2018). Furthermore, currently, pharmacotherapies seem to slow down the progression of AD. However, the normal pharmacological treatments only target the symptoms of AD, but cannot pause or modify the progression of AD (Tang and Taghibiglou, 2017). Moreover, there are still some limitations, such as limited efficacy and substantial side effects (Jiang et al., 2012). Due to the current prevalence of AD, the situation highlights the urgent need of applying effective non-pharmacotherapies to treat AD patients.

Combined physical activity and music intervention is a non-pharmacological therapy that combines music and physical exercises during the treatment process (Wittwer et al., 2013; Anderiesen et al., 2014; Satoh et al., 2014; Brett et al., 2016; van der Wardt et al., 2017). The phrase "physical activity" refers to any skeletal muscular movement that causes energy expenditure (Sharif et al., 2018). These movements include sports, structured exercises, or dance lessons (Terry et al., 2020). Physical activities have various advantages for elderly adults with regards to their mental and physical health, and music interventions or music based interventions have been noted to improve various types of physical activities (Terry et al., 2020). In addition, four main music-based interventions are commonly distinguished in therapeutic practice, which may overlap or be mixed, namely, music-based activities, such as choir singing or drumming, that include improvising, listening, recreating, and composing (Stegemann et al., 2019). Previous studies have proved that music therapy can be applied to the clinical practice of various neurological and psychiatric disorders (Boso et al., 2006; Baker et al., 2021). Furthermore, combined physical activity and music interventions produce considerable benefits for patients with AD, including improved heart rates, skin conductance, motor patterns, neuroendocrine response, and immunological functions (Ooishi et al., 2017). With combined physical activity and music intervention, positive effects have been explored on psychomotor speed and memory on AD patients (Wittwer et al., 2013; Anderiesen et al., 2014; Brett et al., 2016; Satoh et al., 2017; van der Wardt et al., 2017). More recent research has verified that while implementing physical exercise and music intervention simultaneously, physical exercise has displayed positive effects on AD patients, but no positive effects have been discovered from music intervention alone (Pitkänen et al., 2019). On this basis, the employment of combined physical activity and music intervention on patients with AD and its effect has not reached a consensus. With its universal appeal, combined physical activity and music intervention can be an innovative adjunct to standard pharmacologic therapy for patients with AD.

This systemic review is to determine whether combined physical activity and music intervention is effective for AD patients. We focus on recent systematic reviews in the literature to gain a better understanding of evidence-based best practices in the promotion of combined physical activity and music intervention for health benefits among patients with AD based on studies worldwide. We hypothesize that a combined physical activity and music intervention, as suggested by numerous international health and fitness organizations, will be associated with significantly and clinically relevant health benefits, particularly in patients with AD. We hope that our study will provide a more comprehensive understanding of combined physical activity and music intervention for patients with AD. This study will provide a more comprehensive understanding of combined physical activity and music interventions for patients with AD.

Methods

Search strategy

The online databases, namely, PubMed, Web of Science, SAGE Premier, EBSCO, and Cochrane, were applied to identify publications in the field. We edited strategies of these databases into the following table (**Table 1**).

Inclusion criteria

The inclusion criteria include: (1) patients diagnosed with dementia; (2) AD patients receiving combined physical activity and music intervention; (3) availability during the intervention and testing phases; (4) randomized controlled trials (RCTs), crossover study, case series/report, and single-subject design study; and (5) publications indexed in databases from January 2002 to March 2022 provided they are written in English.

Exclusion criteria

The exclusion criteria include: (1) publications that do not have access to at least the abstracts; (2) documents that are not published in the form of a peer-reviewed article,

TABLE 1 Search strategy table.

Search strategy for PubMed, Web of Science, SAGE Premier, EBSCO, and Cochrane.

Using PubMed database	
1	TI/AB = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
2	TI = "exercise" OR "train" OR "training" OR "physical activity" OR "physical activities" OR "strength" OR "endurance" OR "resistance" OR "stability" OR "walk*" OR "tai chi" OR "yoga" OR "motor control" OR "core control" "stretch*" OR "run" OR "muscle energy technique" OR "pilates*" OR "hydrotherapy" "water sports" OR "kinesitherapy"
3	TI/AB = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
4	Strategy 1 AND 2 AND 3
Using Web of Science database	
1	TS = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
2	TI = "exercise" OR "train" OR "training" OR "physical activity" OR "physical activities" OR "strength" OR "endurance" OR "resistance" OR "stability" OR "walk*" OR "tai chi" OR "yoga" OR "motor control" OR "core control" "stretch*" OR "run" OR "muscle energy technique" OR "pilates*" OR "hydrotherapy" "water sports" OR "kinesitherapy"
3	TS = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
4	Strategy 1 AND 2 AND 3
Using SAGE Premier database	
1	TI = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
2	AB = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
3	TI = "exercise" OR "train" OR "training" OR "physical activity" OR "physical activities" OR "strength" OR "endurance" OR "resistance" OR "stability" OR "walk*" OR "tai chi" OR "yoga" OR "motor control" OR "core control" "stretch*" OR "run" OR "muscle energy technique" OR "pilates*" OR "hydrotherapy" "water sports" OR "kinesitherapy"
4	TI = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
5	AB = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
6	Strategy 1 AND 2 AND 3 AND 4 AND 5
Using EBSCO database	
1	TI = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
2	AB = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
3	TI = "exercise" OR "train" OR "training" OR "physical activity" OR "physical activities" OR "strength" OR "endurance" OR "resistance" OR "stability" OR "walk*" OR "tai chi" OR "yoga" OR "motor control" OR "core control" "stretch*" OR "run" OR "muscle energy technique" OR "pilates*" OR "hydrotherapy" "water sports" OR "kinesitherapy"
4	TI = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
5	AB = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
6	Strategy 1 AND 2 AND 3 AND 4 AND 5
Using Cochrane Library database	
1	TI = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
2	AB = "dementia" OR "cognitive impairment*" OR "cognitive dysfunctions" OR "neurocognitive disorder, mild" OR "cognitive decline" OR "mental deterioration"
3	TI = "exercise" OR "train" OR "training" OR "physical activity" OR "physical activities" OR "strength" OR "endurance" OR "resistance" OR "stability" OR "walk*" OR "tai chi" OR "yoga" OR "motor control" OR "core control" "stretch*" OR "run" OR "muscle energy technique" OR "pilates*" OR "hydrotherapy" "water sports" OR "kinesitherapy"
4	TI = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
5	AB = "Music" OR "music therapy" OR "sing" OR "rhythm*" OR "tempo*" OR "Music Therapy"
6	Strategy 1 AND 2 AND 3 AND 4 AND 5

TI, Title; AB, Abstract; and TS, Topic (Title, Abstract, Author Keywords, Keywords Plus).

such as dissertations, theses, conferences, editorial letters, and commentaries; (3) duplicate items; (4) participants with other diseases; (5) combined physical activity and music interventions that are not part of the treatment for patients with AD; and (6) the absence of combined physical activity and music intervention-related outcome measures. **Figure 1** presents the flow chart of the search for bibliographic references of this study.

Data extraction

All the potential studies were reviewed by two researchers independently. Abstracts and titles were reviewed and scored. If the abstracts and titles satisfied the criteria, the full texts would be examined to determine which research met the inclusion or exclusion criteria. If a disagreement ensued, a team discussion would be made by researchers to approach a final decision. In this processes, researchers extracted various details, including the information of authors and publication year, subject features, and intervention from studies. The outcomes of studies were also extracted.

Quality assessment

The study quality was assessed by Grading of Recommendations Assessment, Development and Evaluation system, it was developed by Guyatt et al. (2011). In general, this system is for systematic review and health technology assessments, as well as guidelines (Guyatt et al., 2008). This appraisal tool consists of 15 items focused on study design, experimental control, study participants, methodology, and outcomes. The first item, addressing study design, is worth five points. Each additional item is worth one point, for a maximum score of 20. Both researchers ranked articles simultaneously, and disagreements were resolved to reach a consensus.

Results

Studies included and excluded

Our team of researchers identified two hundred studies from screening potential studies. After screening all studies. 68 duplicate records were removed. A total of 135 records were screened based on the title, abstract, and keywords; and 19 full-text articles were eligible. Finally, eight studies were included (see **Figure 1** flow chart). Out of the eight studies, six examined the effect of combined physical activity and music treatment to AD patients, two studies explored the effect of cognitive stimulation (CS) by strengthening exercise and music therapy.

Study designs

Five studies applied RCT design (Van de Winckel et al., 2004; Satoh et al., 2017; Chen and Pei, 2018; Pitkänen et al., 2019; Higuti et al., 2021), one study applied crossover design (Johnson et al., 2012), one used a case report design (Langhammer et al., 2019), and one applied a single-subject design (Mathews et al., 2001). The four RCTs included the treatment and control arms, and one RCT had more than two arms (three-armed RCT).

Quality assessment tool applied

The quality assessment consisted of 15 items (see **Table 2**), the whole assessment tool worth 20 points. The items involved these categories, such as study design, experimental control, participants, methodology, and outcomes. In terms of this assessment tool, studies were marked as high, medium, and low quality. Articles were ranked simultaneously by researchers.

The quality assessment is presented in **Table 2**. No low-quality study was detected. We obtained two studies that have high-quality, and six that are medium-quality. All studies have a clear description of subjects/groups, observable and measurable clear target behaviors, clear descriptions of intervention methods, and clear description of observable or measurable outcomes. Five studies were reported as RCTs, and one each of single-subject design study, crossover study, and case report study. The eight studies reported appropriate statistical analysis and clear conclusions drawn from the results.

Combined physical activity and music intervention

Nowadays, music intervention has a similar purpose when compared to physical activity in patients with AD, but music intervention may use totally different techniques to achieve these goals. Music intervention utilizes methods such as rhythmic auditory stimulation (RAS), therapeutic instrumental music performance, and musical neglect training to patients' movement (Wittwer et al., 2019; Braun Janzen et al., 2021). Studies about combined physical activity and music intervention are very limited, but it has proven important for patients with AD. For example, physical activity accompanied with RAS produced significant improvements in strength, functional activity promotion of synchronized movements.(Minino et al., 2021). In this current study, among these searched articles, music interventions always came with physical activities or movements, such as sitting and standing balance activities, or stretching, strengthening, and breathing exercises (**Table 3**). Also, Several studies utilized the intervention consisting of singing and playing instruments using a fast tempo and well-pronounced beat (Johnson et al.,

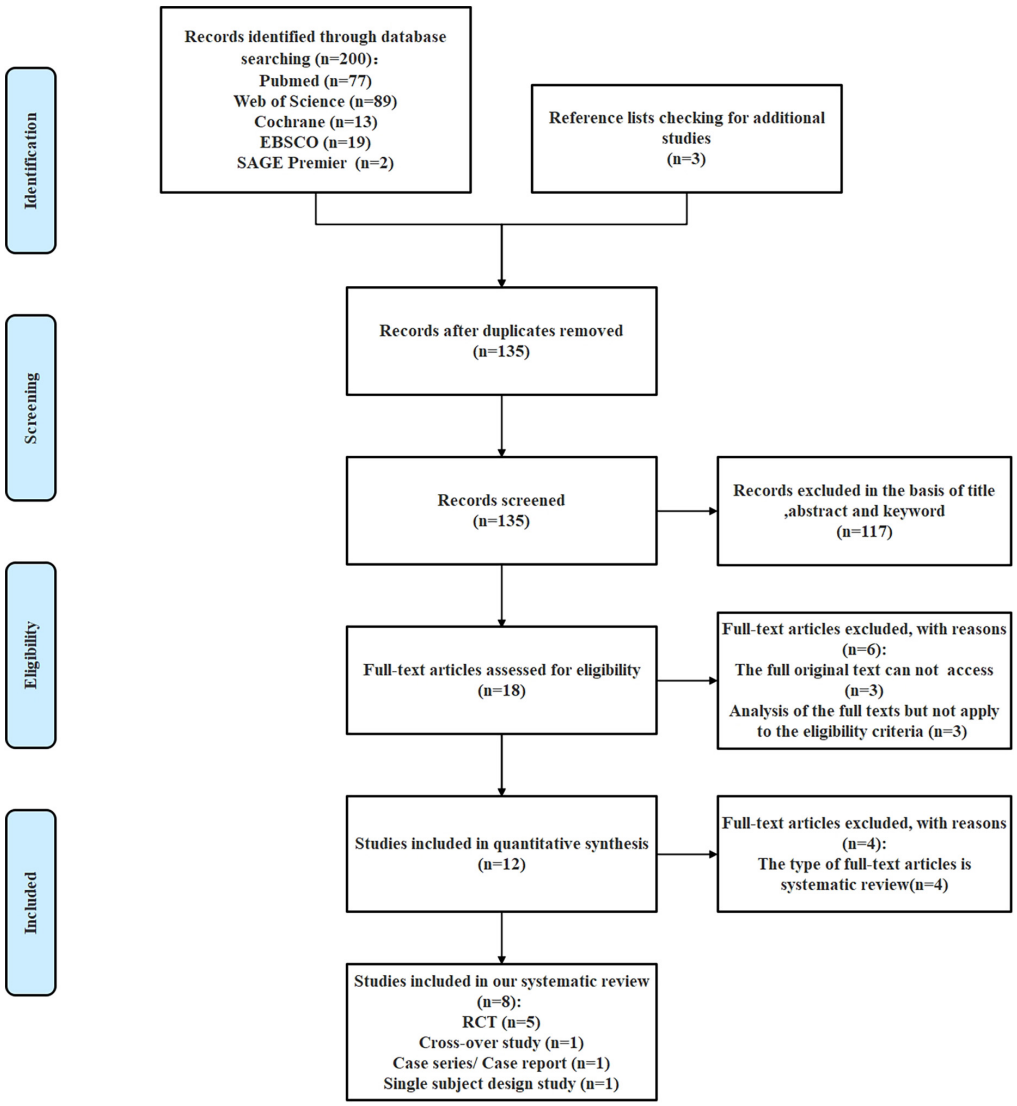


FIGURE 1
Flow chart.

2012; Chen and Pei, 2018; Ptomey et al., 2018; Langhammer et al., 2019). In addition, other music interventions consisted of music training for the upper and lower extremities while clapping to music (Satoh et al., 2017). Moreover, physical activities included walking on the ward or outside of it. Singing or listening to known songs was also among the interventions.

Music therapy with cognitive stimulation

Cognitive stimulation has various methods such as: using portable game consoles and drills involving easy calculations, mazes, and mistake-searching in pictures (Satoh et al., 2017). Satoh et al. (2017) performed a CS in which the subjects utilized the software named "Yawaraka-atama-juku" (which means "flexible thinking club"). Higuti et al. (2021) applied CS using seven extraordinary songs relevant to their age, evoking positive personal memories. After the CS test, participants were guided to perform the same type of exercises.

Dosage of interventions

In these eight studies, the dosage of each intervention ranged from 1 to 25 weeks. Each intervention session was lasting 22 to 45 min. These studies did not mention the unsupervised adherence rates, thus, we presumed that per week adherence of the same duration as guided by investigators (Gilat et al., 2021).

Assessment tool used in the eight studies

Barthel index (Satoh et al., 2017; Pitkänen et al., 2019; Higuti et al., 2021) and functional independence measure were used to assess the daily functional score. Mental health was assessed by the mini-mental state examination (MMSE; Van de Winckel et al., 2004; Pitkänen et al., 2019; Higuti et al., 2021). Psychological, functional, and health status were used to evaluate the cognition situation. Pitkänen et al. (2019) used a scale tool called Alzheimer's disease cooperative study-activities of daily living.

TABLE 2 Quality evaluation of references.

References	Higuti et al., 2021	Langhammer et al., 2019	Johnson et al., 2012	Satoh et al., 2017	Pitkänen et al., 2019	Van de Winckel et al., 2004	Mathews et al., 2001	Chen and Pei, 2018
Study design criteria	5	1	2	5	5	5	3	5
5-Randomized controlled trial								
4-Cohort study								
3-Single subject design study								
2-Crossover study								
1-Case series/Case report								
Additional criteria (1 point each)								
Clear experimental controls used	1	0	1	1	1	1	0	1
Prospective study completed	0	0	1	0	0	0	0	0
Blinding of assessors used	1	0	1	0	0	1	0	0
Clear description of subjects/group	1	1	1	1	1	1	1	1
Balanced baselines between groups or stable across single subject	0	0	0	0	0	0	0	0
Target behaviors observable and measurable	1	1	1	1	1	1	1	1
Clear description of intervention methods	1	1	1	1	1	1	1	1
Attrition rate explained or minimal (<20%)	1	1	1	0	1	1	0	1
Clear description of observable or measurable outcomes	1	1	1	1	1	1	1	1
Statistical analysis described or conducted appropriately	1	1	1	1	1	1	0	1
Appropriate reliability methods described or used	0	0	0	0	0	0	0	0
Appropriate validity methods described or used	0	0	0	0	0	0	0	0
Clear conclusions drawn from results	1	1	1	1	1	1	0	1
Clear description of follow-up and maintenance outcomes	0	0	0	0	0	1	0	0
Total score	14	8	12	12	13	15	7	13

Studies were then ranked as high (14–20 points), medium (7–13 points), and low quality (1–6 points).

TABLE 3 Physical activity combined music for individuals with AD-current research summary table.

N (% completing study) and drop outs	Study design	Intervention group	Control group	Intervention conducted by	The length and frequency of the intervention of the study	Outcomes	Significant findings
Higuti et al., 2021 17 (94% completed) 1 dropped out (6%)	RCT	Group 1: the Training without Music Group performed a set of light exercises lasting 25–30 min per session focused mainly on maintaining/improving global mobility. Group 2:the Training with Music Group was initially submitted to cognitive stimuli with music.	No intervention	Physiotherapy students, researcher.	Once a week for 12 weeks; lasting 25–30 min per session; 6 of 12 sessions	Assess functional capacity: The BI and PPS Assess cognition: MMSE, 24 Severe MMSE, and VFT	No improvement or worsening in cognitive or functional aspects was found after 12 weeks of training in either group.
Langhammer et al., 2019 16 (100% completed) 0 dropped out (0)	Case series/Case report	A combination of physical activity (activities or movements such as sitting and standing balance activities, stretching, strengthening exercises, breathing exercises, and different sport activities) with balls music (activities or movements such as singing, playing musical instruments, moving to the music, or simply listening to enhance relaxation), and walking.	No intervention	Physiotherapist, music therapist	Once per week for 8 weeks; lasting 45 min per session	Brøset Violence Checklist. NPI-Q The primary caretaker (nurse assistant) documented compliance to the program by recording weekly activities in a logbook.	Implementation of a systematic combination of music and a physical activity program was feasible in a group of individuals with severe dementia, and helped reduce anxiety, restlessness, irritability, and aggression.
Johnson et al., 2012 12 (100% completed) 0 dropped out (0)	Crossover study	The intervention consisted of music during an exercise program. The musical selection included seven songs with a medium to fast tempo and a well-pronounced beat. An exercise program was developed to simulate common movements found in typical exercise. Exercises were choreographed with the beat of the music for the intervention condition.	The control condition consisted of the exercise program described above without music.	Care givers	Once per week for 8 weeks; lasting 30 min per session (including five 2-min breaks)	A chart was used to track participation. Each exercise session was divided into intervals of 30 s. Within these time intervals, reviewers examined each resident and assigned a mark of one if the resident participated in the correct exercises for the whole interval and a 0 if the participant stopped participating at any point during the interval.	The use of music may be considered a supplemental intervention utilized to increase participation in exercise programs for older adults with dementia. Increasing participation in exercise programs can increase strength, decrease risk of falls, and improve quality of life.

(Continued)

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TABLE 3 (Continued)

N (% completing study) and drop outs	Study design	Intervention group	Control group	Intervention conducted by	The length and frequency of the intervention of the study	Outcomes	Significant findings
Satoh et al., 2017 62 (72% completed) 23 dropped out (28%)	RCT	The program consisted of muscle training for the upper and lower extremities, hand clapping to music, breath and voice training, and singing.	No intervention	Musicians, nursing-care facility staff (nurses, certified care workers, or psychiatric social workers)	Once per week for 6 months; lasting 45 min per session	Neuropsychological batteries. FIM, VSRAD.	Exercise with music produced greater positive effects on cognitive function and ADLs in patients with mild to moderate dementia than CS, excluding memory. Optimal interventions for dementia will likely be achieved by combining Exercise with music and CS.
Pitkänen et al., 2019 175 (50%completed) 173 drop out	RCT	The physical exercise interventions included balance, flexibility and strength training either when seated or standing, relaxation and exercise with a restorator. Music was the part of the exercise sessions, included singing or listening to familiar songs.	Medication and multidisciplinary treatment	Music therapist, physiotherapist, the chief physician and nursing director	Six times a week; lasting 45 min per time	NPI, MMSE, BI, ADCS-ADL	Physical exercise may have some positive effects for both neuropsychiatric symptoms and the level of functioning in some patients with dementia while no positive effects regarding music interventions were found.
Van de Winckel et al., 2004 25 (100% completed) 0 drop out	RCT	Patients attended a group- based exercise programme. The therapist used specific one-step verbal instructions, combined with continuous visual demonstration. The exercises focused on upper and lower body strengthening, as well as balance, trunk movements and flexibility training.	the therapist had a daily one-to-one conversation with each of participants separately. No music was played and patients were not asked to perform any movements.	Physical therapist	Daily per session for 3 months; lasting 30 min per session	MMSE, ADS 6, BOP scale	The present study suggests a beneficial effect of cognition using a music-based exercise programme in a group of patients with moderate to severe dementia.

(Continued)

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TABLE 3 (Continued)

N (% completing study) and drop outs	Study design	Intervention group	Control group	Intervention conducted by	The length and frequency of the intervention of the study	Outcomes	Significant findings
Mathews et al., 2001 21 (100% completed) 0 drop out	Single subject design study	Use of rhythmic music during exercise activities. The sequence of exercises included: shoulder roll; hand flex and hand pronate/supinate; knees together/apart; arms across chest; knee extensions; bicep curls; toe taps and heel lifts; bucket lifts; rowing; marching; arm adduction/abduction and internal/external rotation; head rotation and ear to shoulder; ankle circles; and arm extensions.	No control group	Physical therapist	Once per week for 25 weeks; lasting 22 min per session	The observer used a 30-s partial interval recording system to score individual resident engagement.	Results showed increased levels of participation during the experimental condition observations where rhythmic music accompanied the exercise activities. The music intervention was most successful on those generally most willing to participate in social activities
Chen and Pei, 2018 28 (93.33% completed) 2 drop out	RCT	The MDTT protocol included a musical task and a walking task. The musical task comprised two types of activities: singing and playing simple percussive musical instruments. In the walking task, the participants either walked forward or stepped sideways. The participants were instructed to perform all eight combinations progressively within a session.	Non-musical cognitive and walking activities.	Music therapist	Once per week for 8 weeks; lasting 60 min per session	TMT part A, Army Individual Test Battery, dual-task performance in gait analysis included the forward digit recall dual-task condition, backward digit recall dual-task condition, and single-task (control) condition, TUG test, FES-I, CMAI-C	MDTT intervention demands a high level of cognitive processing, enhances attention control, falls efficacy, and helps alleviate agitation in patients with mild-to-moderate dementia.

RCT, randomized controlled trial; BI, barthel index; PPS, palliative performance scale; MMSE, the mini mental state examination; VFT, verbal fluency test; NPI-Q, neuropsychiatric inventory–questionnaire; FIM, the functional independence measure; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; ADL, activities of daily living?; CS, cognitive stimulation ?; NPI, neuropsychiatric inventory; ADCS-ADL, Alzheimer's disease cooperative study–activities of daily living; ADS 6, amsterdam dementia screening test 6; BOP scale, stockton geriatric rating scale; MDTT, musical dual-task training; TMT part, trail making test part A; TUG, Timed Up and Go; FES-I, falls efficacy scale international; and CMAI-C, chinese community-version cohen-mansfield agitation inventory scale.

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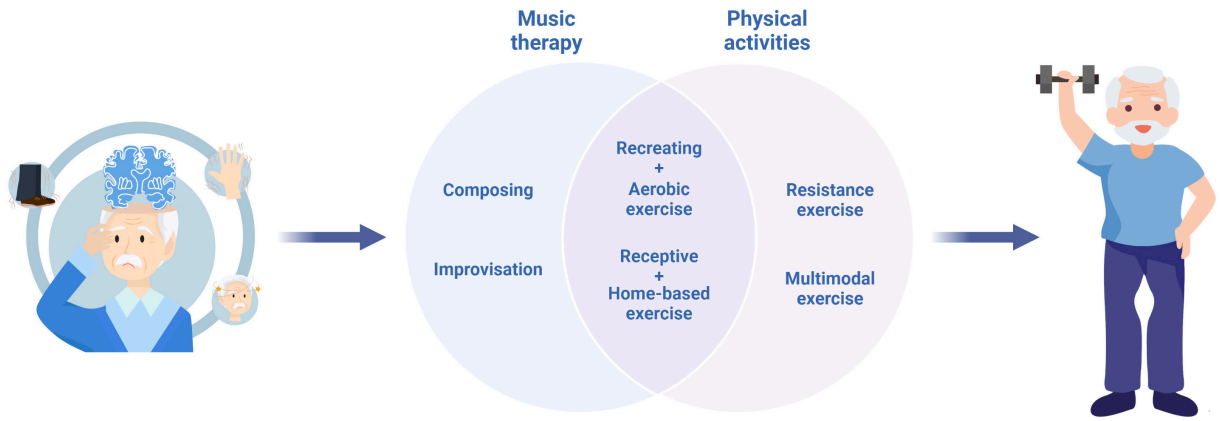


FIGURE 2
Combined physical activity and music interventions for patients with AD.

Langhammer et al. (2019) and Pitkänen et al. (2019) performed neuropsychiatric inventory to assess neuropsychiatric condition. Other behavioral and functional assessments used included dual-task performance in gait analysis, such as the forward and backward recall the number dual-task condition, and single-task (control) condition, timed up-and-go test (TUG; Chen and Pei, 2018); 30-s partial interval recording system for scoring individual resident engagement (Mathews et al., 2001); and Stockton Geriatric Rating Scale (Van de Winckel et al., 2004).

Other studies have used different assessment tools to evaluate the neuromuscular function of patients with AD, such as switching the mind attention dual-task, paired associative learning, and decreasing the reaction time (Ptomey et al., 2018).

Study population

Table 2 summarizes the information on each of the 8 studies we explored in this systemic review. The participants from each group in the last 8 studies ranged from 6 to 175, with a median of 29 patients in each group. The intervention groups had 51% male and 41% female (49%), whereas the control groups had 41% male and 59% female. The sex of the participants in the two studies was not reported (Van de Winckel et al., 2004; Satoh et al., 2017). The average age for all the groups was 81.6 (3.8) years, with the intervention groups demonstrating and average of 80.4 (3.7) years, and the placebo groups an average of 79.8 (3.1) years. The range was between 53 and 94 years. The number of years since clinical diagnosis was recorded in four studies, and the Clinical Dementia Rating has been reported in the study (Higuti et al., 2021). The group averages on the MMSE were described as an accurate and effective cognitive screening test in three studies (Van de Winckel et al., 2004; Pitkänen et al., 2019; Higuti et al., 2021).

Results obtained

Previous systematic reviews have examined the effect of music or physical exercise in isolation. This review was the first to conclude that the combination of these interventions improved cognitive and physical function, and quality of life of AD populations. Langhammer et al. (2019) found that combining physical activity with music therapy is effective for reducing anxiety, restlessness, irritability, and aggression in a sample of people with severe dementia. Johnson et al. (2012) concluded that music may be used as a supplemental element to increase participation of physical exercise programs for patients with AD. Increasing exercise involvement may enhance strength, and reduce the risk of falling. Mathews et al. (2001) showed that music accompanying exercise activities increased the levels of participation during experimental condition observations. Those who were most eager to participate in activities benefited the most from music-based intervention. Furthermore, Chen and Pei (2018) noted that in patients with mild to moderate dementia, music combined with physical exercise intervention needs a high level of cognitive processing. Therefore, this treatment enhances their attention and fall efficacy, and can reduce their agitation. Satoh et al. (2017) further stated that combined music and physical exercises are more effective than a single intervention for prevention of AD.

No significant association regarding music-based physical activity in patients with AD were found in the other two studies. Pitkänen et al. (2019) noted that exercise has effects on neuropsychiatric symptoms and the function among some AD patients, but it has no positive effects relative to music based interventions. Higuti et al. (2021) noted no enhancement or

decline with both cognitive or functional characteristics among AD patients after 12-week intervention.

Discussion

This systematic review was performed to assess the influence of combined physical and music intervention as a strategy to improve function and quality of life for patients with AD. Nowadays, there are various studies available regrading physical therapy and music therapy treatment to patients independently (Guo et al., 2020), but current studies using a collaboration of these two disciplines is limited. Applying music to stimulate a sense of rhythm will assist to stimulate certain brain areas and improve the synchronized physical exercise (Matthews, 2015; Song and Ryu, 2016; Zhang et al., 2017). This current review indicates that irrespective of the treatment modalities or combination chosen, music-based physical activities can act as a non-pharmacological treatment beneficial to patients with AD. Supporting combined physical and music intervention will play a key role in helping clinical guidelines for both physical therapists and music therapists.

Effect of combined physical activity and music intervention to patients with Alzheimer's disease

Most of the reviewed studies identified the effect of combined physical activity and music treatment on cognitive and physical functions of patients with AD (Mathews et al., 2001; Van de Winckel et al., 2004; Satoh et al., 2017; Chen and Pei, 2018; Ptomey et al., 2018; Langhammer et al., 2019; Giuli et al., 2020). This phenomenon could be due to the fact that combined physical activity and music intervention helps patients with mild to moderate dementia reduce anxiety, restlessness, irritability, and aggression. Increased participation among physical exercise programs can increase strength for patients (Johnson et al., 2012), reduce risks of falls, and promote quality of life (Langhammer et al., 2019). The music-based physical exercises effect on the functional and cognitive characteristics of older persons with mild to advanced dementia were explored in two studies. Depending on the form or stage of dementia, exercise before or after music intervention, such as listening to music can assist in slowing the development of dementia, and can be used in conjunction with existing cognitive behavioral and pharmacological therapies (Moreno-Morales et al., 2020).

No modern technologies had been applied to support combined physical activity and music intervention among the previous studies that we analyzed. A number of technologies for patients with AD have emerged over the past 20 years, and other modern technologies, such as cellphones or wearable fitness trackers, could be examined to assist patients with dementia engage in physical activities while listening to music (van der Wardt et al., 2017). In addition, patients with dementia may use modern technology, and smartphones, apps, and other similar technologies may soon become the standard, as they are expected to be used by the majority of people on a regular basis (Rosenberg et al., 2012; Rosenberg and Nygård, 2014). Consequently, older patients with dementia may be familiar with such equipment.

The effectiveness of adherence techniques is expected to differ between patients with AD. No strong findings have been found about the usefulness of an adherence support program, and existing evidence is weak. More evidence is needed to determine what works best for whom and under what conditions. Thus, traditional systematic reviews are unlikely to provide solutions, necessitating the adoption of a realism epistemology.

Clinical guidance

Various individual factors influence the responses of patients with AD to combined physical activity and music intervention. These key factors include, but are not limited to age, gender, cognitive function, familiarity with, and preference for the music-based physical activity types. The potential success of combining music and physical activities provides professionals, therapists and researchers a new treatment option to study and apply. The review showed that these treatments could help modify the progression of decline seen among people with dementia, as well as improve daily abilities for AD patients (Higuti et al., 2021). Per what is reviewed above, we would like to offer the following clinical guidelines for the use of combined physical activity and music intervention for practices. **Figure 2** shows the major combined physical activity and music interventions for patients with AD.

- To improve the physical and cognitive functions of AD patients, the environment needs to be adjusted to promote music-based physical activities. One major modification in implementing health care is to update the physical environment to a more home-like environment, and suggest physical exercises that fulfill the needs of patients with AD (Richards et al., 2015). At the same time, playing the patients' preferred music combined with exercise has the adjunct effect on cognition in patients AD (Li et al., 2015; van der Wardt et al., 2017).
- Various types of combined physical activity and music interventions should be explored in collaboration with people with AD, as well as their caregivers. Moreover, some of these tactics can be utilized in public health programs to encourage this population to participate in exercise classes or physical activity programs (van der Wardt et al., 2017).

- With the purpose of conducting interventions in this population, highly trained professionals who can comprehend and acculturate the signals and requirements of AD patients are vital.

Research direction

In view of relatively weak evidence, the effectiveness of adherence support strategies varies among patients with AD. A larger sample of RCTs is urgently needed to evaluate the types of combined physical activity and music intervention, the population for whom it is used, the circumstances in which it is used, and explanation for why it is used. Few studies have analyzed the mechanism of music-based physical activities for patients with AD and how they improve cognition, mood and behavior of patients with AD. Furthermore, the development of new combined physical activity and music interventions should be explored in collaboration with people with AD, as well as their caregivers. Such interventions will assist in guiding health experts, such as physical therapists, so that a rehabilitation approach to dementia care can be implemented, thereby improving the quality of life of patients with AD.

Study limitations

Although it has many strengths, this review also has some weaknesses. First, the three most truthful world databases used in this study gathered a large amount of scientific publications. However, future revisions should also search through more databases. Second, the term of "music therapy" or "music based intervention" can have several meanings. In this study, we have attempted to unify the term based on the definition of the World Federation of Music Therapy. However, some publications may apply different implications of this term, which can modify the results found within the bibliographic search. Third, the treatment standards of music combined with different exercise types, such as music with aerobic exercise, music with resistance exercise, music with combined aerobic and resistance training, music with home-based exercise, and music with multimodal exercise, are lacking. Fourth, only English-language studies were considered in this paper. Thus, several studies in other languages may have been overlooked.

Conclusion

This systemic review attempted to state the feasibility and efficacy of combined physical activity and music intervention for patients with AD. The results of this systemic review support that combined physical activity and music interventions have been proved to be preferred, acceptable, and effective for patients with mild to moderate AD. In addition, combined physical activity and music interventions that combine strength, balance, flexibility, and endurance are the most common combinations that produce major improvements in the health of patients with AD.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors contributed toward data analysis, revising the manuscript and agreed to be accountable for all aspects of the work. KL and H-YH designed and performed the study and drafted and revised the manuscript. H-YH, HZ, LJ, and RL analyzed the results and were involved in the research design and execution. CC revised the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor LL is currently organizing a Research Topic with the author KL.

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Yijinjing Qigong intervention shows strong evidence on clinical effectiveness and electroencephalography signal features for early poststroke depression: A randomized, controlled trial

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Objective: Although Traditional Chinese Yijinjing Qigong Exercise (YJJQE) as mind–body intervention is popularly used among adults to ameliorate depressive symptoms in China, no randomized controlled trials (RCTs) are available to evaluate the effects of YJJQE in patients with poststroke depression (PSD). This study aims to explore the clinical efficacy and the neurological and psychiatric mechanism in brain network functional connectivity underlying electroencephalography (EEG).

Materials and methods: A total of 60 patients, diagnosed with mild PSD, were randomly (1:1) assigned to YJJQE group (n = 30) and control group of routine segmental rehabilitation training group (n = 30) for a 60-min exercise session once a day for 3 weeks. All outcome measures were collected at baseline and 3-weeks ending intervention. The primary outcome was the 24-item Hamilton Depression Scale (HAMD-24) score, evaluation at more time points for 1 month of follow-up. The secondary outcomes were EEG data in four frequency domains (δ, θ, α, and β), global efficiency (GE), local efficiency (LE), GE/LE curve [areas under the curve (AUC)], Phase Lag Index (PLI), (HAMD-24) Score and EEG correlation analysis.

Results: All patients showed no significant differences in baseline data. After 3 weeks and 1 month of follow-up, the YJJQE group demonstrated significant decreasing changes compared to the control group on the HAMD-24 scores ($p < 0.001$). Furthermore, the YJJQE group also showed a significant reduction

in θ wave, and an increase in both GE and LE. Compared to the control group, the YJJQE Qigong group showed significantly greater functional connectivity in the δ, θ, and β frequency bands in the brain network of the degree of phase synchronization ($p < 0.001$). HAMD-24 Score and EEG correlation analysis negative correlation in the Qigong group θ wave ($p < 0.001$).

Conclusion: Our findings demonstrated that YJJQE is estimated to effectively alleviate the depressed mood of patients with PSD by promoting the efficiency in information transmission of network functional connectivity and its integration ability in different brain regions. Therefore, the YJJQE would be useful as a non-pharmacological treatment to prevent PSD.

Clinical trial registration: [http://www.chictr.org.cn/showproj.aspx?proj=55789], identifier [ChiCTR2000035588].

KEYWORDS

poststroke depression, traditional exercise, Yijinjing Qigong exercise, EEG, brain functional connectivity network

Introduction

Globally, a stroke has been the second leading cause of death (Medeiros et al., 2020). From 1990 to 2019, the absolute number of incident strokes increased by 70.0%, prevalent strokes by 85.0%, and disability-adjusted life-years due to stroke by 3.20% (GBD 2019 Stroke Collaborators., 2021). Approximately one-third of stroke survivors developed poststroke depression (PSD), and the frequency is highest in the first year after a stroke (Virani et al., 2021). Previously, several investigators attempted to prevent the development of poststroke depression without success (Starkstein and Hayhow, 2019). Conversely, conventional antidepressants of pharmacotherapy may result in more side effects in increasing the risk of cardiovascular disease and stroke in PSD patients (Rasmussen et al., 2003; Almeida et al., 2006; Loubinoux et al., 2012; Swartz et al., 2016; MacQueen et al., 2017; Kapoor et al., 2019; Legg et al., 2019). Therefore, there is an urgent need for non-pharmacological treatments that are effective, safe, and easy to promote.

In recent years, there has been increasing clinical evidence of using traditional Chinese Tai Chi Qigong exercise to alleviate the symptoms of PSD (Lyu et al., 2021). Yijinjing Qigong exercise (YJJQE), which is similar to Tai Chi in China, but easier to learn, is a multicomponent traditional Chinese mind–body practice that combines meditation with slow, gentle, stretching muscle movements, deep diaphragmatic breathing, and relaxation (Guo et al., 2018; Chen et al., 2019; Yeung et al., 2019; Xing et al., 2020). Previous studies have shown that Yijinjing can effectively strengthen the muscles and ligaments around the spine, improve flexibility and balance, and help regulate a person's physical and mental states (Xiang et al., 2006; Gao et al., 2021). We have proven that YJJQE can improve psychological well-being by reducing stress, anxiety, depression, and mood disturbance to manage KOA (Zhang D. et al., 2021; Zhang S. et al., 2021). However, no RCTs have been conducted specifically using YJJQE to evaluate its therapeutic benefits for those with PSD.

It is important to quantitatively analyze the neurological and psychiatric states of patients with PSD in order to develop personalized treatment plans that maximize outcomes. Quantitative electroencephalography (EEG) may also be a reliable instrument for detecting alterations of interhemispheric interaction poststroke that provide the functional electrical activity of neuronal assembles in the brain, including the integrity of the afferent sensory tract and the corticospinal tract as well as local and network electrical activity in the cortex (Kuriakose and Xiao, 2020; Vatinno et al., 2022). PSD has been associated with a dysregulation in the brain's ability of cell communication (Leuchter et al., 2015). The functional brain network randomization linked to depressive disorders shows a low characteristic path length due to damage in the "core nodes" of the mood-related brain areas, leading to "disconnection" symptoms in the mood regulation pathway and ultimately reducing the operation efficiency of the whole brain network (Brakowski et al., 2017; Yu et al., 2019).

Overall, the objective of this study was to explore the efficacy of traditional Chinese Qigong exercise on PSD and quantitatively analyze the neurological and psychiatric mechanisms underlying EEG characteristics.

Materials and methods

Study design

This single-blinded, randomized controlled trial was approved by the Ethics Committee of Yue Yang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated with Shanghai University of Traditional Chinese

Medicine (project number: 2019-125), and registered in the Chinese Clinical Trial Registry (ChiCTR2000035588), and conducted in the same hospital in accordance with the Declaration of Helsinki. The study procedure and results were reported according to the CONSORT checklist. All participants gave us informed consent before inclusion.

Participants

A total of sixty patients were enrolled between December 2019 and December 2021 at the inpatient Department of Rehabilitation Medicine in Yueyang Hospital. We obtained informed consent prior to the baseline assessments for eligibility. Patients were required to satisfy the following inclusion criteria: (1) the PSD patients were diagnosed following the international classification of the central nervous system (G00-G09) and the standard of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Chen Zhiluo, 1995; Xiande, 1996; The Psychiatry Branch of the Chinese Medical Association, 2001); (2) patients' age was > 60 years and <75 years; (3) stroke from cerebral infarction diagnosed between the first and eighteenth month *via* computed tomography or magnetic resonance imaging; and (4) consequent evaluation HAMD-24 score ≤ 28 points. Alternately, the exclusion criteria were as follows: (1) severe encephalopathy, epilepsy, gastrointestinal bleeding, and heart failure and those in the drug withdrawal stage that lead to life-threatening conditions; (2) medical history of psychiatric or neurological disorder, or being diagnosed with moderate or severe depression; (3) psychopharmacological drug consumption; (4) had a history of substance abuse or alcoholism; and (5) were unable to independently complete the treatment, the scale assessment, and EEG examination, as required by the protocol.

Power and sample size

We estimated the sample size based on a comparison between the intervention and control groups (Xu et al., 2021; Xue et al., 2021), which was characterized by the improvement in the HAMD-24 scores as the primary outcome. Previous studies demonstrated that the mean ± standard deviation (SD) of the HAMD-24 score in the intervention group was 28.69 ± 4.16 and that in the control group was 26.22 ± 3.98. Considering the statistical power to be 90% ($\alpha = 0.05$), with a 10% attrition rate, we calculated the sample size by applying the formula. Based on the above parameters, the minimum sample size per group was 30, and the recruitment of 60 participants was needed.

Randomization and masking

A total of sixty patients were randomly assigned to the intervention group for YJJQE combined with routine rehabilitation training and control group for only routine rehabilitation training group in a 1:1 ratio. The patients were requested not to change their ordinary physical activity and start any new intervention programs. In this context, independent scholars (third party) generated 60 unique seven-bit codes using random number functions in SAS 9.4 version software (SAS Institute Inc., Cary, NC, United States), then randomly split them into two groups, sequentially numbered them, and placed them in a sealed and opaque envelope to ensure confidentiality. Accordingly, the patients were divided into either the intervention or control group by picking a code from the envelope. The assessors, who measured all the patients and collected the outcome data, were unaware of any assigned intervention. All statistical analyses were performed while maintaining the data masking.

Intervention program

Both groups of routine segmental rehabilitation training treatments were performed by the same therapist who was required to have more than 10 years of professional experience. A Yijinjing Qigong master with over 15 years of practice and instruction experience taught all classes.

Control group

Routine segmental rehabilitation training

The control group was given single routine segmental rehabilitation training therapy, which was performed in a 60 min/session and once a day for 3 consecutive weeks. Briefly, for the arms, the patient lay on the back and the therapist treated the dysfunctional side with posthemiplegia manipulation; for the trunk, the patient lay on the back, with knees/hips bent and both hands tucked around the knees and the therapist gently shook the patient' s body to the left and right; and for the legs, the therapist stretched the iliopsoas, quadriceps, hamstrings, and calf triceps (Jiang et al., 2022).

Intervention group

Yijinjing Qigong exercise+routine segmental rehabilitation training

In addition to the routine segmental rehabilitation training, the patients were trained therapeutically with specifically tailored Yijinjing Qigong movements. The Qigong master displayed and guided the exercise action face to face for

patients every day and the therapist helped these patients practice by driving the affected side with the healthy side. All the patients were taught in a group together. The patients in this group practiced a 60 min/session once a day for 3 consecutive weeks. Each session included a 10-min warm-up, 40-min practice, and refinement (explaining some theories and procedures of Qigong and training motion control for muscle and joint, and meditation and rhythmic breathing

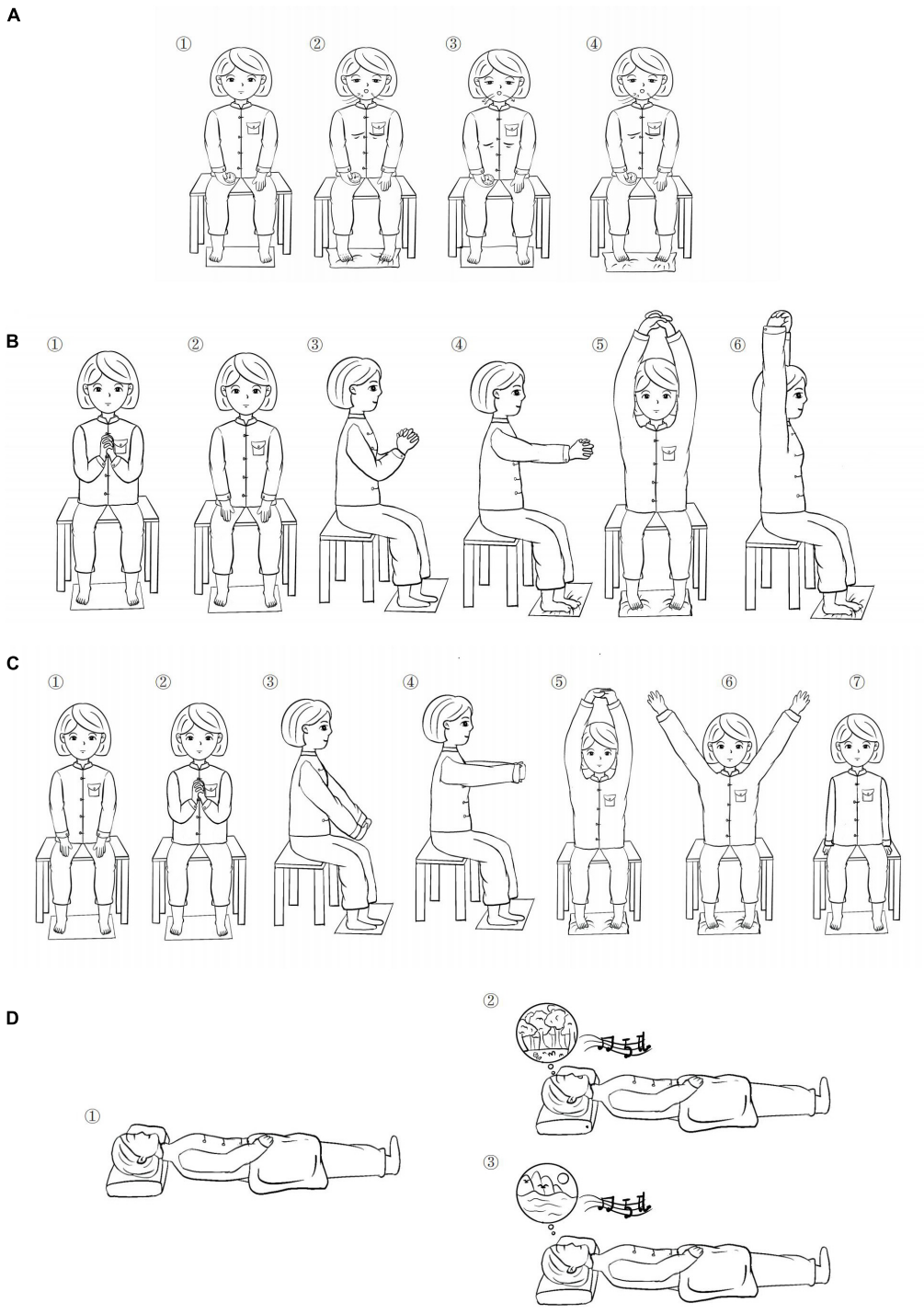


FIGURE 1
Qigong operation steps. **(A)** Action 1 Breathing practice; **(B)** Action 2 Sitting position Yijinjing (YJJ); **(C)** Action 3 Sitting position YJJ; and **(D)** Action 4 meditation and relaxation.

techniques), and a 10-min cool-down period (Figure 1 and Table 1).

Outcome measurements

We assessed the therapeutic effects using the changes in the HAMD-24 score; a decrease in the score indicates an improvement in the depressive state. In addition, we used EEG to probe the effect of Qigong on brain activity. Digital EEG (EEG-9200K, Nihon Kogyo Co., Ltd. Huancheng North Road, Fengxian District, Shanghai) was used for EEG recording. The EEG data collection of patients is operated by a professional engineer according to the strict operation standard unified process. We placed the electrodes by the international 10–20 system standard and two reference electrodes were used, one on each earlobe. A 21-wire EEG was recorded; the corresponding of each recording electrode to its name was: FP1-FP2-F3-F4-C3-C4-P3-P4-O1-O2-F7-F8-T3-T4-T5-T6-Fz-Cz. The two reference electrodes were A1 (left ear) and A2 (right ear) (Figure 2). We kept all electrode impedances < 10 kΩ, and continuously recorded the signals at a sampling rate of 200 Hz.

TABLE 1 Details of the operation of Yijinjing Qigong exercise (YJJQE).

Sequence of details	Action details
Action 1	Let the patient warm up and adjust the mood and enter the exercise stage for 10 min, Subject is sitting in a stable chair or a wheelchair suitable for his position, the healthy hand held a timer, the affected hand remained relaxed, the abdominal wall is relaxed, focus on breathing deep and evenly; when inhaling, scratching toes, adjust the eyes in a relaxed state, attention to the chest and abdomen, position is kept for 10 s, and then exhale, relax the toes, feel deep breathing attention to the fluctuations of the chest and abdomen. While in the process, feel your scratching toes and press the timer, this phase of the operation also lasts for 10 s. Repeat for 15 min.
Action 2	Watching the video under the exercise training, subject sitting in a stable chair positions, steady center of gravity, tight abdomen, comfortable head, flat eyes, tongue against palate, dropped shoulder, elbow, knee, are kept at 50–90°, normal breathing, intertwined hands with 10 fingers crossed, the healthy hand drives the affected hand, continue to raise-up to the chest position, slowly stretch forward, arms raised, inhale for 10 s while scratching toes, relaxed shoulder, straight-up body, Continue to reach your hands toward your head and ears, keep balance for 10 s. Subject assessed according to the upper limb movement function with angle adjustment for 10 min.
Action 3	Repeat exercise in motion, attention to the change in the wrist, crossed fingers, down palms, keep stretch, steady center of gravity, tight abdomen, straight-up body, slowly forward arms and palms, inhale for 10 s, shoulder relaxed, hands continue to extend-up to the head, scratching toes, keep balance for 10 s. ease your arms down from the sides, repeat for 10 min. Subject assessed according to the upper limb movement function with angle adjustment.
Action 4	Subject in a supine position, Supported and inclusive environment, undisturbed place with a sense of security, quiet, then listen to a 15-mins musical meditation, body relaxed, knee joint in a comfortable state to relax, with soft blankets, warm, and comfortable lights, temperature, and volume, staff open the meditation music, to stabilize the emotions. breathing with closed eyes, with the sound prompt; in a soft music scene imagination (forest, flowers, and water), feel the fragrance of the sun, air, and grass, feel the breeze, the strength of the sea, close to nature and self-connection. Practice for 15 min.

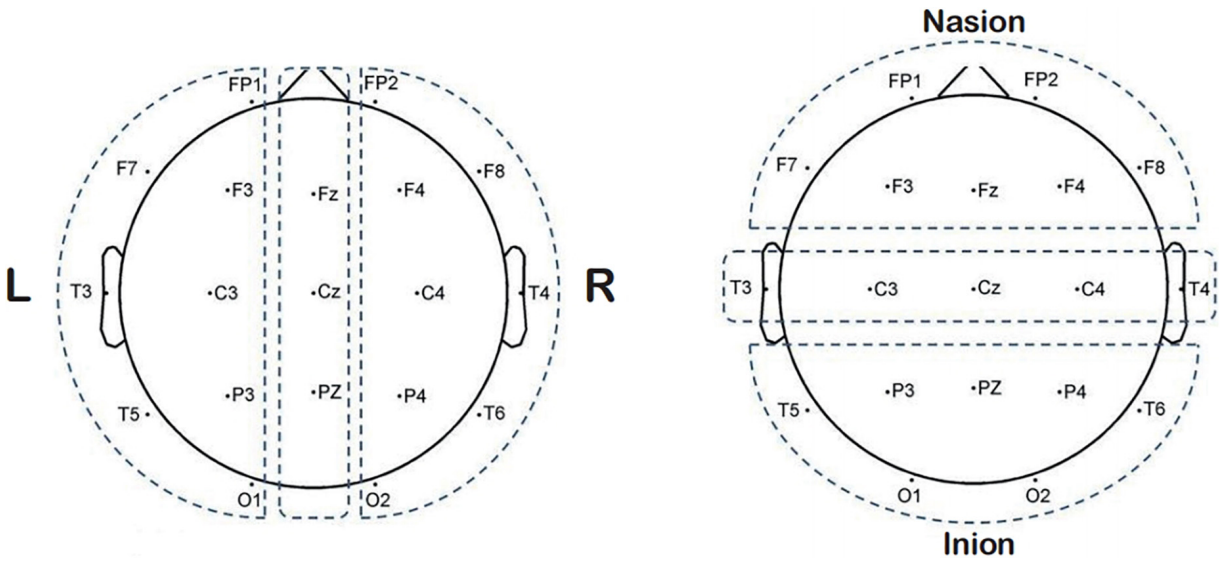


FIGURE 2
Electrode position diagram.

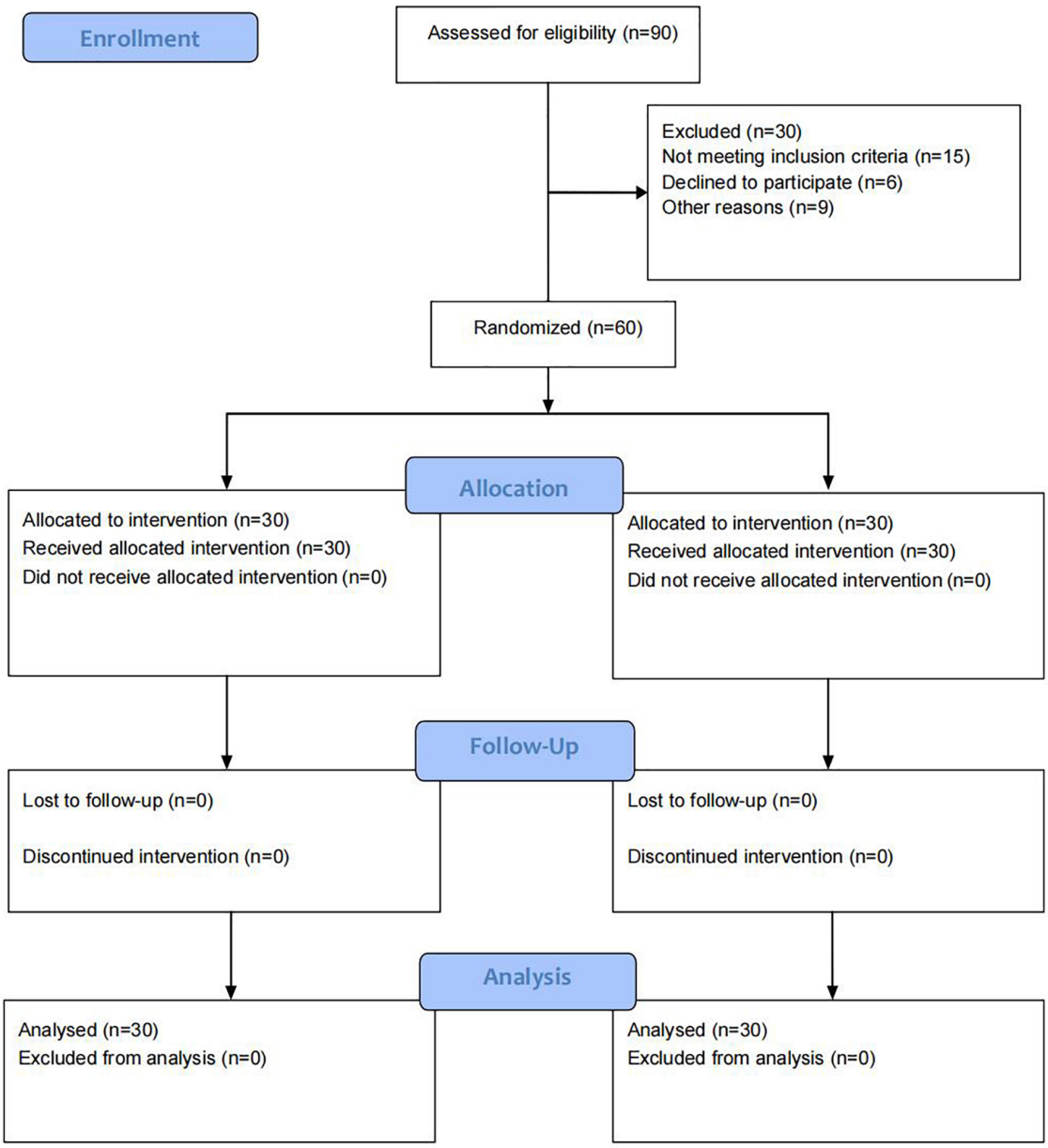


FIGURE 3
Recruiting process flowchart.

We amplified the EEG signal and divided the data into four frequency bands (delta: 1–4 Hz, theta: 4–8 Hz, alpha: 8–13 Hz, and beta: 13–30 Hz). Thereafter, the examination environment was quiet, at room temperature, with appropriate light, and the patient was not disturbed by vision and hearing. We asked the patients before the examination to not use psychotropic active substances and drugs (i.e., psychotropic drugs), nor another form of stimulant, and to have regular sleep the night before recording (Ríos-Herrera et al., 2019). About 2 h after the meal, we informed them about the purpose and scheme of the experiment. In the awake state during the whole test process, we asked the patients to avoid shaking their bodies. Noting that the electrodes should be far away from any interference source, such as power supply or electronic equipment, EEG data and signals were preprocessed using the EEG Matlab toolkit based on the Matlab software platform (R2012a, The Mathworks, Natwick, MA, United States). Spectrum analysis is a process used to quantify EEG. It decomposes a complex EEG signal into its component frequencies by applying the Fourier transform. The power spectrum reflects the amount of activity in the frequency band, and the relative power ratio can be used to assess the relative contribution of a specific frequency to the

TABLE 2 General information of enrolled subjects.

Characteristics		Control ($n = 30$)	Qigong ($n = 30$)	χ^2 or t	p
Sex (%)	Male	17 (56.67%)	17 (56.67%)	0	1
	Female	13 (43.33%)	13 (43.33%)		
Age		65.23 ± 6.29	62.03 ± 7.37	1.809	0.076
BMI		24.91 ± 3.23	24.82 ± 3.46	0.107	0.915
Smoking example (%)	Yes	8 (13.33)	9 (15.00)	0.082	0774
	No	22 (36.67)	21 (35.00)		
Alcohol drinking example (%)	Yes	12 (20.00)	14 (23.33)	0.271	0.602
	No	18 (30)	16 (26.67)		
Hypertension		4/26	2/28	0.741	0.671
Diabetes		12/18	15/25	0.606	0.436
Past cardiovascular disease		28/2	18/12	1.2	0.273
Paraparetic side of the limb	Left	18	15	0.606	0.436
	Right	12	15		
Disease duration (m)		7.53 ± 4.09	7.97 ± 5.27	0.356	0.723
Stroke type	Infarct	26 (86.67)	23 (76.67)	1.002	0.317
	Hemorrhagic	4 (13.33)	7 (23.33)		

EEG signal (Cozac et al., 2016). The Phase Lag Index (PLI) was used to analyze the Phase characteristics of synchronous oscillation signals in different EEG bands in the exercise therapy group before and after treatment. After calculating the change of PLI between EEG lead pairs before and after treatment, the acute index was superimposed and averaged, and the global PLI was calculated. The PLI measures the asymmetry of the distribution of instantaneous phase differences between different EEG signals.

$$PLI = \left|\left\langle sign\left(\Delta\phi_{rel}\left(t\right)\right)\right\rangle\right| = \left|\frac{1}{N}\sum_{n=1}^{N} sign\left(\Delta\phi_{rel}\left(t_n\right)\right)\right|$$

where N represents the time point and φrel the phase difference of two-channel signals at time TN; the sign is a sign function, PLI values range from 0 to 1, where 0 indicates there may be no coupling, 1 indicates complete phase lock, and a higher value indicates stronger phase synchronization between the two signals (González et al., 2018).

TABLE 3 HAMD-24 scores at the baseline 3 weeks and follow-up 1 month after treatment.

Scale		Control ($n = 30$)	Qigong ($n = 30$)	f	p
HAMD-24	Baseline	16.23 ± 4.19	14.57 ± 4.66	2.121	0.151
	3 weeks	16.60 ± 4.55	12.10 ± 4.75*#	14.028	<0.001
	1 month follow-up	16.37 ± 4.95	9.87 ± 4.27*#	29.633	<0.001

#Tip: Statistically significant using the repeated measurements comparison.
*Statistically significant using the multivariate analysis.

Global efficiency (GE) reflects the information processing efficiency of the whole brain.

$$\frac{1}{N\left(N-1\right)}\sum_{i\neq j}\frac{1}{l_{ij}}$$

TABLE 4 Areas under the curve (AUC) of global efficiency (GE) and local efficiency (LE) associated with different sparsity levels in the electroencephalography (EEG) examination.

EEG feature		Control ($n = 23$)	Qigong ($n = 26$)	t	p
GE-δ	Baseline	0.164 ± 0.005	0.165 ± 0.003	1.061	0.294
	3 weeks	0.162 ± 0.007	0.157 ± 0.010	2.061	0.045*
GE-θ	Baseline	0.160 ± 0.007	0.156 ± 0.008	2.061	0.045
	3 weeks	0.158 ± 0.006	0.164 ± 0.005	3.771	<0.001*
GE-β	Baseline	0.164 ± 0.006	0.165 ± 0.005	0.419	0.677
	3 weeks	0.161 ± 0.006	0.158 ± 0.007	1.868	0.068*
GE-α	Baseline	0.146 ± 0.009	0.139 ± 0.011	2.346	0.023
	3 weeks	0.151 ± 0.010	0.144 ± 0.014	2.051	0.046
LE-δ	Baseline	0.116 ± 0.015	0.112 ± 0.002	0.769	0.446
	3 weeks	0.119 ± 0.018	0.131 ± 0.022	2.033	0.046*
LE-θ	Baseline	0.115 ± 0.018	0.121 ± 0.018	1.185	0.242
	3 weeks	0.121 ± 0.013	0.099 ± 0.018	4.993	<0.001*
LE-β	Baseline	0.117 ± 0.016	0.139 ± 0.011	2.332	0.024
	3 weeks	0.120 ± 0.020	0.122 ± 0.175	0.284	0.778
LE-α	Baseline	0.115 ± 0.016	0.132 ± 0.016	3.175	0.004
	3 weeks	0.128 ± 0.017	0.144 ± 0.020	2.912	0.006**

*Statistically significant using the Bonferroni multiple comparison. **$p < 0.01$ significant statistical differences were observed.

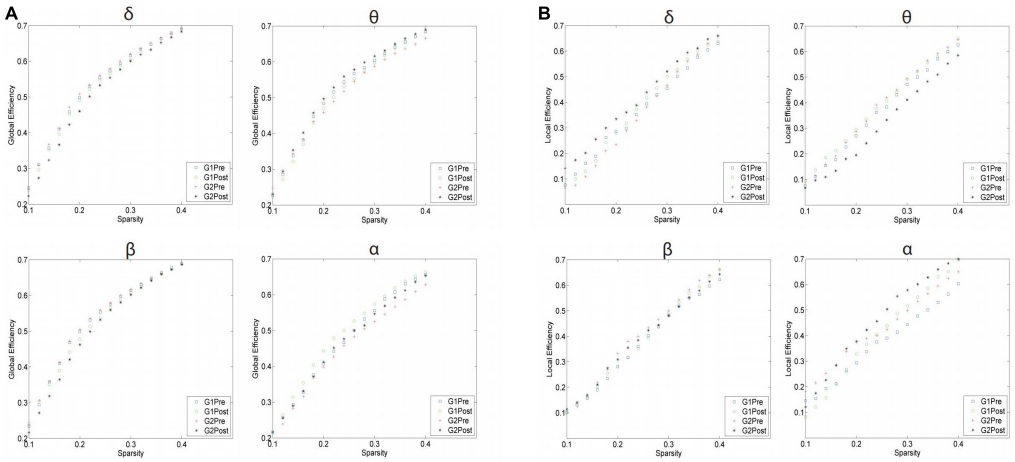


FIGURE 4
Difference of topological parameters of global efficiency between Qigong group and control group in **(A)** Delta band; Theta band; Beta band; and Alpha band before and after treatment. The sparsity was set as 0–80%. Delta band: δ; Theta band: θ; Beta band: β; and Alpha band: α. Difference of topological parameters of local efficiency (LE) between Qigong group and control group in **(B)** Delta band δ, Theta band θ, Beta band β, and Alpha band α before and after treatment. The sparsity was set as 0–80%.

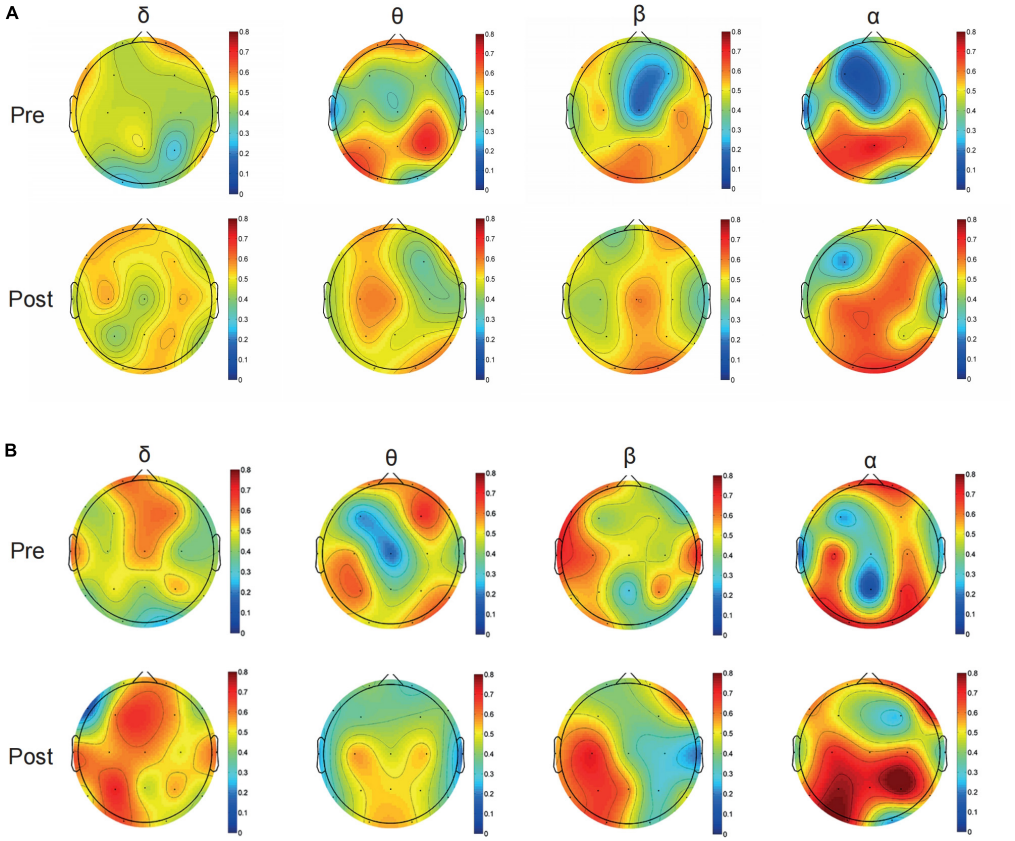


FIGURE 5
Typical topographical maps of power density [using the average local efficiency (LE)] Delta band, Theta band, Beta band, and Alpha band of control group **(A)** and Qigong group **(B)** after treatment, the frequency spectrum of (Fp1.Fp2.F3.F4), (T3.T4.T5), (P3) are mainly different in δ band; the frequency spectrum of the whole brain is different in θ band; and (T3.T5), (C3), (P3.Pz), (O1), and a small part (F8) are different in β band; the frequency spectrum of (FP1.FP2), (P3), and (O1.O2) are different in α band.

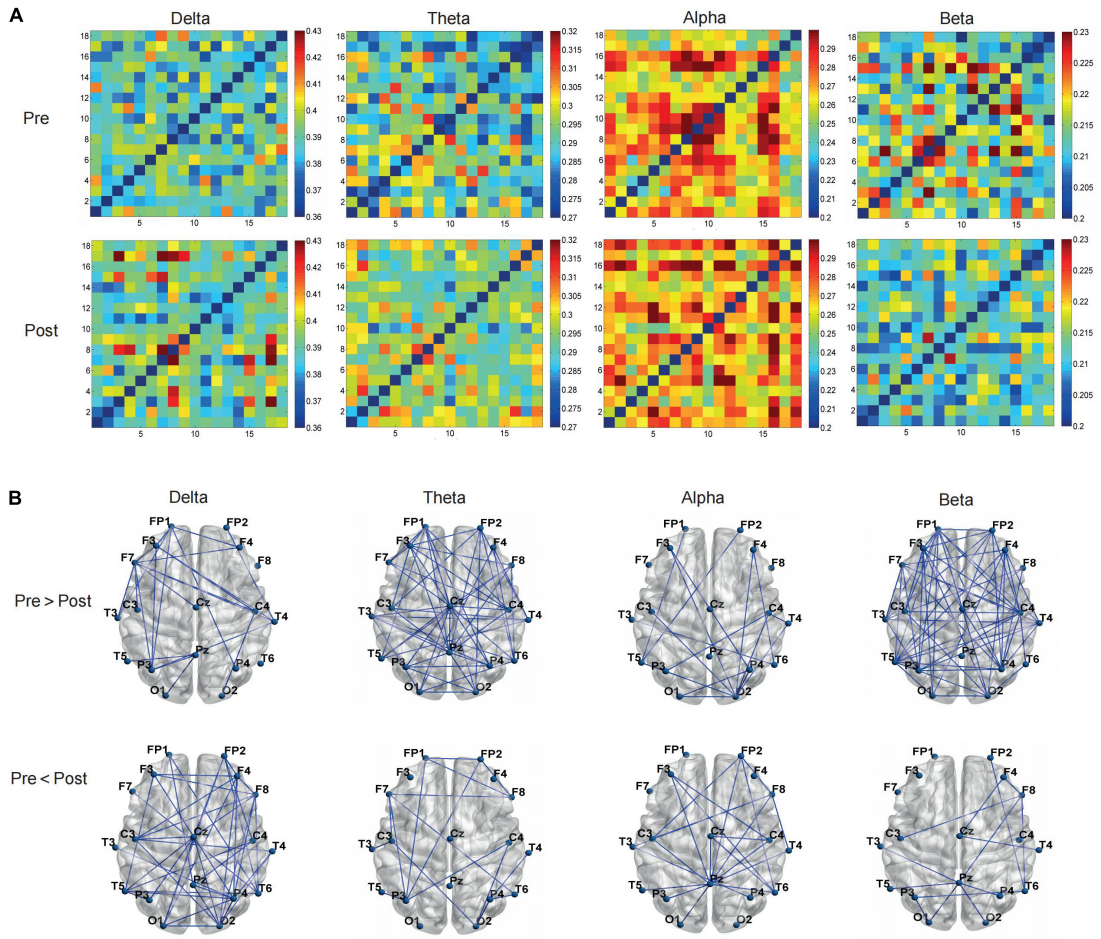


FIGURE 6
The Qigong group **(A)** by regarding phase lag index (PLI) value as the strength, verified 18*18 PLI functional connection moments, calculated global, and local topological parameters **(B)** on the brain network from the graph theory.

Local efficiency (LE) reflects the information processing efficiency of a local node (Kasakawa et al., 2016).

$$E_{loc}(i) = \frac{1}{N_{Gi}(N_{Gi}-1)} \sum_{j,h \in G_i} \frac{1}{l_{jh}},$$

In this context, we documented the average LE and GE of each node in the brain network for the whole brain of every patient. Simultaneously, to analyze the brain network from the graph theory regarding PLI value as the strength, we generated the nodal topo-plots for each band *via* the digital EEG system (sparsity = 0.3) and the differences in the areas under the curve (AUC) under different sparsity degrees were determined.

Data analysis

Categorical data were presented as percentages and compared by χ^2 test; numerical variables were expressed as mean ± SD and compared between the two groups *via* a *t*-test. ANOVA of duplicate measurement data was used for observation of indicators at different time points, and multivariate analysis was used for comparison of the same observation index at different time points. The EEG data (GE or LE) were compared using the Wilcoxon rank-sum test. In a normal *t*-test or χ^2 test, a p-value < 0.05 was regarded as statistically significant. For EEG analysis (four frequency bands), Matlab R2013b and its toolkit EEGLAB were applied, and we performed the Bonferroni multiple comparison corrections, wherein a p-value < 0.003 ($P_{Bonferroni} = 0.05/16$) was considered significant. Correlation analysis was performed first. If the scatter plot showed a linear distribution, and the data were normally distributed, the Pearson linear correlation test (Pearson correlation coefficient test) was performed. However, if the data did not show a normal distribution, correlation analysis using the Spearman correlation test was performed. If the scatter plot showed a non-linear distribution, a non-linear correlation analysis was performed.

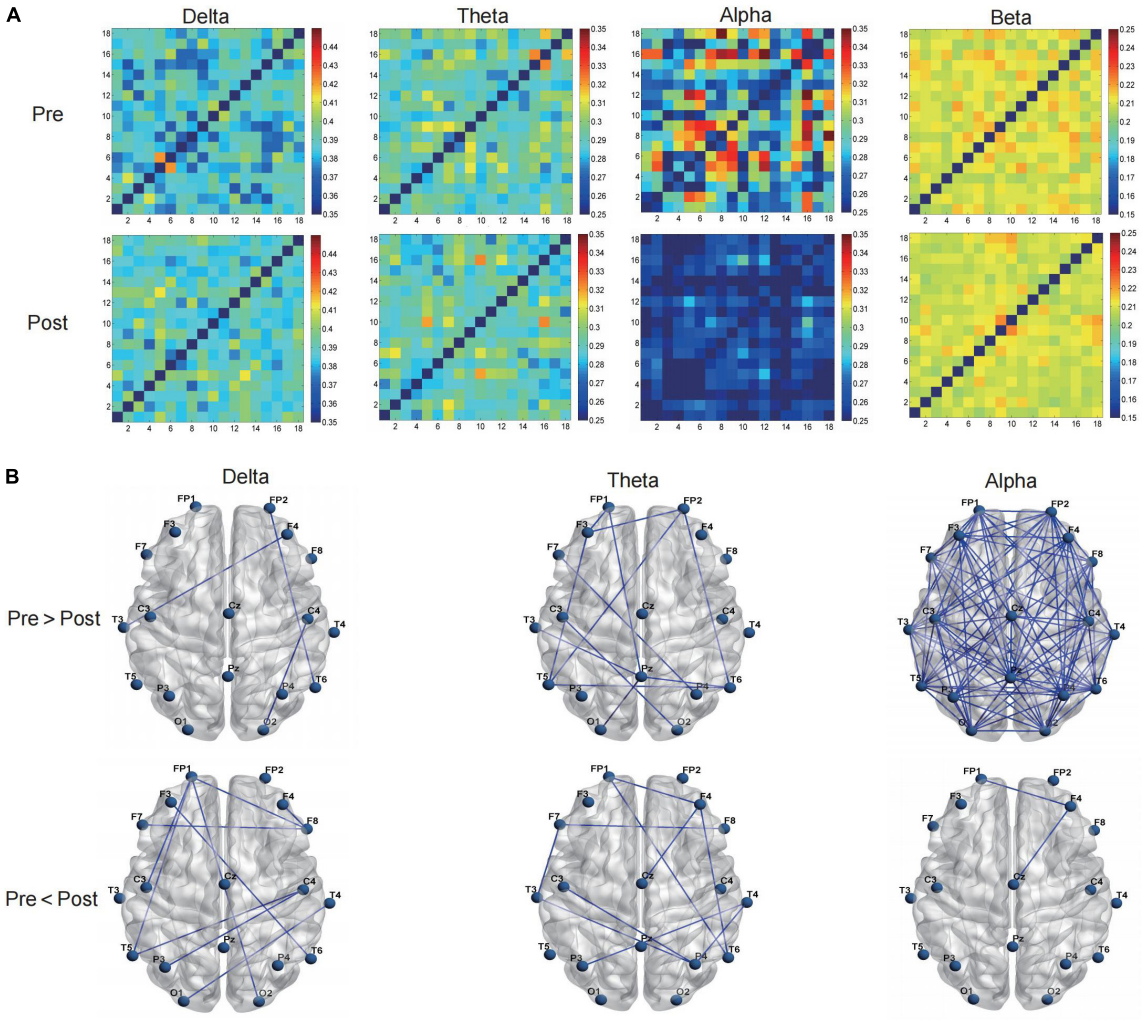


FIGURE 7
The control group **(A)** by regarding phase lag index (PLI) value as the strength, verified 18*18 PLI functional connection moments, calculated global, and local topological parameters **(B)** on the brain network from the graph theory.

Results

Participants and baseline characteristics

The flow diagram of the study is presented in Figure 3. A total of 90 patients were enrolled of which, 15 did not meet the inclusion criteria, six refused to participate in the study, and nine patients were unable to complete the entire study for various reasons. The remaining 60 patients met the eligibility criteria (30 in the Qigong group and 30 in the control group), and then completed the 3-weeks treatment and assessment, and 1 month of follow-up applying the HAMD-24 score. The EEG data of 49 patients before and after treatment were analyzed because the signal quality of seven in the control group and four in the treatment group was disturbed seriously by shaking of the small facial muscle group which interfered with the collection of signal in the EEG. No significant difference was observed between the two groups at the baseline as shown in Table 2 ($p > 0.05$). The average age of the patients in the control and Qigong groups was 65.37 ± 6.52 and 62.70 ± 8.63 years, respectively. In addition, there were no significant differences between the two groups in terms of body mass index, smoking, and alcohol drinking history, hypertension, diabetes, past cardiovascular disease, paraparetic side of the limb, disease duration, and stroke types ($p > 0.05$) (Table 2).

Effect of Qigong on HAMD-24 score

The effect of Qigong on the HAMD-24 score was assessed at the baseline after 3-weeks and 1-month follow-up treatment.

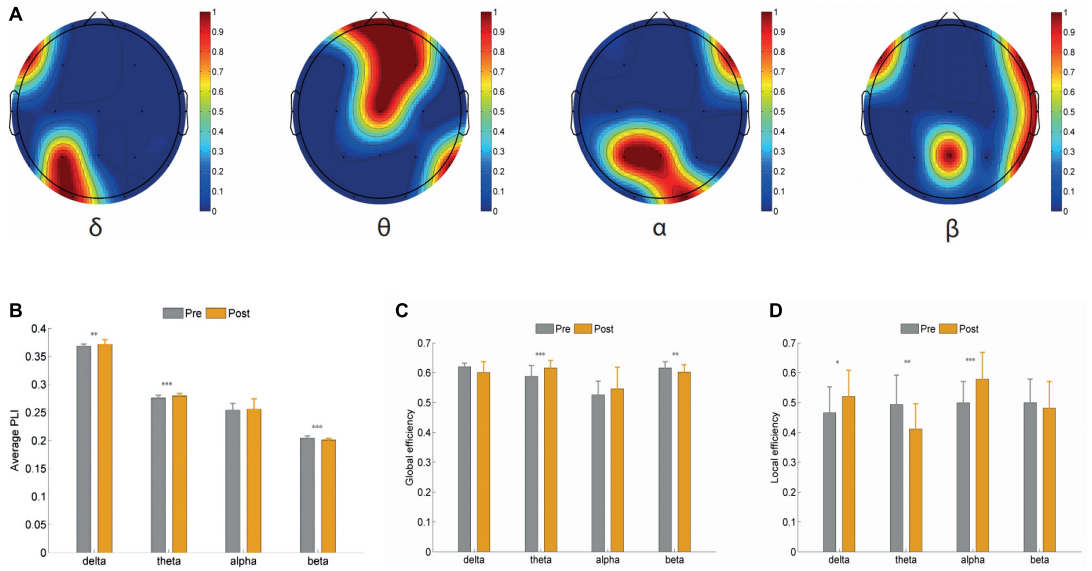


FIGURE 8
(A) Global efficiency (GE) local efficiency (LE) of each frequency band was evaluated when the average phase lag index (PLI) sparsity of brain functional connections **(B)** different frequency bands was equal to 0.3 before and after Qigong group, Delta band, Theta band, Alpha band, and Beta band. **(C)** The sparsity was set as 30%, GE of each frequency band was evaluated. **(D)** The sparsity was set as 30%, LE of each frequency band was evaluated. *$P < 0.05$, have statistical differences. **$P < 0.01$, significant statistical differences. ***$P < 0.001$, significant statistical differences.

Table 3 showed that the HAMD-24 scores at the baseline were similar. The Qigong groups can effectively improve depression at different times. Over time, the effect became much more obvious. The patients were followed up for 1 month, whereas the average score significantly decreased in the Qigong group compared with the control group (9.87 ± 4.27 vs. 16.37 ± 4.95, $p < 0.001$). This outcome proved that YJJQE might have positive clinical effectiveness in improving PSD.

Effect of Qigong on the electroencephalography signal features

As shown in Table 4, we compared the AUC for GE and LE regarding each sparsity using the four bands and evaluated the overall difference in AUC between the two groups. θ wave was significantly reduced after treatment compared with the control group (0.164 ± 0.005 vs. 0.158 ± 0.006; $p < 0.001$) and (0.099 ± 0.018 vs. 0.121 ± 0.013; $p < 0.001$). GE and LE brain network efficiency increased compared to the control group; the YJJQE group showed a significantly greater functional connectivity in the δ, θ, and β frequency bands in the brain network of the degree of phase synchronization ($p < 0.001$).

The curves of GE and LE regarding different sparsity levels are presented in Figure 4, and for the 2o groups each wave band, the nodal topo-plots constructed using average LE are shown in Figure 5. Before treatment, the θ wave mostly appeared in the right frontal lobe, frontal lobe, left frontal lobe, right temporal lobe, right anterior temporal lobe, left posterior temporal lobe, and left parietal lobe. The PSD patients reduced the power of the right temporal lobe in the prefrontal cortex (FP2.FP1.F4), which reduced the length of the feature path, accelerated the information exchange between neighbor nodes, improved the speed of information transmission between brain networks, and improved the network efficiency. We continued to evaluate functional brain connections in different frequency bands before and after the Qigong group. We verified 18×18 PLI functional connection moments and calculated global and local topological parameters (Figure 6).

The average PLI of the brain functional connectivity in different frequency bands before and after the Qigong group practice was evaluated as follows: the δ frequency bands (0.3680 ± 0.0028 vs. 0.3718 ± 0.0066; $p < 0.01$), θ frequency bands (0.2755 ± 0.0039 vs. 0.2791 ± 0.0032; $p < 0.001$), and β frequency bands (0.2037 ± 0.0030 vs. 0.2006 ± 0.0020; $p < 0.001$). The sparsity was set as 30%, Statistics were performed for the electrical signals at each electrode and the brain network topology map was depicted. The results showed that the local efficiency of the δ frequency network was enhanced in the F7 left anterior temporal, O1 left occipital, left parietal P3 (0.4659 ± 0.0843 vs. 0.5204 ± 0.0854; $p < 0.05$). Global and local efficiency enhancement of θ band network in FP1, right prefrontal FP2, F3, F4, right frontal, central region of CZ, and right posterior temporal T6 was (0.5872 ± 0.0347 vs. 0.6159 ± 0.0231; $p < 0.001$), (0.4932 ± 0.0966 vs.

0.4112 ± 0.0824; $p < 0.01$). The local efficiency of the α frequency band network was significantly enhanced in F8 right anterior temporal, P3 left parietal lobe, PZ top, and midline, and O2 right occipital lobe (0.4989 ± 0.0694 vs. 0.5780 ± 0.0878 $p < 0.001$). The global efficiency enhancement of the β frequency band network was located in F7 left anterior temporal; PZ midline; and F8 right anterior temporal, T4 right middle temporal, and T6 right posterior temporal, (0.6161 ± 0.0184 vs. 0.6021 ± 0.0225; $p < 0.01$). Power density Comparison between the two groups showed statistical significance in the enhancement of alpha frequency power density ($p < 0.05$). The changes in δ, θ, α, and β band power density in the two groups before and after treatment are shown in Figures 9, 10.

Discussion

To the best of our knowledge, this is the first randomized, controlled study to demonstrate that YJJQE can alleviate the depressed mood of patients with PSD after 3 weeks of intervention. The findings showed that the YJJQE after treatment resulted in significant improvements in mental and physical anxiety symptoms, such as restlessness, sweating, dry mouth, sleep quality (falling asleep became easier and the number of night awakenings was also reduced), and physical symptoms of fatigue and gastrointestinal disorders. Our study presented the YJJQE as a mind–body intervention to be useful as a non-pharmacological treatment to prevent PSD.

Previous studies on the rehabilitation of patients after stroke patients through traditional Chinese exercise have shown that they can enhance the ability of patients to control their trunk as well as leg strength and mobility. Traditional Chinese exercise can also improve the function of respiratory muscles and significantly improve patients' cognition and quality of life (Zhang et al., 2016; Yuen et al., 2021). Meanwhile, in another study on poststroke mind–body problems, acupuncture combined with YYJQE revealed superior improvement effects on the motor function scores and self-rated depression scale scores. To date, previous studies of evidence-based Qigong exercises for treating PSD were extremely limited

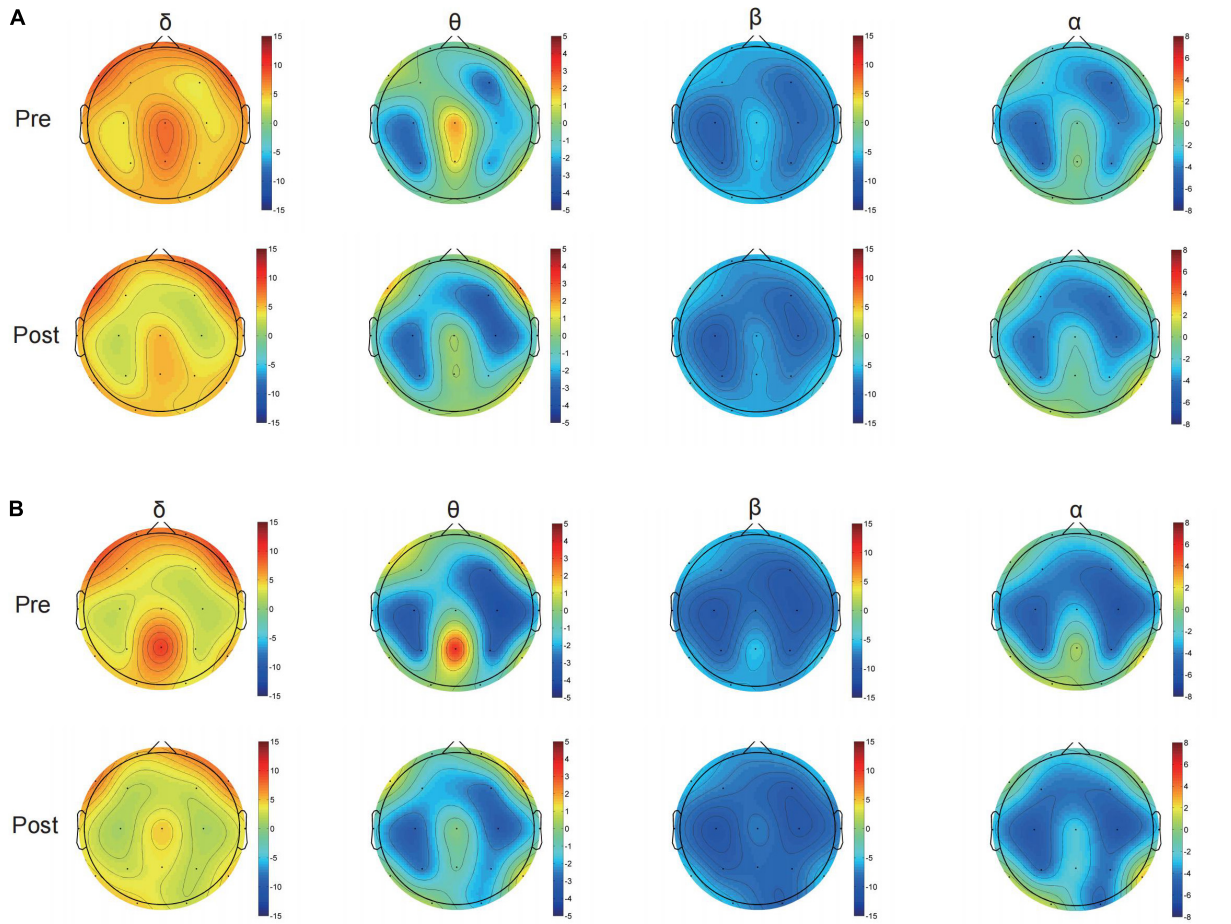


FIGURE 9
Power spectral density before and after treatment in the **(A)** control and **(B)** Qigong groups.

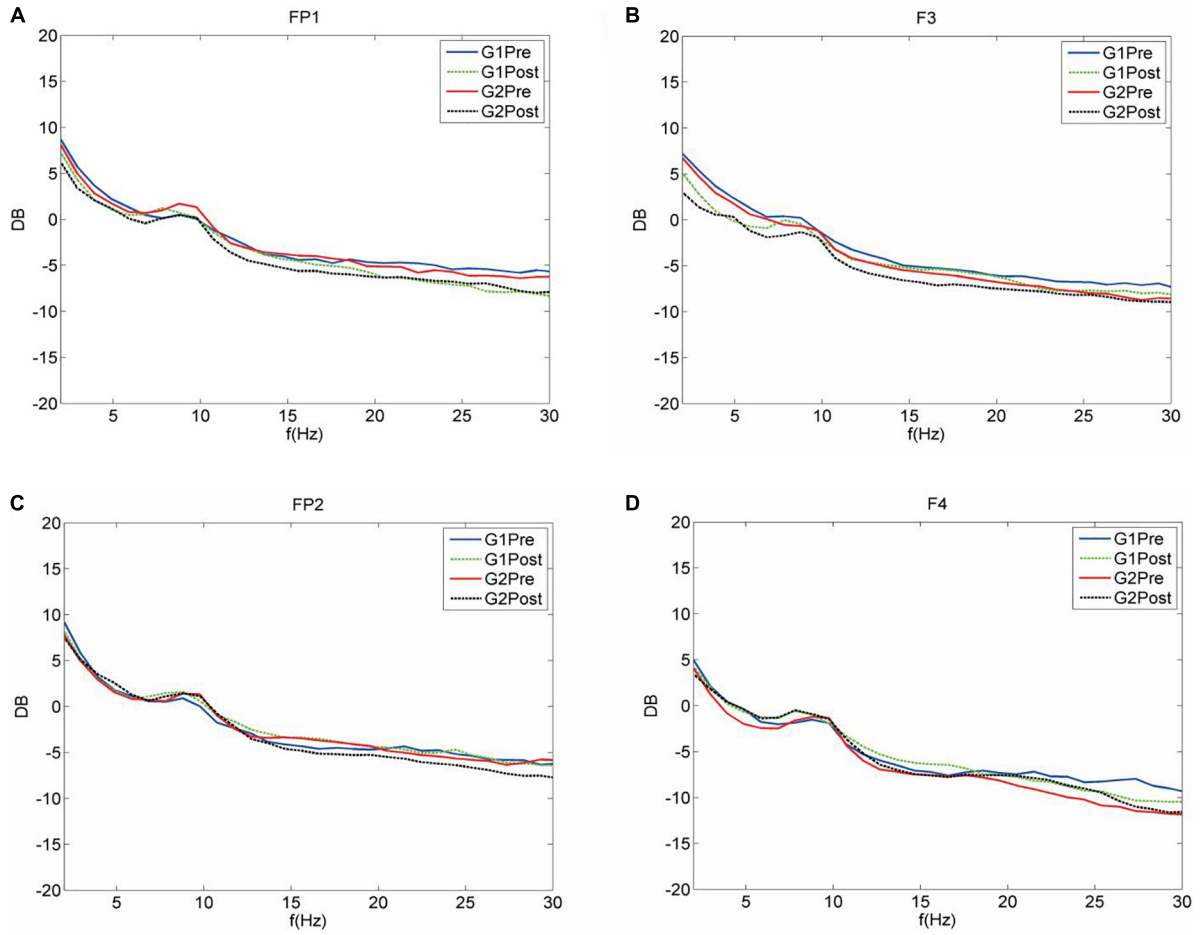


FIGURE 10
Average spectrum curves of the full leads. The average spectrum curves of both groups were significant before and after treatment (Fp1.Fp2.F3.F4). Delta band (1–4 Hz); theta band (4–8 Hz); alpha band (8–13 Hz); and beta band (13–30 Hz). **(A)** FP1 G1 of the control group before treatment. The values for the delta and theta band power increased, whereas, those for the alpha band power decreased. However, the alpha band power increased after treatment. G2 before treatment of the treatment group. Increasing trend in the powers of four frequency bands. The powers of the four frequency bands decreased after treatment. **(B)** F3 left frontal lobe G1 of the control group before treatment, Delta, theta, alpha, and beta bands showing an increasing trend in power. After treatment, the delta and beta bands showed a decay of power, whereas the theta band power increased. G2 of the treatment group. The powers of four frequency bands showing an increasing trend. The powers of the four frequency bands decreased after the treatment. **(C)** FP2 G1 of the control group before the treatment. The alpha band power showed an increasing trend, whereas the powers of the delta, theta, and beta bands showed a decreasing trend. After treatment, the alpha and beta band powers increased. G2 of the Qigong group showed a delta power coast down and increases in the delta, alpha, and beta powers. After treatment, the delta power increased, whereas the theta and beta powers showed a coast down. **(D)** F4 G1 of the control group before the treatment showed decreases in the delta, theta, alpha, and beta band powers. After treatment, the delta and beta bands showed a decay of power, whereas the alpha band power increased. G2 of the Qigong group showed decreases in the delta, theta, and beta band powers. After treatment, the delta, theta, and beta band powers increased.

(Thomas et al., 2019; Hordacre et al., 2021). One meta-analysis has been proposed but with a lack of evidence concerning its effects conclusion (Dong et al., 2020). Nevertheless, Qigong is one of the effective complementary therapies for treating depression (Haller et al., 2019). Qigong could improve the self-rating depression scale and anxiety scale scores, which exert auxiliary effects on improving lung function in patients with COPD (Wu et al., 2019). In addition, several studies have suggested its potentially beneficial effect on symptoms of anxiety among individuals with drug abuse (Liu et al., 2020). However, several studies demonstrated no benefits of Qigong in treating depression; thus, further research using randomized controlled trials and rigorous designs is needed (Oh et al., 2013.)

This study indicated that the YJJQE treatment showed a significant reduction in θ wave and an increase in the GE and LE of the network functional connectivity in different brain regions by EEG. A recent study evaluating the brain network performance of patients with PSD using EEG mutual information showed significantly weakened connections between the left and right cerebral hemispheres,

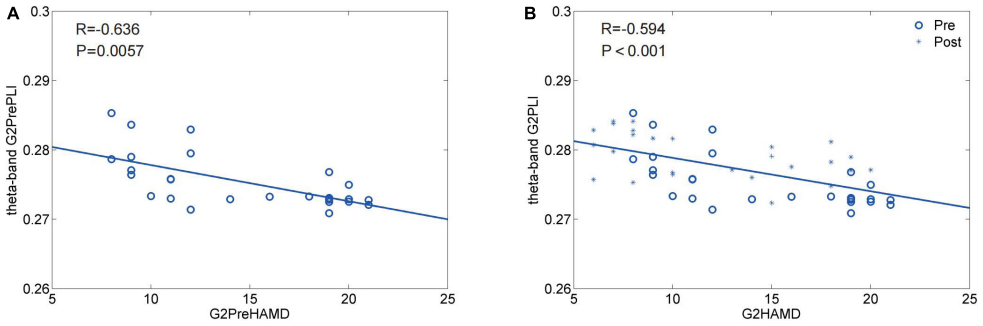


FIGURE 11
(A,B) HAMD-24 score and EEG correlation analysis before and after treatment in both groups. G2 of the Qigong group Theta band pretherapy, By After correction $p = 0.0057$; It has relevance, $R = -0.636104330651571$ negative correlation. G2 of the Qigong group Theta band post-treatment, By After correction $p = -8.446060534953326e-05$, There was a significant correlation. $R = -0.593536751161075$ had a negative correlation.

and this feature was more obvious with an increasing degree of depression (Sun et al., 2018; Xu et al., 2019). The right PFC is more related to negative emotions. An injury of the right PFC leads to a lack of the ability to experience positive emotions, even depressive symptoms (Morris, 1997). We found that PSD patients reduced the strength of the right temporal lobe in the prefrontal cortex [(FP2), FP1.F4], enhanced connectivity in the left prefrontal cortex, and improved the network efficiency after treatment. At a sparsity level of 0.3, the θ waves in our study showed the most significant changes in the prefrontal cortex and the right temporal lobe and significantly enhanced functional brain connectivity in the Qigong group. These regions are associated with the regulation of emotion, motivation, learning, attention, social behavior, and behavioral decision-making. The brain activity shows that the interconnection between the nodes changed due to the Qigong meditation training. It was attributed to relaxation, concentration, and behavior control. Moreover, θ waves are also involved in the edge-PFC interaction and the synchronization of brain network activities. The interaction between the above regions can be mediated by the θ waves, which support the important communication mechanisms between memory, executive function, and depression-related brain regions.

At a sparsity level of 0.3, the β wave decreased, the α and δ waves increased, and the network efficiency was significantly increased in the Qigong group. Previous studies found that within 3–6 months after the stroke, the EEG abnormalities in PSD patients showed a decreased α frequency and a slow wave increase in the frontal lobe (Coito et al., 2019), which have been considered independent predictors of PSD (Zheng et al., 2018). The α and δ low-frequency activity of the wave, as well as the anomalous oscillations, have an asymmetry between the left and right hemispheres (Pierre et al., 2004; Wang et al., 2017; Rochais et al., 2018), β wave increasing in bilateral or right frontal waves in patients with depression, the anxiety-type depression group in elderly depressed patients showed an enhanced β 1-wave activity in the parietal and occipital regions (Suzuki et al., 1996; Volf and Passynkova, 2002; Pizzagalli et al., 2018). The association between low β2 main peak frequency in the EEG and the vulnerability to depression has also been noticed in animal models (Claverie et al., 2016).

In this study, the HAMD-24 scores and EEG correlation analysis in the Qigong group, which had a negative correlation, indicated that depression decreases with increase in Qigong training; those in the control group were not correlated (**Figure 11**). The control group was not correlated. The EEG data strongly supported the results of the HAMD-24 score, which indicated that Qigong could enhance the GE-θ of the brain network in patients with PSD while homogenizing the LE-θ. Although there has been published evidence, the link between the θ band rhythm and PSD was not fully revealed. Our result is logically consistent with the recognized knowledge that enhanced θ-activity and symmetry are associated with better outcomes of PSD. The improvement of the θ frequency band preliminarily indicates that practicing the modified YJJQE (focusing on breathing and limb movements) during meditation could enhance brain network activity, improve the efficiency of information communication/integration between different brain areas, and alleviate negative emotions. This exercise could be widely applied and further studied in relation to the mechanism of brain connectivity.

This study has several limitations. Due to the small sample size, we compiled patients with different locations of stroke lesions to analyze EEG, yet it is ambiguous whether this might impact the results of the brain network topology; further studies are required to screen patients with a lesion in a specific area to confirm our conclusion. The period of intervention was only 3 weeks, and it remains unclear whether long-term intervention could also provide better efficacy.

Conclusion

This is the first randomized controlled study to use a YJJQE training protocol specifically designed for patients with PSD and determine the mechanism of network functional connectivity in different brain regions by EEG. The findings added increasing evidence regarding the clinical benefits of Yijinjing Qigong as a non-pharmacological therapeutic modality for patients with PSD to improve depressive symptoms. The PSD patients after YJJQE intervention reduced the length of characteristic path, and accelerated the information exchange between neighbor nodes, and improved the transmission speed of information and the network efficiency between brain networks. Therefore, this study provides a non-drug therapy for the treatment of PSD. Further evidence is needed to support the conclusions of this exploratory study.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PS, SZ, LJ, CY, ZM, QZ, and MF drafted, reviewed, and revised the manuscript. QZ and MF managed the methodology of the study. All authors have read and approved the theory and manuscript of the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of exercise intervention on executive function of middle-aged and elderly people: A systematic review of randomized controlled trials

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Background: Executive function will gradually decline with the increase of age, which will have a negative impact on the quality of life and general health. Exercise intervention can improve executive function and prevent its deterioration, but the evidence from randomized controlled trials is not consistent.

Aim: To assess the effect of exercise intervention on executive function of healthy middle-aged and elderly people, and briefly describe its mechanism.

Methods: A search was conducted using PubMed, Web of science and EBSCO. The searches were limited to English articles published from January 2010 to January 2022. The information is extracted from searched articles included or excluded based on certain criteria.

Results: The search returned 2,746 records, of which 11 articles were included in the systematic review, and 8 articles were supplemented according to the references included and related reviews. The results show that different types of exercise intervention have positive effects on the executive function of the middle-aged and elderly people. The intervention prescriptions in most studies are executed in medium to low frequency, medium intensity and medium duration, while only 11% of the studies were followed up.

Conclusions: The intervention, which was executed twice a week with 30–60 min single intervention time and over 12 weeks total duration, showed a good intervention effect. Exercise intervention is to improve executive function by affecting the activation of brain network and the synthesis of neurotransmitters.

KEYWORDS

executive function, exercise intervention, elderly people, middle-aged people, system review

Introduction

Executive function (EF) is the advanced cognitive ability of individuals, as well as the core of cognitive, emotional and social functions. The core content of EF includes three aspects: inhibition control, working memory and cognitive flexibility (Miyake et al., 2000). The decline of EF will seriously impact people's daily life, as they both closely related to each other. When the EF is impaired, it will be difficult for individuals to focus their attention on a certain point, or they will appear behavioral reactions that deviate from the target, as well as the symptoms of memory persisting declination, etc. (Chang et al., 2014). If there is no timely intervention and prevention, it can lead to inability of coordination of thinking and behavior to adapt to the changes of the environment, then gradually developing into Alzheimer's disease (AD), which has a great impact on the quality of life of the middle-aged and elderly people. Therefore, improving the EF of the middle-aged and elderly people is of great significance in improving the quality of life in the late stage of life and realizing the successful aging of the elderly people.

Distinguished from drug therapy, exercise intervention is a way to improve EF, which has attracted the attention of researchers *via* its safety and non-invasive. It has been proved and reported by a large number of studies that the appropriate exercise intervention or physical activity could bring beneficial effect to human health. Spirduso was the first to find a positive effect of physical activity on cognitive function (Spirduso and Clifford, 1978). Epidemiological studies have shown that people who take moderate exercise have a lower risk of mental disorders than sedentary people. And the beneficial effects of physical activities are most obvious in the EF (Etnier and Chang, 2009).

A randomized controlled trial (RCT) is a type of scientific experiment that aims to reduce certain sources of bias when testing the effectiveness of new treatments. Results of RCTs may be combined in systematic reviews which are increasingly being used in the conduct of evidence-based practice (Chalmers et al., 1981). The results from RCTs show that different forms of exercise including aerobic exercise, resistance exercise and physical and mental exercise for a period of time can promote memory updating, inhibition control and other EF of healthy middle-aged and elderly people (Northey et al., 2018). Also, the appropriate level of physical activities can help the elderly people with mild cognitive impairment to improve the EF to a certain extent (Zheng et al., 2016), even effectively prevent and delay the occurrence and development of AD (Cammisuli et al., 2017; Panza et al., 2018b).

However, other RCTs have pointed out that exercise intervention cannot improve cognitive and EF, high-intensity exercise may cause exercise fatigue even damage to EF (Van Duinen et al., 2007). The inconsistent results observed in RCTs make it impossible for clinical workers and researchers to summarize more accurately on the effects of exercise intervention and cognitive health of the middle-aged and elderly people. In addition, there are some experimental design defects and method limitations in the previous system review. In addition, although some researchers have made relevant reviews in the field of exercise affecting executive function, there are few reviews on middle-aged and elderly people. And few researchers focus on exercise prescription variables to explore and review the impact of exercise on executive function. Thus, it is necessary to systematically review the newly published RCTs on the effects of exercise intervention on the EF of the middle-aged and elderly people.

Therefore, this systematic review of RCTs attempts to clarify the differences observed in recently published RCTs. It also discusses the influence of exercise prescription variables on EF and the mechanism of exercise intervention to improve the EF of the middle-aged and elderly people, so as to provide reference for formulating intervention strategies and improving the quality of life of the middle-aged and elderly people.

Methods

Eligibility criteria

This systematic review included studies that met the following criteria: (a) the subjects were healthy middle-aged and elderly people over 40 years old with normal cognitive function. (b) Intervened target should be the EF (inhibitory, updating and switching) of the middle-aged and elderly people. (c) The experimental method must be a randomized controlled trial. (d) The EF was evaluated after the intervention. (e) Non-middle-aged and elderly people (infants, children, adolescents and others) and non-exercise intervention studies were excluded according to the title of the retrieved literature. (f) Reviews, degree papers, conference papers and non-English articles were not included in the search scope. (g) Studies that did not report detailed data results in full text or abstracts were also excluded.

Literature search

Systematic searches of the literature published from January 1, 2010 to January 1, 2022 were conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) using the electronic databases Web of Science, PubMed, EBSCO and MEDLINE The databases were searched by either title or title and abstract. The search items included 4 groups: (a) population: elderly, aging, middle-aged, older. (b) EF: executive function, executive control, inhibition, updating, working memory, switching. (c) Exercise: physical activity, sport, exercise. (d) Experimental

design: randomized controlled trials, randomized clinical trials, controlled clinical trials.

Study selection

First of all, Boolean logic word "AND" and "OR" were to connect the search items for retrieval. Secondly, the full text and references that meet the retrieval conditions were searched manually to supplement the missed documents in the first round of retrieval. Finally, the references of the reviewed literature were searched manually to supplement the missing documents in the first two rounds of retrieval.

Data extraction

The literature information is extracted by the two authors, respectively, and the inconsistent information is judged by the communication between the two authors. The data extracted from the final included literature includes: first author, year of publication, sample characteristics, exercise intervention prescription, execution of functional tasks, and result measurement. The specific literature information included in this review is shown in Tables 1, 2, established on the basis of Table 1, is the result of a quantitative summary of the characteristics of each study.

Risk of bias in individual studies

The quality and level of the evidence of included studies were assessed by two authors using the Cochrane Collaboration's tool for assessing risk of bias for RCTs (Higgins et al., 2011). Each item is judged independently by two authors on the risk of material bias. When there is a difference in the evaluation between the two authors, it must be discussed.

Subcomponent of executive function

Miyake et al. believed that executive function is not a single-structure system, but a multi-dimensional cognitive structure composed of multiple sub-functions, including inhibition, updating and switching (Miyake et al., 2000). Researchers often use task paradigms such as Stop-signal, Stroop, Flanker, Simon, and Go/Nogo to measure individual inhibitory control ability. Memory refresh is mostly measured by task paradigms such as alphabet (number) activity memory task, tracking task, number refresh task and N-back paradigm. Attention switching is often assessed using the task switching paradigm. Task types include digital part-of-speech switching, more-odd switching, plus-minus switching, local-global tasks, etc.

Results

As shown in Figure 1, according to the search strategy, a total of 2,746 articles were retrieved, of which, 11 articles were included after screening, and 8 articles were supplemented based on the included references and related reviews. Finally, 19 articles were included with 63.16% articles published from 2010 to 2015 and 36.84% from 2016 to 2022.

Demographic factors

We found that the average age of 84.2% of the subjects was between 65 and 75 years old. Fifty-five to sixty-five year-old subjects accounted for 5.3% of the total included in the study, and 10.5% were older than 75 years old. In addition, there were no middle-aged subjects under the age of 55 in the included study. 31.6% of the subjects in these studies were sedentary.

In terms of gender, 15.8% of the studies conducted exercise intervention only on men, 31.6% of the studies only on women, and the remaining 52.6% of the studies used overall (male and female) samples for exercise intervention.

Risk of bias

All the studies included were RCTs designed and reported randomized allocation. All randomized controlled intervention studies used EF assessment tools with good validity. Of these, <10% of the studies used a double-blind design, and 44.4% of the studies used a single-blind design.

The study included with a sample size of 30–60 and more than 90 accounted for 36.8 and 31.6%, respectively. Studies with a sample size of 61–90 accounted for 26.3%. 5.3% of the studies had a sample size of <30 people.

Intervention prescription

According to Table 1, we can find that so far, various types of exercise intervention measures have been carried out among the middle-aged and elderly people with normal cognitive function, with different intervention duration and frequency.

In terms of the time of single intervention, 68.4% of the research intervention time was concentrated in 30–60 min. 21.1% of the studies had an intervention time of more than 60 min, and another 5.3% of the studies had an intervention time of <30 min. In terms of the frequency of intervention, 78.9% of the studies had an intervention frequency of 2–4 times a week, 15.8% of the studies were <2 times a week, and 5.3% of the studies were more than 4 times a week. From the perspective of the overall intervention cycle, the time of intervention ranges from 4 to 52 weeks. 57.9% of the research intervention time was

TABLE 1 Intervention characteristics of included studies.

Study	Grouping	Exercise characteristics	Sample characteristics	CF or EF Task	Outcome measurement
Martin-Willett et al. (2021)	LICT group ($n = 64$) MICT+IT group ($n = 78$)	Freq.: 3 days/week Int.: 50% HRmax (LICT) and 60-95% HRmax (MICT+IT) Type: AE Time: 30 min Length: 16 weeks	Age: >60 Gender: Both PF: Sedentary	Stroop Keep Track task Category Switch task	Compared with the baseline, both: EF↑*
Kleinloog et al. (2019)	Intervention group ($n = 17$) Control group ($n = 19$)	Freq.: 3 days/week Int.: 70% Pmax Type: AE Time: 50 min Length: 32 weeks	Age: >65 Gender: Male PF: Sedentary	MTT SSP	Compared to the control group, Intervention: frontal lobe CBF↑*, OGTT↓*, EF↑*
Norouzi et al. (2019)	mMtt group ($n = 20$) mCtt group ($n = 20$) Control group ($n = 20$)	Freq.: 3 days/week Int.: NM Type: RE Time: 60–80 min Length: 4 weeks	Age: 60–70 Gender: Male PF: Fit	n-back	Compared to the control group, The other 2: EF (WM)↑*; mCtt group improved more significantly
Wang et al. (2018)	Experimental group ($n = 16$) Control group ($n = 11$)	Freq.: 3 days/week Int.: 70–75% HRmax (ET) and 75–80% (RE) Type: Multicomponent exercise Time: 60 min Length: 12 weeks	Age: >65 Gender: Both PF: Fit	C-EXIT25	Compared to the control group, Experimental: EF↑**, GP↑**
Tsai et al. (2017)	Closed-skill group ($n = 22$) Open-skill group ($n = 21$) Control group ($n = 21$)	Freq.: 3 days/week Int.: 70–75% HRmax (AE) NM (CE) Type: AE and CE Time: 30 min (AE) 40 min (CE) Length: 24 weeks	Age: 60–80 Gender: male PF: Sedentary	N-back Task switching	Compared to the control group, The other 2: TS RT↓*, n-back ACC↑*, P3 amplitudes↑
Albinet et al. (2016)	Swimming ($n = 19$) Stretching ($n = 17$)	Freq.: 2 days/week Int.: 40–65% HRR Type: AE Time: 40 min Length: 21 weeks	Age: 60–75 Gender: Both PF: Sedentary	Stroop RNG Hayling Task RST N-back DST Plus-Minus task DLT	Compared to the stretching group, Swimming: HRV↑*, Inhibition↑*, WM*↑,
Falbo et al. (2016)	Single task group ($n = 16$) Physical-cognitive dual task group ($n = 20$)	Freq.: 2 days/week Int.: NM Type: CE Time: 60 min Length: 12 weeks	Age: 65–80 Gender: Both PF: Fit	RNG task	Compared with the baseline, both: EF↑*; Physical-cognitive dual task group improved more significantly

(Continued)

TABLE 1 Continued

Study	Grouping	Exercise characteristics	Sample characteristics	CF or EF Task	Outcome measurement
Eggenberger et al. (2015)	VR dance group ($n = 24$) Memory group ($n = 22$) Walking group ($n = 25$)	Freq.: 2 days/week Int.: NM Type: AE Time: 60 min Length: 24 weeks	Age: >70 Gender: Both PF: Fit	TMT-B ECT	Compared to the VR dance group, The other 2: EF↑*; Memory group improved more significantly
Iuliano et al. (2015)	Resistance group ($n = 20$) Cardiovascular group ($n = 20$) Postural group ($n = 20$) Control group ($n = 20$)	Freq.: 3 days/week Int.: 80–85% 1 RM (RE) 70–80% HRR (AE) Type: RE and AE Time: 30 min Length: 12 weeks	Age: >55 Gender: Both PF: Sedentary	Stroop TMT	Compared to the control group, The other 3 groups: Stroop RT and ACC=, TMT=
Barcelos et al. (2015)	Tour group ($n = 34$) Game group ($n = 30$)	Freq.: 3–5 days/week Int.: 80% HRmax Type: ACE Time: 20–45 min Length: 12 weeks	Age: 82.2 Gender: Both PF: Fit	Stroop test DST Color Trails 1 and 2	Compared with the baseline, both: EF↑*; Game group improved more significantly
Gothe et al. (2014)	Yoga group ($n = 61$) Control group ($n = 57$)	Freq.: 3 days/week Int.: NM Type: Yoga Time: 60 min Length: 8 weeks	Age: 55–79 Gender: Both PF: Sedentary	Task switching running memory span N-back	Compared to the control group, Yoga: WM↑*, Shifting↑*
Vaughan et al. (2014)	Intervention group ($n = 25$) Control group ($n = 23$)	Freq.: 2 days/week Int.: NM Type: Combined exercise Time: 60 min Length: 16 weeks	Age: 65–75 Gender: Female PF: Fit	TMT LNS Stroop Test COWAT	Compared to the control group, intervention: WM↑*, BDNF↑*
Nouchi et al. (2014)	Combination group ($n = 32$) Control group ($n = 32$)	Freq.: 3 days/week Int.: 60–80% HRmax Type: Combined exercise Time: 30 min Length: 4 weeks	Age: >60 Gender: Both PF: Sedentary	VFT DST Stroop test	Compared to the control group, Combination: EF↑*
Fallah et al. (2013)	RT group 1 ($n = 52$) RT group 2 ($n = 54$) BAT group ($n = 49$)	Freq.: 1–2 days/week Int.: 7 RM Type: RE Time: 60 min Length: 52 weeks	Age: 65–75 Gender: Female PF: Fit	Stroop test TMT VDT	Compared to the BAT group, RT 1 and 2: EF↑
Dao et al. (2013)	RT group 1 ($n = 37$) RT group 2 ($n = 41$) BAT group ($n = 36$)	Freq.: 1–2 days/week Int.: NM Type: RE Time: 60 min Length: 52 weeks	Age: 65–75 Gender: Female PF: Fit	Stroop test	Compared to the BAT group, RT 1 and 2: inhibition↑*

(Continued)

TABLE 1 Continued

Study	Grouping	Exercise characteristics	Sample characteristics	CF or EF Task	Outcome measurement
Maillot et al. (2012)	Training group ($n = 16$) Control group ($n = 16$)	Freq.: 2 days/week Int.: NM Type: NM Time: 90 min Length: 14 weeks	Age: 65–78 Gender: Both PF: Fit	Stroop test TMT LST	Compared to the control group, Training: inhibition↑*, WM↑*
Klusmann et al. (2010)	Exercise group ($n = 91$) Control group ($n = 76$)	Freq.: 3 days/week Int.: NM Type: Combined exercise Time: 90 min Length: 24 weeks	Age: >70 Gender: Female PF: Fit	VFT Stroop Test TMT	Compared to the control group, Exercise: inhibition↑*, WM↑*
Liu-Ambrose et al. (2010)	RT group 1 ($n = 52$) RT group 2 ($n = 54$) BAT group ($n = 49$)	Freq.: 1–2 days/week Int.: 6–8 RM Type: RE Time: 60 min Length: 48 weeks	Age: 65–75 Gender: Female PF: Fit	Stroop test TMT VDS	Compared to the BAT group, RT 1 and 2: inhibition↑*, WM↑
Kimura et al. (2010)	Exercise intervention group ($n = 86$) Health education group ($n = 85$)	Freq.: 2 days/week Int.: 60% 1RM Type: RE Time: 90 min Length: 12 weeks	Age: >65 Gender: Female PF: Fit	Task switching	Compared to the health education group, Intervention: HRQOL↑, EF=

Freq., frequency, Int., intensity; PF, physical fitness level; CF, cognitive function; MTT, the multitasking test; SSP, spatial span; RE, resistance exercise; AE, aerobic exercise; ET, endurance training; mMtt, a motor-motor dual-task training; mCtt, a motor-cognitive dual task training; C-EXIT25, The Chinese version 25-item executive interview; CE, coordination exercise; NM, not mentioned; RNG, the random number generation; RST, running span task; DST, the dimension-switching task; DLT, the digit-letter task; TMT, trail making test; ECT, executive control task; RM, repetition maximum; HRR, heart rate reserve; LNS, the letter-number sequencing; COWAT, control oral word association test; VFT, verbal fluency test; VDT, verbal digits forward and backward tests; BAT, balance and tone; VDS, verbal digit span; ACE, aerobic and cognitive exercise; CBF, cerebral blood flow; OGTT, oral glucose tolerance test; GP, gait performance; TS, task switching; HRV, cardiac vagal control; WM, working memory; BDNF, brain derived neurotrophic factor; HRQOL, health-related quality of life; =, No change or no difference; ↑, Elevated or higher; *, $p < 0.05$; **, $p < 0.01$.

concentrated in 12–24 weeks, among which, intervention time of 15.8% of the studies was <12 weeks, and 15.8% was more than 24 weeks.

The intervention measures mainly include aerobic training, resistance training, multi-component training and other training. Among them, 26.3% of the studies used aerobic training for intervention studies, while 26.3% used resistance training. In addition, joint training studies accounted for 21.0% of the total included studies, and 26.3% of the studies adopted other training methods such as yoga and Pilates, or specific types of interventions were not mentioned in the text.

Surprisingly, 1/3 of the studies did not mention the specific intensity of exercise intervention. In the studies with recorded intervention intensity, the data were mostly concentrated between 60 and 80%HRmax or 6–8 RM.

Discussion

Other subcomponents of executive function, such as switching, was seldom measured in previous studies. The current system review included all three aspects of executive function. In addition, this review pays more attention to the influence of exercise prescription variables (e.g., type, frequency, intensity and duration of exercise) on executive function in the middle-aged and elderly population, and attempts to explore which exercise prescription has a better effect on the improvement of executive function.

Demographic variables and risk of bias

Most of the subjects in the included studies were from 65 to 75 years old. There are few studies on middle-aged and elderly people over 75 years old. Erickson's research shows that, compared with children and the elderly, the research on the impact of physical activity on the EF of young and middle-aged groups is lack of relevant systematic review and META analysis (Erickson et al., 2019). In negligible quantity of studies on this group, the results of the study on the effects of medium-and high-intensity exercise on cognition are not consistent. The lack of longitudinal studies on people over 75 years old will lead to a lack of further understanding of the relationship between

TABLE 2 Summary of intervention characteristics of included studies.

Characteristics	Percentage (%)	Characteristics	Percentage (%)	Characteristics	Percentage (%)
Published year		**Time**		Both	52.6
2016–2022	36.84	<30 min	5.3	**PF**	
2010–2015	63.16	30–60 min	68.4	Fit	68.4
Exercise type		>60 min	21.1	Sedentary	31.6
Aerobic	26.3	**Sample size**		**EF domains**	
Resistance	26.3	<30	5.3	Inhibition	66.7
Combined	21.0	30–60	36.8	Updating/WM	83.3
Others	26.3	61–90	26.3	Shifting	50.0
Frequency		>90	31.6	**Tools**	
<2	15.8	**Age**		Stroop test	55.6
2–4	78.9	55–65	5.3	N-back	22.2
>4	5.3	65–75	84.2	TMT	38.9
Length		>75	10.5	Task switching	16.7
<12	15.8	**Gender**		Others	11.1
12–24	57.9	Male	15.8		
>24	15.8	Female	31.6		

PF, physical fitness level.

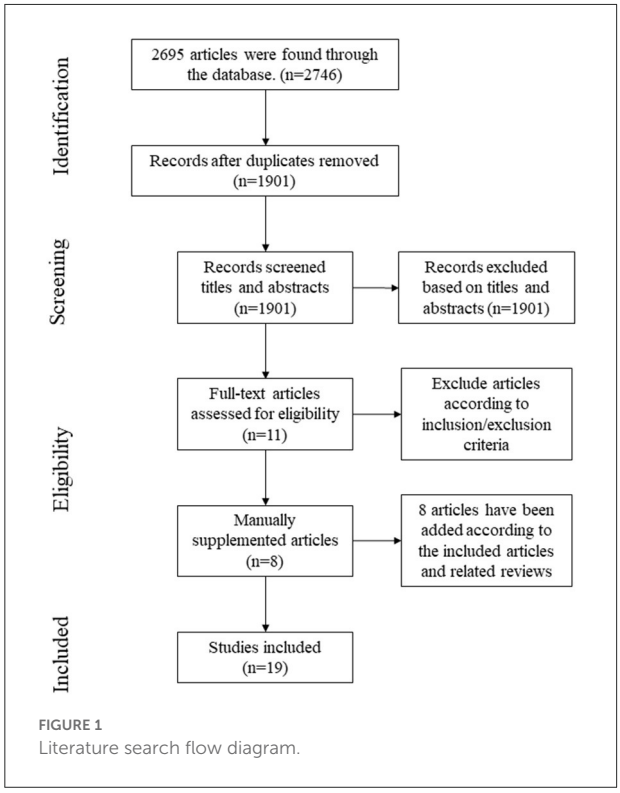


FIGURE 1
Literature search flow diagram.

the effect of exercise intervention and age. Therefore, additional research is needed on several of the groups mentioned above.

Most studies did not describe whether there were gender differences in the intervention results, as only male (female) subjects were selected in some studies. Although some other studies have investigated both male and female subjects, there is no further discussion on the results. In fact, according to a review of gender differences in the improvement of cognition by physical exercise published by Barha et al. (2017), we can learn that among the effects of exercise intervention on EF, gender is an important regulator of cognitive (executive) function, and women can benefit more from exercise than men for EF (Barha et al., 2017). Other studies have also shown that in terms of EF, studies with a higher proportion of female subjects reported with a larger impact, indicating that gender is an important moderator of the effect of exercise on cognition (Colcombe and Kramer, 2003; Barha et al., 2017). When formulating the prescription of exercise intervention, the future research should fully consider the effects of biological, cognitive and sociological factors on the EF for the middle-aged and elderly people of different genders.

As for physical fitness level, we found that some studies used sedentary people as research subjects. However, one study in sedentary people did not find a significant improvement in executive function with exercise intervention (Iuliano et al., 2015). The explanation given by the authors was that the ineffective outcome of this intervention may be due to the short duration of the high-intensity phase of exercise to produce no significant improvement in executive function. This is slightly different from the results of some later studies. In addition, we found that there seems to be no study comparing the effect of exercise on the improvement of executive function in people with different physical activity levels.

In addition, the studies included are all RCTs to ensure the integrity of the result data and present a complete research plan as far as possible, so that it can minimize the distribution bias and balance the prognostic factors (Higgins et al., 2011). The internationally recognized and widely used CONSORT statement provides a standard method for writing randomized controlled trial reports (Altman et al., 2001), the reports based on which are helpful for people to strictly evaluate the experimental design, explain the results, and find out problems difficult to explain or potential biases. However, only 1/3 of the included studies reported the CONSORT statement, while most of the studies did not provide complete information in the CONSORT statement. It is suggested that future RCTs should be strictly designed based on the CONSORT statement in order to reduce the possible deviation of the experiment.

The samples sizes selected in the experiment ranged from 27 to 171. In more than half of the studies, the number of the sample size was between 30 and 90. Theoretically, the size of the sample depends on the main variables, variance and allowable error. In their research about sample size design, Barlett et al. pointed out that under the condition that the effect is 0.8 and the significance level is 0.05, it is appropriate to take a 21 people group as the minimum sample size (Kotrlik and Higgins, 2001). It is suggested that future studies should be based on this theory when determining the sample size of the intervention experiment. In addition, we should comprehensively consider the maneuverability of the experiment, the control of non-sampling error, budget, etc., and strive to achieve the choice of the optimal sample size.

Effect of the different types of exercise on EF

Included studies have discussed the effects of exercise interventions such as aerobic exercise, resistance exercise, multi-component exercise and physical and mental exercise. In the early years, there were many studies on aerobic exercise, while in recent years, other kinds of exercise began to be concerned by researchers. At present, the research evidence shows that exercise intervention has the greatest benefit to EF and memory (Colcombe and Kramer, 2003; Northey et al., 2018), which depends on the type of training to a certain extent.

Barha et al. found that aerobic exercise has the greatest influence on cognitive EF (Barha et al., 2017). The report from World Health Organization (WHO) also shows that aerobic exercise is related to the improvement of neurocognitive function, especially EF (World Health Organization, 2008; Guiney and Machado, 2013). Kleinloog et al. conducted a comparative study of aerobic exercise intervention and stretching exercise intervention on healthy elderly men over 65 years old, which found that EF improved as the latency of response was reduced by 5% ($P = 0.034$) in aerobic exercise group (Kleinloog et al., 2019). Another study of 71 healthy elderly people also showed that 24-week aerobic exercise intervention played an important role in improving EF. Among them, 47 subjects showed faster attention switching ability ($p = 0.075$) and stronger working memory ability ($p = 0.051$) after intervention (Baker et al., 2010). In addition, swimming was deeply loved by the elderly people because of its characteristics such as mobilizing the body muscle participation, low pressure on joints, low risk of sports injury and so on. A study published in 2016 showed that the participants in the water exercise group significantly improved their vagally-mediated HRV, as well as their performance for the Stroop test and the verbal running-span test at the end of the program. A study focused on the effects of closed sports such as swimming and open sports effect of table tennis on EF, etc. and so on. The results of which showed that the two exercise modes produced varying degrees of neuropsychological benefits on RT of task switching paradigm (i.e., reducing RTs) and ARs of N-back task (i.e., increasing ARs) (Tsai et al., 2017).

Similar to aerobic exercise, resistance exercise may have different effects on cognitive function and affect the performance of specific tasks. We found that resistance training can effectively improve the inhibition ability and working memory of the middle-aged and elderly people. Liu-Ambrose et al. randomly divided 155 elderly women aged 65–75 into a resistance training groups executed, respectively, once a week, twice a week and a control group. The duration of each intervention was 60 min, including warm-up, formal training and relaxation, with stroop task used to evaluate the subjects' selective attention and inhibition ability. The results showed that the 12-month resistance training intervention had a positive effect on the selective attention and inhibition ability of older women ($p = 0.03$). The weekly and twice-weekly training frequency increased the subjects' performance on the stroop task by 12.6 and 10.9%, respectively, while the control group decreased by 0.5% (Liu-Ambrose et al., 2010). A study in 2019 also showed that 4-week resistance exercise significantly improved the working memory ability of healthy men aged 60–70 years old with a significant time × group interaction compared with the control group ($p < 0.01$) (Norouzi et al., 2019).

Colcombe and Smith believe that the combination of aerobic exercise and resistance training is more effective than aerobic exercise alone in improving the performance of attention and working memory tasks (Colcombe and Kramer, 2003; Smith et al., 2010). A Meta-analysis by Patrick et al. also pointed out that multi-component exercise intervention has a stronger effect on the protection and improvement of attention and working memory of the elderly people than aerobic or anaerobic exercise alone. The reason may be that comprehensive exercise intervention is more helpful to reduce the risk factors of cardiovascular and cerebrovascular diseases, so as to alleviate white matter degeneration and brain ischemia and hypoxia

(Patrick et al., 2010). Several recent randomized controlled trial for people over 60 years old have also shown that multi-component exercise can improve EF in different dimensions (Nouchi et al., 2014; Vaughan et al., 2014; Wang et al., 2018). Nouchi et al. randomly assigned 64 healthy elderly people to multi-component exercise group and control group. The multi-component exercise group was intervened 3 days a week (aerobic, strength and stretching training) for 4 weeks (a total of 12 exercises), without the intervention in the control group. The results showed that compared with the control group, the intervention group improved EF, episodic memory ability and information processing speed (Nouchi et al., 2014), based on which, new studies have found that compared with simple multi-component exercise, exercise intervention, combined with cognitive activities, can produce greater cognitive benefits (Eggenberger et al., 2015).

In addition, physical and mental exercises represented by Taijiquan, yoga and Pilates have attracted the researchers' attentions *via* their comprehensive characteristics, including aerobic, anaerobic and flexibility training. The evaluation of EF includes Task switching and running memory span and N-back. The results showed that the performance of EF indexes in the yoga intervention group, such as working memory capacity, mental set transformation and flexibility, was significantly better than that in the control group (Gothe et al., 2014). Therefore, physical and mental exercise can play a certain role in protecting the EF of the elderly people.

In conclusion, different ways of exercise intervention play a positive role in improving and maintaining the EF of the middle-aged and elderly people. Future research should not be limited to the influence of a single type of exercise on the EF of the middle-aged and elderly people. The combined exercise intervention should be considered in the future.

Effect of exercise intensity, duration and frequency on EF

The reason why exercise intervention can improve the EF of the middle-aged and elderly people is that exercise can promote the process of energy metabolism *via* a certain intensity and load. However, we found that many included RCTs did not mention the explicit intensity of intervention. In these studies, as different types of motion have different standards, unified standards are required to be established for definition and measurement of medium intensity.

A 2017 intervention study explored the effects of HIIT and MCT on executive function in healthy elderly people without training experience from the perspective of overall cognitive function. The exercise intensity of the MCT group was set at 70–75% HRR and the HIIT group was set at 90–95% HRR. After a 16-week intervention trial, it was found that the HIIT group showed a significant improvement in the response time of information processing tasks, that is, Stroop neutral (ES = 1.11). In the MCT group, the reaction time of performing cognitive tasks was significantly improved, that is, Stroop inconsistency and interference (ES 1.28, 1.31, respectively) (Coetsee and Terblanche, 2017). It shows that MCT is better than HIIT in improving the executive function of the elderly people, while HIIT is more conducive to the improvement of information processing speed.

The Physical Activity Guidelines for Americans points out that the intensity of intervention can be divided into absolute intensity and relative intensity. Absolute intensity is the amount of energy expended during the activity, without considering a person's cardiorespiratory fitness or aerobic capacity. It is usually expressed in units of metabolic equivalent (MET). The MET level of moderate intensity exercise ranges from 3 to 5.9 Met. Relative intensity is the ratio of effort required to do an activity to an individual's ability. The relative strength can be estimated on a scale of 0 to 10, in which the sitting posture is 0 and the highest effort level is 10. At this level, the moderate intensity of activity is 5 or 6. This may provide a reference standard of intervention intensity for future research (Piercy et al., 2018).

Northey et al. suggested that exercise of any frequency lasting 45–60 min is beneficial to cognitive function (Northey et al., 2018). However, most of the included studies only considered a single factor, intervention frequency or single intervention time or intervention weeks. Overall, the current research still requires a clear time basis for intervention. From the point of view of the effectiveness of the intervention, it was found that the exercise intervention with a single intervention duration of 30–60 min, at least twice a week and a total duration of more than 12 weeks could significantly exert the intervention effect. However, it is worth noting that two of these studies did not report the effectiveness of exercise intervention on EF (Kimura et al., 2010; Iuliano et al., 2015). This maybe because the intervention time of RCTs is slightly shorter than the time required for exercise intervention on the brain, it is difficult to observe the effect of intervention at the behavioral level. In addition, as the recruited subjects are all healthy middle-aged and elderly people, their EF may be at a relatively healthy level. Therefore, it is difficult to determine the improvement of EF during the intervention period of short-term RCTs. Further follow-up research is needed to for conformation.

The follow-up investigation after the intervention is very important. Epidemiological studies have shown that it may take years for exercise to affect brain health (Panza et al., 2018a). However, we found that in the included studies, only two studies have been conducted follow-up research (Eggenberger et al., 2015; Norouzi et al., 2019), among which, the follow-up study of Patrick et al. shows that the effect of exercise intervention can be maintained for at least 1 year. Even in the TMT-B test, from the 6-month test to the follow-up test, the performance of all groups continued to improve, which may reflect the delayed effect of

exercise intervention (Eggenberger et al., 2015). The follow-up study of Norouzi et al. also proved the time effect of exercise intervention on improving working memory (Norouzi et al., 2019). Unfortunately, due to financial and human effect reasons, most of the studies have not been followed up and tested. Therefore, it is impossible to evaluate and analyze the follow-up impact of the intervention. In future studies, when conducting the impact of exercise intervention on EF, it is recommended to conduct a follow-up survey within a period of time after the end of the intervention, which is one of the important ways to evaluate the effectiveness of exercise intervention.

Possible reasons why exercise affects executive function

The researchers have successively proposed the selective improvement hypothesis (Kramer et al., 1999) and the cardiovascular function hypothesis (Etnier et al., 2006) to explain the mechanism, by which exercise intervention affects EF. The researchers pointed out that the frontal lobe is an important material basis of EF, and aerobic exercise can selectively improve the function dependent on the prefrontal lobe by promoting the aerobic fitness of individuals. However, this theory cannot explain the effects of exercise other than aerobic exercise on general cognitive function. Another theory holds that cardiovascular function is the physiological intermediary variable of exercise affecting cognitive EF, which is related to the changes of brain structure and the levels of BOLD and BDNF caused by exercise.

In recent years, the exercise-cognitive intermediary model (Spirduso et al., 2008) and cognitive reserve theory (Stern, 2002) newly proposed by researchers have attracted more attention. Exercise-cognitive intermediary model not only describes the direct impact of exercise on cognitive function, but also fully reflects the three intermediary variables of physical resources, psychological resources and chronic diseases. However, there is no confirmatory research report on this model. Cognitive reserve theory mainly describes the protective effects of psychological resources and exercise on cognitive function. Under the premise of similar neuropathological symptoms, individuals with higher cognitive reserves can show mild cognitive impairment and pathological changes through potential cognitive protection and compensation mechanisms. Exercise intervention can delay the decline of EF in the middle-aged and elderly people by activating individual cognitive reserve (Fratiglioni et al., 2004) Studies based on this theory show that exercise promotes the balance of energy metabolism, stimulates the brain to synthesize BDNF and binds to cholinergic receptor TrkB to activate corresponding signal transduction pathways to regulate the proliferation and differentiation of nerve cells and promote the growth of new neurons and synapses (Nithianantharajah and Hannan, 2009; Gomez-Pinilla et al., 2011). However, some studies have pointed out that serum BDNF levels in patients with MCI and AD are significantly higher than those in normal people, which is irrelevant to the severity of the disease, antidepressants and the use of acetylcholine inhibitors (Angelucci et al., 2010).

Event-related potential (ERP) technique can record the characteristics of brain information processing in a very short time. N2 and P3 are two components that are paid more attention to in the research of EF. N2 has been associated with the detection of response conflict, the mismatch of a stimulus with a mental template, and/or the upregulation of cognitive control during early stages of response inhibition. The amplitude of P3 is sensitive to the amount of attentional resources engaged during task performance, while the latency is generally believed to index the time required to detect and process a target stimulus (Alderman et al., 2016). Hillman et al. found that the latency of P3 in the prefrontal region of the middle and high intensity aerobic exercise group was significantly shorter than that of the low intensity exercise group. The amplitude of P3 wave of the middle and high intensity aerobic exercise group was larger than that of the young control group (Hillman et al., 2008). Other researchers have found that exercise intervention can increase the overall electrophysiological effects from frontal lobe to parietal cortex (that is, increased amplitude of P3) (Tsai et al., 2017).

Although ERP technology has millisecond time accuracy, it is weak in spatial resolution. FMRI technology can accurately locate the degree of brain activity through blood oxygen-dependent horizontal (BOLD), which can make up for the lack of spatial resolution of ERP technology. Studies have found that exercise can change the activation patterns of brain regions, such as prefrontal lobe (dorsolateral and ventrolateral), cingulate gyrus (anterior cingulate gyrus), cerebellum, parietal lobe and striatum (ventral). The three sub-functions of EF can be improved *via* increasing the functional network connection between these brain regions. In addition, exercise can also improve EF by enhancing neural information transmission (Harrison et al., 2005; Voss et al., 2016; Erickson et al., 2019). The study of Venkareaman et al. further confirmed that compared with the control group, the 12-month walking intervention significantly improved the accuracy of Digit symbol substitution tasks in the elderly people, and was positively correlated with the activation of the left middle frontal gyrus and the right parietal cortex (Venkatraman et al., 2010). A randomized controlled study of patients with MCI showed that aerobic exercise showed a wide range of cognitive improvements compared with the control group. Aerobic fitness was particularly correlated with the larger thickness of (DlPFC) in the dorsolateral prefrontal cortex, while the volume of

hippocampus was positively correlated with aerobic fitness over time, indicating that the exercise dose was related to the increase of brain-derived neurotrophic factor, as well as the increase of gray matter volume in PFC and ACC. The study also pointed out that the improvement of memory is related to the increase of DLPFC, and the improvement of EF is related to the increase of miRNA-9 expression (Anderson-Hanley et al., 2018).

Future research is bound to continue to start from the perspective of measurement methods, adding more measurements such as neurophysiology and imaging indicators, to further explore the physiological mechanism of exercise intervention to improve EF.

Conclusion

The results of this system review support the view that exercise intervention is beneficial to improve the executive function of the middle-aged and elderly people. In terms of exercise prescription, we found that the intervention with a single intervention duration of 30–60 min, at least twice a week, and a total duration of more than 12 weeks showed a good intervention effect. However, the interpretation of the results should be cautious, as there is still some limitations in the included studies. The sample size of some of the included studies is small. The duration and frequency of intervention are short, the mode of intervention is single, and the standard of intervention intensity is vague.

In terms of mechanism, exercise intervention can induce individual cognitive reserve, maintain the activation of EF network in prefrontal cingulate cortex, reduce the loss of brain tissue during aging, and protect the function of specific brain areas. At the same time, exercise intervention can also affect the synthesis of neurotransmitters to a certain extent, to regulate the expression level of related target genes and the excitability of hippocampal synapses, and then delay the decline of cognitive function in the elderly people.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

CX generated the idea, conducted literature search, and drafted the paper. JZ and XS conducted literature search and revised the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Exercise-induced modulation of myokine irisin in bone and cartilage tissue—Positive effects on osteoarthritis: A narrative review

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Osteoarthritis is a chronic degenerative musculoskeletal disease characterized by pathological changes in joint structures along with the incidence of which increases with age. Exercise is recommended for all clinical treatment guidelines of osteoarthritis, but the exact molecular mechanisms are still unknown. Irisin is a newly discovered myokine released mainly by skeletal muscle in recent years—a biologically active protein capable of being released into the bloodstream as an endocrine factor, the synthesis and secretion of which is specifically induced by exercise-induced muscle contraction. Although the discovery of irisin is relatively recent, its role in affecting bone density and cartilage homeostasis has been reported. Here, we review the production and structural characteristics of irisin and discuss the effects of the different types of exercise involved in the current study on irisin and the role of irisin in anti-aging. In addition, the role of irisin in the regulation of bone mineral density, bone metabolism, and its role in chondrocyte homeostasis and metabolism is reviewed. A series of studies on irisin have provided new insights into the mechanisms of exercise training in improving bone density, resisting cartilage degeneration, and maintaining the overall environmental homeostasis of the joint. These studies further contribute to the understanding of the role of exercise in the fight against osteoarthritis and will provide an important reference and aid in the development of the field of osteoarthritis prevention and treatment.

KEYWORDS

osteoarthritis, bone mineral density, bone metabolism, cartilage, cartilage metabolism, exercise, myokines, irisin

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease. According to incomplete statistics, OA affects ~240 million people worldwide, representing ~3.8% of the total population worldwide. The prevalence of osteoarthritis is significantly higher in older adults, and that the prevalence in adults older than 65 years is accounting for more than 1/3 of the total population (Hawker, 2019). Its prevalence is expected to continue to rise significantly in the future, along with the increasing aging of the population.

Osteoarthritis has become a global public health problem (Kloppenburg and Berenbaum, 2020). It is characterized clinically by loss of articular cartilage and subchondral bone changes (Donell, 2019), causing outcomes, including joint space narrowing, joint pain, stiffness, deformity, and even disability (Suri et al., 2012; Kraus et al., 2015; Katz et al., 2021). OA greatly affects the quality of life of patients and places a considerable medical burden on individuals and society (Sharif et al., 2015), so the medical burden on individuals and society is considerable (Sharif et al., 2015).

Exercise is considered to be a key factor in treating osteoarthritis (Nelson et al., 2014) and is central to a non-pharmacological treatment (Regnaux et al., 2015). Physical activity is based on the skeletal muscle activity (Rannou and Poiraudeau, 2010). Exercise therapy (Fransen and McConnell, 2009) can be effective in reducing the pain associated with osteoarthritis, improving physical function, and (Penninx et al., 2001; Latham and Liu, 2010) significantly reducing the risk of disability in osteoarthritis (Alghamdi et al., 2004). Notably, age does not appear to affect the benefits of exercise training (Nelson et al., 2014), and the improvements in joint function following training are similar in older and younger people. Despite the decline in dependency among the elderly, exercise has been generally shown to delay skeletal sarcopenia and osteopenia and to reduce the risk of diseases, such as mechanical arthritis of the knee and hip, that accompany the process of muscle loss (Bains, 2020). Therefore, exercise deserves further attention as a relatively safe treatment method (Bricca et al., 2020), but the mechanisms that exercise modulating osteoarthritis are, as yet, unclear.

Current research studies have found that exercise can act as a secretory organ by stimulating the skeletal muscle system *in vivo* (Pratesi et al., 2013), causing the release of myokines (Pedersen, 2011; So et al., 2014) and providing new ideas to explain the beneficial effects of exercise in the treatment of osteoarthritis. Myokines, a class of cytokines or peptides synthesized and secreted by muscle fibers during muscle contraction (Pedersen et al., 2003), act on the muscle itself and other organs in an autocrine, paracrine, and endocrine form (Pedersen and Febbraio, 2012). Myokines are involved in regulating metabolic processes and achieving coordination between skeletal muscle and organs (Trayhurn et al., 2011; Pedersen and Hojman, 2012; Severinsen and Pedersen, 2020). In 2012, a new myokine was discovered and named irisin (Bostrom et al., 2012). It is produced by cleavage of fibronectin type III domain containing protein 5 (FNDC5) and has been shown to be induced by exercise (Wrann et al., 2013). Since its discovery, irisin has been reported to regulate a variety of metabolic disorders (Polyzos et al., 2018) acting in a variety of tissues, including bone. Exercise-induced irisin plays a potentially important role in the prevention and resistance to the progression of osteoarthritis (Figure 1). In the past, many studies have focused on the role of irisin in the regulation of bone metabolic homeostasis. In recent years, there has been an increasing interest in research articles on the role of irisin in cartilage and the extracellular matrix of cartilage, some of which have been published. However, the role of irisin in the development of osteoarthritis has not been systematically reviewed. An overview of the regulatory role of irisin in bone and cartilage tissues would help to gain insight into the development of osteoarthritis and explain the molecular mechanisms of exercise against osteoarthritis. In this article, we review the studies on the exercise-induced regulation of bone density and articular cartilage by the myokine irisin, and discuss the implications of irisin in the treatment of osteoarthritis.

Generation and structure of irisin

Irisin is a newly identified myokine that is released into circulation primarily from skeletal muscle (Bostrom et al., 2012). Since the concept of myokines was introduced in 2003 (Pedersen and Febbraio, 2012), more than 300 myokines have been identified in the last 20 years, such as interleukin-6 (IL-6), interleukin-15 (IL-15), fibroblast growth factor 21 (FGF21), myostatin, among others, which also includes irisin. These muscle factors have been shown to be involved in adipose tissue, liver, bone (Trayhurn et al., 2011; Zymbal et al., 2019), central nervous system (Voss et al., 2019; Lee et al., 2021), and immune system (Flori et al., 2021). They play a role in driving browning of white fat (Lee et al., 2014), insulin-sensitive states (Lee et al., 2015), optimizing whole-body energy metabolism, preventing metabolic diseases, and playing a protective role in low-level inflammation on a systemic scale (Tanabe et al., 2017; Flori et al., 2021).

It has been shown that irisin is a cleaved and secreted fragment of fibronectin type III structural domain protein 5 (FNDC5). FNDC5 is a transmembrane protein consisting of 209–212 amino acid residues with a typical fibronectin III structural domain. The c-terminal fragment is located in the cytoplasm and n-terminal portion is located outside the cell that can be cleaved by protein hydrolysis to produce a hormone. The n-terminal fragment is located in the cytoplasm, while its extracellular portion can be cleaved by protein hydrolysis to produce a hormone substance known as irisin (Bostrom et al., 2012; Flori et al., 2021). Irisin consists of 112 amino acid residues that contain two glycosylation sites. Irisin is released into the circulation after glycosylation to exert hormonal effects. Its amino acid sequence is highly conserved in mammals, demonstrating its stable function across species. Irisin, which usually occurs as a homodimer (Schumacher et al., 2013), has been shown to be expressed in almost all tissues and organs of eukaryotes and is particularly highly expressed in skeletal muscle and skeletal muscle-rich tissues.

Most studies suggest that exercise induces the expression and secretion of irisin in muscle tissue. Exercise stimulation promotes the production of irisin by FNDC5 cleavage (Bostrom

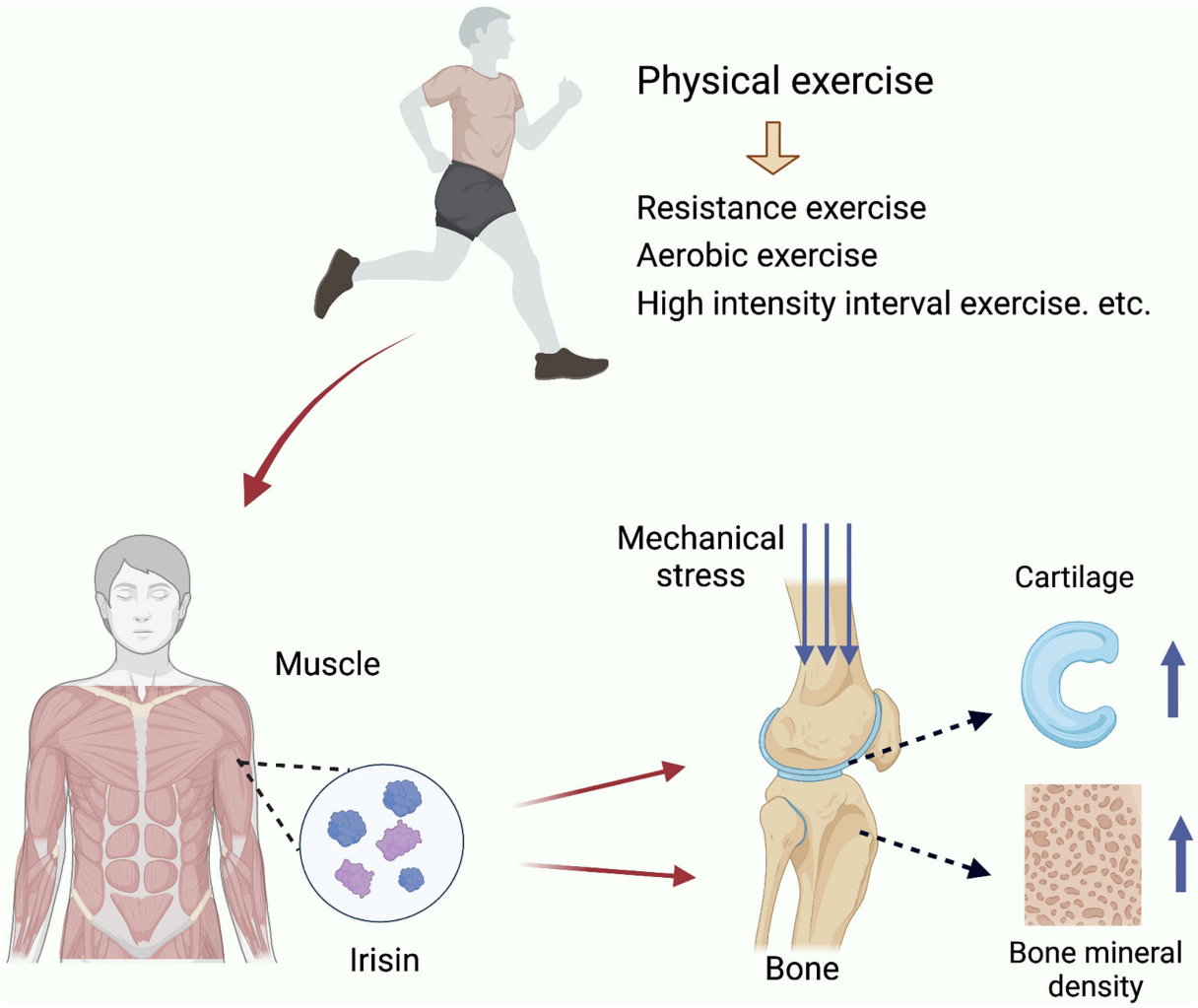


FIGURE 1
Exercise inducted effects of Iris and its regulation in OA. Irisin is secreted by skeletal muscle in response to exercise stimulation and increases bone density, enhances the mechanical support of cartilage by subchondral bone, improves cartilage tissue, and promotes chondrocyte proliferation.

et al., 2012; Huh, 2018). Several studies have shown that exercise can activate the mitogen-activated protein kinase (MAPK) pathway and increase the expression of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) transcript levels (Akimoto et al., 2005; Guo et al., 2021). PGC-1α is a transcriptional coactivator that is thought to play a key role in lipid and metabolic regulation (Cheng et al., 2018), that directly regulates the expression of FNDC5-irisin (Bostrom et al., 2012). According to a study in 2018, PGC-1α expression was elevated in muscle cells during simulated exercise with the transcription factor CREB, and overexpression of PGC-1α in complex with CREB-activated FNDC5 transcription in C2C12 cells (Yang et al., 2018). However, Pekkala et al. (2013) found that changes in FNDC5 expression were not consistent with serum irisin, which predicts the existence of other pathways than transcription for irisin release in muscle. At present, the complete mechanisms of irisin production are not clear and need further study.

Effects of different types of exercise on irisin

Exercise induces irisin expression, and most studies concluded that moderate intensity and resistance exercise significantly increased irisin levels (Liu et al., 2021). However, different types of exercise showed greatly different effects on the induction of irisin (Supplementary Table 1). In a recent study, Tavassoli et al. designed a resistance exercise training (RET) experiment for rats on a high-fat diet. After 12 weeks of training, serum levels of total cholesterol (TG)

and triglycerides (TC) decreased and serum concentrations of irisin increased in the rats participating in the RET. Tavassoli et al. (2022) hypothesized that the increased serum levels of irisin in rats were related to muscle contraction during training. In a 2019 mouse experiment, exercise-induced irisin exerted an anti-oxidative stress effect *via* Nrf2 and improved smoking-induced emphysema (Kubo et al., 2019). Li et al. also recently demonstrated that different types of exercise, including aerobic, resistance and vibration exercise, and skeletal muscle electrical stimulation all upregulated irisin/FNDC5 expression in mouse myocardium, which resulted in promoting mitochondrial phagocytosis, enhancing antioxidant function, and thus improving cardiac function with having a more significant effect of resistance exercise (Li H. et al., 2021). There is a prominent role of resistance exercise in increasing serum irisin concentrations (Tsuchiya et al., 2015; Cosio et al., 2021). In addition, a study in 2014 compared in detail serum irisin levels at different stages of exercise in subjects with different levels of training in two different forms of exercise, cycling and sprinting (Huh et al., 2014). The researchers found that irisin expression was independent of the type of acute exercise and the training status of the subjects, but that running caused a longer duration of irisin elevation compared to cycling. The difference in the duration of irisin upregulation may be due to the higher rate of fat oxidation in running compared to cycling at the same relative intensity (Capostagno and Bosch, 2010). In a recent study, Colpitts et al. (2022) reported that during aerobic exercise at 35 min, high-intensity interval (HIIT) training triggered a higher peak irisin response in the serum of healthy adolescents compared to moderate continuous intensity (MCI) exercise. HIIT triggered a higher peak irisin response in the serum of healthy adolescents compared to MCI exercise, whereas the induction of irisin was not evident in either exercise modality in obese or overweight adolescents. Differences in fat oxidation rates provide a possible explanation for the differences in irisin expression across exercise forms.

Not all results for the modulation of irisin in exercise are consistent. In 2015, the results of a meta-analysis covering 12 studies in 8 articles reported that chronic resistance training unexpectedly and significantly reduced circulating concentrations of irisin in a randomized controlled trial and that irisin also tended to be reduced in endurance exercise (Qiu et al., 2015). In a study conducted by Rodziewicz et al. (2020), the effects of a single incremental exercise on the plasma concentrations of irisin and BDNF were evaluated in subjects applying a treadmill for maximal fitness testing. While the study found a significant positive correlation between irisin concentrations and fasting glucose and insulin, no significant effect of irisin by exercise was observed (Rodziewicz et al., 2020). A recent systematic review and meta-analysis in 2021 compared the effect of exercise on irisin blood levels in 33 studies (Briken et al., 2016), with increased levels of irisin in 23 of these studies and decreased in another 10, with rather inconsistent results in individual studies. In the reported literature, exercises that have caused a decrease in irisin serum levels have included high-intensity circuit training (Yang et al., 2019), mixed physical training (Jandova et al., 2021), periodic sprint training (Gmiat et al., 2017), indoor aerobic training (Murawska-Cialowicz et al., 2015), and high-altitude mountaineering (Ozbay et al., 2020). Furthermore, even in the studies that have reported post-exercise upregulation of irisin, the timing of irisin upregulation is not same. More studies suggest that the upregulation of irisin occur immediately after exercise (Tsuchiya et al., 2015; Kubo et al., 2019; Cosio et al., 2021; Li H. et al., 2021; Tavassoli et al., 2022). In a clinical study involving gerontological neurodegenerative diseases, Briken et al. found that irisin was upregulated only immediately after exercise, while long-term exercise had no effect on serum irisin baseline (Sliwicka et al., 2017). However, it has also been reported that upregulation of irisin levels guided by short-term physical exercise in subcutaneous and visceral adipose tissue was able to persist for 1 week after cessation of the exercise and gradually returned to normal levels only 3 weeks after cessation of exercise (Tsuchiya et al., 2016). The cold environment can induce muscle tremors to achieve similar effects to exercise (Lee et al., 2014). A study in 2021 looked at changes in serum concentrations of irisin after ice swimming (Mu et al., 2020). Interestingly, when the cold environment was combined with exercise, unexpectedly, there was a significant decrease in serum irisin levels in winter swimmers (Mu et al., 2020), perhaps that may be due to the different tissue sources and metabolic environment of irisin. Furthermore, exercise does not always play a positive role in the body's metabolic processes and exercise may cause elevated expression of some inflammatory factors. It has been shown that excessive exercise triggers the activation of JNK/p38/ERK and ultimately significantly increases the levels of inflammatory factors, such as IL-1β, TNFa, and iNOS (Sun et al., 2017). Elevated inflammatory markers in serum are thought to be associated with aging, obesity, and chronic disease. Chronic peripheral inflammation may cause neurodegenerative lesions (Vints et al., 2022). Irisin is often thought to be an exercise-protective myokine that acts as an inflammatory resistance factor against inflammatory factors, used to reveal a possible link between exercise and the prevention of chronic disease (Martinez et al., 2018). A decrease in its expression is often used as a marker of chronic disease. However, as mentioned above, the release of irisin after exercise is closely related to the form and intensity of the exercise, as well as the physical condition and metabolic level of the subjects. The factors and mechanisms underlying exercise-induced irisin expression, the role of irisin in metabolic processes, and the relationship between irisin and other myokines or inflammatory factors need to be further investigated. Despite the partial controversy, the positive role of irisin in exercise-induced metabolic regulation is generally recognized.

Irisin and aging

Exercise-induced expression of irisin is associated with resistance to aging. In fact, in an earlier study, Bostrom et al. reported that exercise was able to induce a significant increase in irisin levels in the circulating blood of elderly subjects (Bostrom et al., 2012). Analysis of gene microarray data by Timmons et al. (2012) indicated that exercise upregulated FNDC5 mRNA expression and that its elevated effect was more pronounced in older than in younger controls. In 2014, Aydin et al. compared serum irisin levels in young vs. older rats (Aydin et al., 2014). Their results showed that serum irisin was higher in young rats than in older rats in the quiet state. After 10 min of floating exercise, serum irisin increased in both young and old rats; however, the increase in irisin was significantly higher in the serum of young rats. Whereas, in another study, it was reported that baseline levels of irisin were significantly lower in older adults, the percentage level of increased irisin after acute exercise was not related to age or health (Huh et al., 2014). Although the effects of exercise modulation of irisin varied slightly in subjects of different ages, these studies suggest the potential of irisin in the alleviation of aging-related diseases. A study in rats compared the effects of age and exercise on irisin levels in heart, liver, and plasma samples from rats. The results showed that aging reduced the levels of irisin in the above tissues. Regular exercise increased irisin expression in all tissues analyzed compared to sedentary inactivity (Belviranli and Okudan, 2018). Recent studies have also shown that irisin is associated with improved neurocognitive performance in older adults and plays a key role in the facilitative effects of exercise on learning and memory (Babaei and Azari, 2021). More importantly, in a 2021 study, Colaianni et al. examined a series of patients undergoing total hip or knee arthroplasty. Serum irisin levels were negatively correlated with age and positively correlated with BMD. Further studies demonstrated that irisin treatment reduced the expression of the senescence marker p21 in osteoblasts *in vitro*, demonstrating the anti-aging ability of irisin in bone tissue (Colaianni et al., 2021).

Above, we mentioned that irisin plays a role in a number of aging-related diseases. Similarly, aging is generally considered to be a very important contributor to the development of osteoarthritis. Aging can cause a reduction in the capacity of articular cartilage cells to repair, destabilize the extracellular matrix of cartilage, and stimulate its degradation. At the same time, irisin causes remodeling of bone in the subchondral bone, causing changes in the mechanical stress of the joint, while causing the progression of osteoarthritis from multiple angles (Rahmati et al., 2017; Coryell et al., 2021). Although the mechanisms of aging in influencing disease development are not fully understood, signaling pathways associated with autophagy, apoptosis, and oxidative stress have been shown to be important in this (Rahmati et al., 2017; Coryell et al., 2021).

In Belviranli and Okudan's study, irisin increased the action of the antioxidant enzyme superoxide dismutase. Exogenous irisin down-regulated the expression of apoptotic proteins in post-ischemic myocardium and inhibited inflammatory markers therein (Belviranli and Okudan, 2018). In another study, the PGC1a/FNDC5/irisin pathway supported exercise-induced selective autophagy, and irisin expression correlated with the expression of mitochondrial fission and mitochondrial phagocytosis markers in myotubes (He W. et al., 2020). A study by Bi et al. systematically analyzed the effects of irisin on the liver in an ischemia-reperfusion (IR) model. The results showed that age could influence the expression of irisin in liver tissue and the ability of liver tissue to repair the damage. At the same time, the levels of irisin expression, telomerase activity, autophagy, and mitochondrial function were lower in the liver tissues of aged rats. Exogenous irisin treatment in aged rats significantly reduced the mitochondrial function-related markers PGC1α and TFAM, and reduced inflammation, apoptosis, and oxidative stress in the injury model. Molecular experiments showed that irisin regulates telomerase activity through involvement in the MAPK pathway. Irisin inhibited the phosphorylation of JNK and increased telomerase activity in senescent hepatocytes to activate autophagy and improve mitochondrial function (Bi et al., 2020). In contrast, *in vitro* experiments, the JNK-MAPK inhibitor, an inhibitor of telomerase activity, eliminated the promotion of autophagy and the protective effect of irisin on mitochondrial function. A similar association was demonstrated in articular chondrocytes. In chondrocytes cultured in three dimensions *in vitro*, r-irisin treatment significantly reduced the phosphorylation levels of JNK, while significantly reducing inflammatory markers, such as IL-1β, and inhibiting the catabolism of chondrocytes with extracellular mechanisms (Vadala et al., 2020). Wang et al. (2020) also demonstrated that irisin promotes the protective effect on chondrocyte mitochondria by modulating the action of key factors, such as PGC1α, UCP1, and Sirt3, improving chondrocyte survival in an inflammatory environment and promoting ECM anabolism. The role of irisin in senescence resistance is shown in Figure 2.

The effects of irisin on osteoarthritis

Irisin and bone mineral density

Presumably, Irisin influences the progression of osteoarthritis by affecting bone mineral density (BMD). The increase in bone density requires the osteogenic effect of osteoblasts over the resorptive effect of osteoclastic bone. This process primarily involves both osteoblasts and osteoclasts, also known as osteogenic and osteoclastic cells. Osteoblasts are derived from mesenchymal stem cells (MSCs) in the bone marrow and eventually differentiate into osteoblasts, bone lining

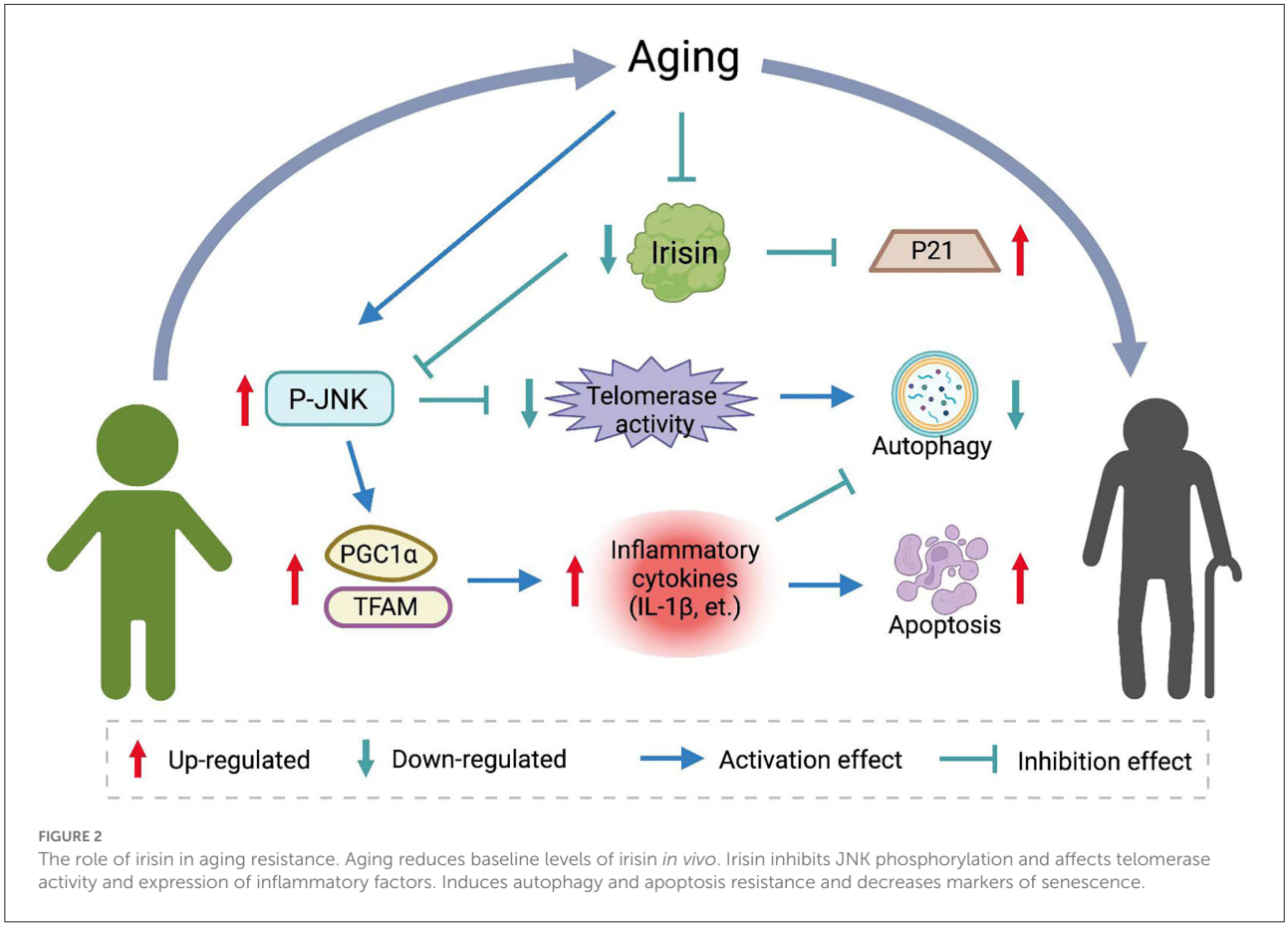


FIGURE 2
The role of irisin in aging resistance. Aging reduces baseline levels of irisin *in vivo*. Irisin inhibits JNK phosphorylation and affects telomerase activity and expression of inflammatory factors. Induces autophagy and apoptosis resistance and decreases markers of senescence.

cells, or undergo apoptosis (Ponzetti and Rucci, 2021). Some studies have shown that progressive loss of bone, associated with the progression of osteoarthritis, is more pronounced especially in the elderly (Zhang et al., 2014; Fang et al., 2021). Xu et al. (2019) observed degenerative changes in articular cartilage. It was observed that the formation of bone redundancy was accompanied by a substantial bone loss in subchondral bone, with loss of normal bone structure in a rat OA model. Other partial findings also support the reduction of bone density in osteoarthritis (Schreiber et al., 2018; Muhlenfeld et al., 2021; Zhu Z. et al., 2021). A review in regard to the relationship between BMD and osteoarthritis of the knee by Choi et al. (2021) showed that patients with moderate and severe OA had significantly lower BMD than the normal ones. Patients with mild OA show an increase in BMD but this is most likely caused by a temporary increase in score due to high turnover of the osteoarthritic subchondral bone (Dequeker et al., 2003). Primary osteoarthritis includes loss of joint space, bone fragments, and cartilage sclerosis, which may lead to erroneous increases in BMD and become a confounding factor in the study.

At all ages, a significant correlation was shown between muscle mass, muscle strength, and bone density (Sutter et al., 2019; Chen F. et al., 2020; Lopes et al., 2021). Irisin, a myokine induced during exercise, is thought to be an osteoprotective factor that acts on bone and affects bone density. The expression of irisin is positively correlated with bone health (Colaianni et al., 2019), and the related studies have been widely reported. In earlier studies, circulating irisin showed a negative association with the incidence of osteoporotic fractures in post-menopausal women with low bone mass (Anastasilakis et al., 2014; Yan et al., 2018). In a study of serum irisin levels in white football players, Colaianni et al. used x-ray bone densitometry to measure the BMD in the whole body and in different bone subregions (head, arms, legs, etc.) and compared the relationship between irisin concentrations and whole-body BMD. The results showed that irisin was linearly correlated with BMD at different bone sites and that there was a systematic association between circulating irisin and bone mass (Colaianni et al., 2017a). Zhang et al. (2020) also demonstrated a positive correlation between irisin levels and BMD in older Chinese men in 2020, and these results supported the idea that irisin exerts a protective effect on bone tissue. In 2022, Wang et al. investigated the relationship between serum levels of irisin and BMD in patients with new-onset type 2 diabetes and observed that decreased serum levels of irisin were negatively associated with BMD. The hindlimb

suspension mouse model, a widely accepted mouse model that simulates weightlessness, was used to determine the effects of unloading conditions on the performance of the musculoskeletal system (Morey-Holton et al., 2005). Bone loss induced by lack of mechanical loading was effectively prevented by the recombinant iris, and the density of femur and tibia in mice treated with recombinant iris for 4 weeks was even higher than in vehicle-treated mice (Colaianni et al., 2017b). Irisin similarly prevents bone loss in a devitalized mouse model (Luo et al., 2020). After Luo et al. treated de-ovulated mice with r-Irisin for 5 weeks, mice in the irisin-treated group exhibited a significant improvement in bone microarchitecture, bone density, and bone volume to tissue volume ratio relative to the control group. Histomorphometric analysis also showed that r-irisin increased the number of osteoblasts and decreased the number of osteoclasts. This result is consistent with the results in the deovulated rat model (Morgan et al., 2021). Irisin protected normal bone structure, maintained bone density, and maintained bone metabolic homeostasis. To further validate the relationship between irisin and bone metabolism, Zhu's team constructed FNDC5/irisin knockout mice in 2021 (Zhu X. et al., 2021) and observed a significant decrease in BMD and delayed bone development and mineralization in knockout mice during development and into adulthood. Knockout of irisin impaired the increase in bone thickness in mice induced by wheel running exercise and reduced the level of fat browning *in vivo*. Notably, the de-ovulatory model is a common means used to induce osteoporosis (Kawao et al., 2021), with osteoarthritis (Xu et al., 2019). In humans, more than 30% of menopausal women are affected by reduced bone mass and deterioration of bone tissue microarchitecture (Rossi et al., 2018), and levels of related hormones such as estrogen are associated with bone density. As mentioned above, exercise-induced expression of irisin ameliorates osteoporosis and osteoarthritis induced by the de-ovulatory model (Morris et al., 2018; Kawao et al., 2021). Another study showed that *in vitro*, irisin treatment significantly upregulated estrogen receptor alpha in cells (Yang et al., 2021). However, although the two together affect metabolic pathways, including insulin resistance (Park et al., 2013; Li et al., 2019), there are no clear reports on whether there is a direct link between the regulatory effects of irisin and the estrogen pathway.

We have described the existence of a relationship between OA and bone density above (Dequeker et al., 2003; Choi et al., 2021), and the role of irisin in modulating bone density to improve bone quality helps to explain the effects of mechanical signal stimulation on inhibiting the progression of osteoarthritis. In 2020, a study by He et al. showed that irisin rescued bone volume fraction and trabecular number in ACLT model mice and improved bone density by reducing osteoblast apoptosis. So that cartilage structure is stabilized that may indirectly stimulate the induction of chondrocyte proliferation and improve the progression of osteoarthritis through mechanical signaling of bone *in vivo* (He Z. et al., 2020). Interestingly, Wang et al. observed a decrease in serum levels of irisin in type 2 diabetic patients in parallel with a study that observed a downregulation of bone transformation markers, including osteocalcin (Wang et al., 2022). Osteocalcin—a protein specifically secreted by osteoblasts—is an important bone factor, the expression of which has been reported to be associated with osteoarthritis (Kalichman and Kobyliansky, 2010; Tarquini et al., 2017). Both irisin and osteocalcin are exercise-induced cytokines and are important components of the constitutive muscle-bone crosstalk (Kirk et al., 2020). Wang's results provide us with the possibility that irisin indirectly regulates osteoarthritis by causing alterations in the expression of bone-derived biochemical signals, and whether there is a direct regulatory effect between irisin and osteocalcin remains to be further investigated.

Irisin and bone metabolism

The metabolic regulation of irisin in bone is achieved in part by binding to integrin proteins to activate the intracellular wnt/β-catenin and ERK/MAPK signaling pathways. Changes in bone metabolism are key to affecting bone density. Changes in the balance between bone resorption and bone formation lead to changes in bone mass and affect bone remodeling (Kobayashi et al., 2016; Shen et al., 2020), thus affecting the mechanical stress state and structural stability of joints. Bone loss and osteocyte death caused by imbalances in bone metabolism lead to bone diseases, such as osteoporosis (Kim et al., 2013), femoral head necrosis (Chen et al., 2019), and the rapid progression to osteoarthritis.

Studies have shown that integrin proteins are the primary receptors for irisin in osteogenic lineage cells. Integrins are heterodimeric transmembrane proteins composed of alpha and beta subunits that mediate cell adhesion, influence cell development, immunity, and participate in hemostatic responses and wound healing. Integrins also act as signal transduction receptors, triggering a series of intracellular signaling pathways that are involved in controlling cell survival, proliferation, and regulating tissue metabolic homeostasis, as well as the progression of a variety of diseases (Barczyk et al., 2010; Ginsberg, 2014). In 2018, Kim et al. found that, as a muscle factor with increased expression induced by exercise, irisin caused the phosphorylation of FAK and Zyxin, the main downstream proteins in the integrin protein signaling pathway in human osteoid cells. Quantitative proteomic analysis confirmed the elevated expression of several integrin family members in response to irisin induction. The αV integrin protein is the possible receptor of irisin. Both αV/β5 and αV/β1 show a strong affinity with irisin. Mass spectrometry analysis further confirmed the direct binding between irisin and integrin αV/β5, while identifying the structural sequences (amino acids

60–76 and 101–118) involved in the binding (Kim et al., 2018). Kim et al. further blocked irisin-induced signals using inhibitors of various αV integrin complexes. These results confirm the important role of the integrin αV complex as an irisin receptor in osteoblasts. It also suggests that the integrin αV complex may also function as an irisin receptor in adipose tissue, mediating irisin-induced lipid metabolic processes. The role between irisin and integrins contributes to the understanding of the regulation of bone metabolism by irisin and the interpretation of the role of exercise in human health.

Irisin is induced by exercise, and the mechanism of its intracellular regulation of the WNT pathway in osteoblast-lineage cells is shown in Figure 3. Physical exercise can resist aging and mineral loss in bones caused by aging *via* regulating the balance between bone resorption and bone formation, which is associated with higher BMD. Current studies have demonstrated that the differentiation process of osteoblasts is regulated by the WNT signaling pathway and that RUNX2 is an important transcription factor in the osteogenesis process (Ponzetti and Rucci, 2021). Wnt/β-catenin pathway plays a key role in this metabolic balance regulated by exercise (Faienza et al., 2020). Previous studies have demonstrated that members of the integrin family (including αV/β1) can activate WNT1 expression and thus form positive feedback in the Wnt/β-catenin pathway by causing the accumulation of β-catenin (Du J. et al., 2016). In 2021, Liu et al. reviewed some of the studies in which exercise promoted the expression of irisin and found that the anti-inflammatory effects induced by irisin in bone tissue were associated with the activation of the classical Wnt signaling pathway (Liu et al., 2021). In a study by Zhu X. et al. (2021), FNDC5/irisin-deficient mice consistently showed reduced BMD. Irisin deficiency inhibited osteoblastogenesis and increased osteoclastogenesis, and a concomitant decrease in adipose tissue browning was observed in model mice. Elevated concentrations of irisin were induced by voluntary rotational exercise and upregulated total protein levels of β-catenin in bone marrow mesenchymal stem cells. The intranuclear expression of irisin activated Wnt/β-catenin pathway and recombinant irisin (r-irisin) induced osteoblast differentiation. It also inhibited the differentiation ability of osteoblasts and contributed to healthy bone anabolism. The result is consistent with the study by Luo et al. (2020). The accumulation of β-catenin promotes the expression of an important transcription factor, Runx2. β-catenin can bind to the promoter sequences of Runx2 and activate its transcription. Overexpression of Runx2 upregulates the expression of Tcf7, Wnt10b, and Wnt1 genes, and realized their mutual regulation with the wnt/β-catenin signaling pathway. Runx2 enhanced the proliferation of pluripotent mesenchymal cells and induced their transformation into pre-osteoblasts through the regulation of the genes involved in hedgehog, wnt, Fgf, and Pthlh signaling pathways (Morris et al., 2018; Qin et al., 2019; Chen D. et al., 2020). The expression of genes, such as Col1a1, Spp1, and Fn1, was upregulated (Komori, 2018, 2019; Chen D. et al., 2020). Taken together, the irisin-integrin-wnt/β-catenin-Runx2 interplay may constitute a signaling axis, providing a possible explanation for the mechanism of action of irisin-induced osteoblast differentiation and improved BMD.

Figure 4 demonstrates the activation of the ERK/MAPK signaling pathway mediated by irisin-binding integrins. The integrin family can activate the expression of the ERK/MAPK signaling pathway (Sheng et al., 2017; Morris et al., 2018). Colaianni et al. found that r-Irisin was able to rapidly induce phosphorylation of Erk and upregulate the expression levels of osteoblast marker genes, such as Atf4 and Runx2 (Colaianni et al., 2015). r-Irisin activated MAP kinases Erk1 and Erk2 and increased the expression of transcription factor Atf4 and down-regulated apoptotic factors caspase-9 and caspase-3 in osteoporotic mouse osteoblasts, MLO-Y4, *in vitro*, which in turn exerted anti-apoptotic effects (Storlino et al., 2020). Recombinant irisin with a conditioned medium containing irisin significantly increased the number of phosphorylated P38 (p-P38) and phosphorylated ERK (p-ERK) in rat primary osteoblasts, but had no effect on total protein. The inhibition of phosphorylated P38 with phosphorylated ERK, along with the inhibition of irisin-induced Runx2 expression, inhibited osteoblast proliferation (Qiao et al., 2016). Recently, Xue et al. showed that irisin promoted phosphorylation of Erk1/2 *via* integrin receptor αV, which in turn increased phosphorylation of STAT3 and promoted increased expression of BMP2. The binding of BMP2 to the membrane surface receptor BMPR2 activated the BMP/SMAD signaling pathway, ultimately promoting osteogenic differentiation (Xue et al., 2022). The role of irisin in the P38/ERK MAPK signaling pathway remains somewhat unresolved, and the regulation of ERK and P38 phosphorylation by irisin may be different in other tissues than in osteoblasts. For example, the investigators demonstrated in macrophages that irisin caused a decrease in the release of pro-inflammatory cytokines, such as IL-1β, TNFα, and IL-6. This was associated with the activation of phosphorylation of the MAPK signaling pathway. Here, irisin significantly reduced the phosphorylation levels of JNK and ERK, but had no effect on p-p38 (Mazur-Bialy et al., 2017). Although its mechanism of action in osteoblasts may differ, irisin exhibits a distinct anti-inflammatory profile. In another study, irisin promoted the proliferation of C2C12 cells *in vitro* by activating the ERK signaling pathway. This is a myogenic cell and treatment with irisin increased ERK; phosphorylation levels in a dose-dependent manner, while having no significant effect on p38 phosphorylation in the short term (Lee et al., 2019). In conclusion, the irisin/P38/ERK MAPK signaling pathway plays a role in resisting osteoblast apoptosis and promoting osteoblast proliferation, enhancing bone formation, and improving bone density and quality.

In addition, the reciprocal regulatory role of irisin in the AMPK signaling pathway has been reported in many tissues. Exercise-induced elevation of irisin is associated with AMPK

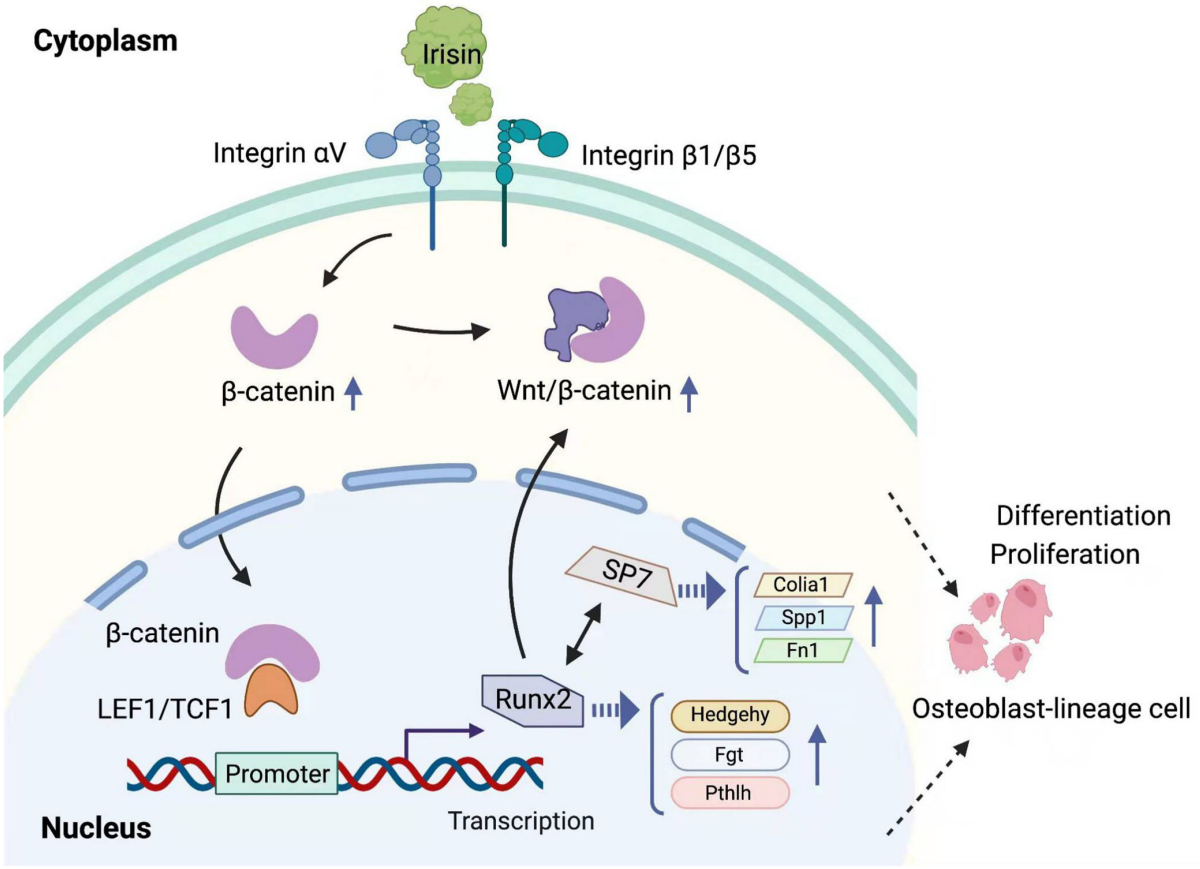


FIGURE 3
Mechanisms of regulation of the Wnt/β-catenin pathway by irisin in osteogenic lineage cells. Irisin affects various steps of the Wnt/β-catenin pathway by binding to integrins and causing the accumulation of intracellular β-catenin.

activity in the kidney. Irisin activates AMPK in renal tubular cells, inhibits the expression of inflammatory factors in the kidney, and exerts a protective effect on the kidney (Formigari et al., 2022). Studies have shown that the irisin precursor protein FNDC5 attenuates inflammation and insulin resistance in adipose tissue through the AMPK-mediated polarization of obese macrophages (Xiong et al., 2018). In bone, recent studies have shown that the induction of osteogenesis by irisin is also associated with macrophage polarization (Ye et al., 2020). Irisin treatment promoted the polarization of M0 macrophages to the M2 phenotype and facilitated osteogenesis. siRNA for the AMPK subunit AMPK-α significantly abolished the Irisin-induced M2 phenotype switch and reduced the osteogenic capacity of Irisin-treated macrophages. This result suggests that the induction of polarization of macrophages by irisin may be achieved through activation of the AMPK signaling pathway. At present, there are relatively few studies of irisin and the AMPK signaling pathway in bone. The regulatory mechanisms associated with irisin in bone metabolism need to be further investigated.

Irisin and cartilage

Along with regulating bone density, irisin can directly influence the development of osteoarthritis by regulating the proliferation and apoptosis of chondrocytes and maintaining the homeostasis of the extrachondral matrix. Chondrocytes are derived from mesenchymal cells in the early embryo (Lefebvre and Smits, 2005). At the onset of skeletogenesis, mesenchymal precursor cells undergo chondrogenesis and differentiate into prechondrocytes. Of these, early chondrogenic cells located within the joint cavity develop into articular chondrogenic cells and eventually differentiate into articular chondrocytes. Articular cartilage is a special transparent tissue that covers the surface of joint bones and is composed of chondrocytes and an extracellular matrix (Madry et al., 2010). Chondrocytes are surrounded by a rich layer of extracellular matrix ECM that regulates chondrocyte differentiation and activity while maintaining the biomechanical properties of the tissue (Lefebvre and Smits, 2005). As a common joint disease, damage to articular cartilage is a key feature of osteoarthritis,

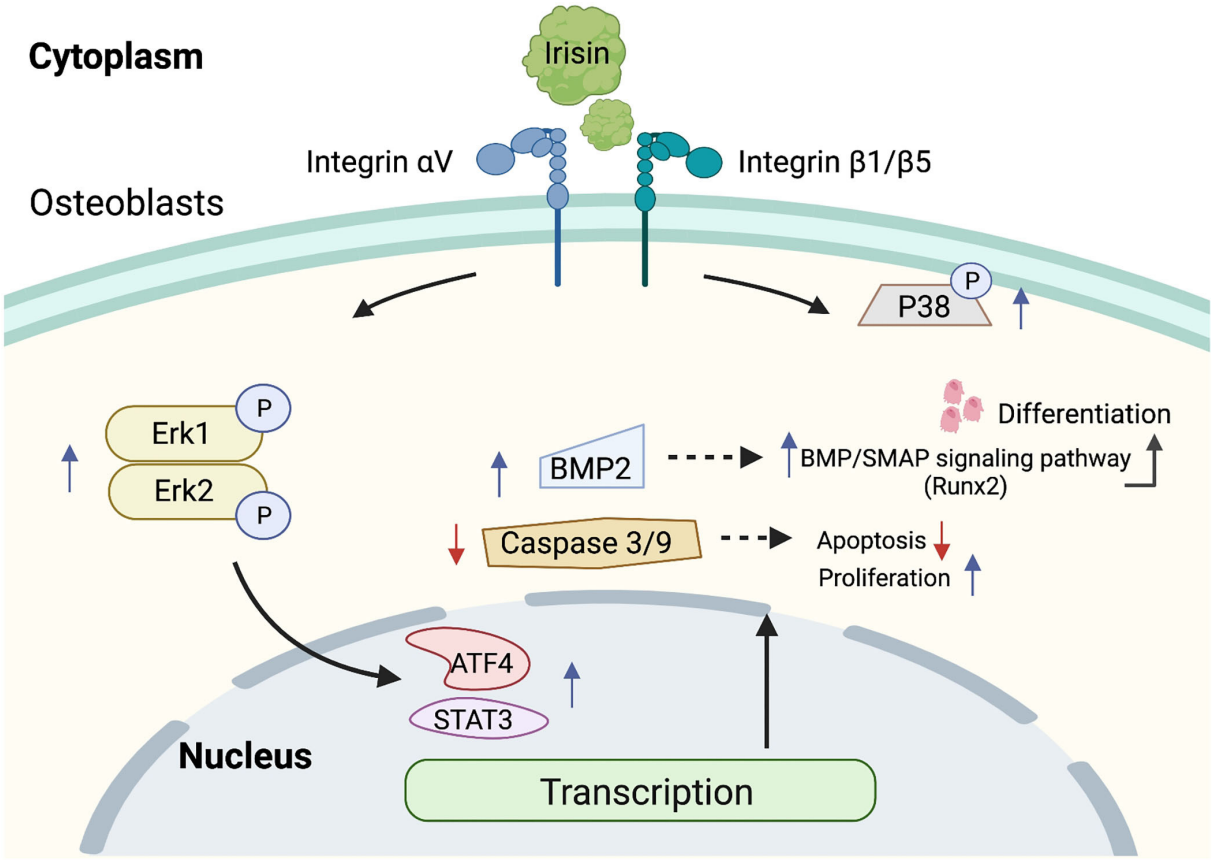


FIGURE 4
Mechanism of regulation of ERK MAPK signaling pathway by irisin. Irisin binds to integrins, increases the amount of p-P38 and p-Erk1/2, activates the ERK MAPK signaling pathway, resists apoptosis, promotes proliferation, and induces osteoblast differentiation.

including inflammation-induced apoptosis of chondrocytes and degradation of the extracellular matrix (Jang et al., 2021). The association between irisin concentrations and osteoarthritis was first analyzed in a study of blood and synovial fluid (SF) from patients with osteoarthritis of the knee. The results showed that irisin concentrations in serum and SF decreased with increasing Kellgren-Lawrence classification and that irisin concentrations were negatively correlated with the imaging severity of osteoarthritis. The expression of C-reactive protein (CRP) in serum was increased with the decrease of irisin concentration (Mao et al., 2016).

Exercise alleviates the inflammatory state of osteoarthritis, and irisin expression shows a correlation with resistance to inflammation. In a recent study, moderate-intensity exercise significantly increased serum protein levels of irisin and the anti-inflammatory factor IL-10, which inhibited expression of the inflammatory factor TNF-α and improved the osteoarthritis index in older women with sarcopenia and OA (Park et al., 2021). In the last 2 years, further studies on the protective effects of irisin on cartilage tissue in osteoarthritis have been reported. *In vitro*, r-irisin increased type II collagen levels in three-dimensionally cultured human osteoarthritic chondrocytes, while decreasing the expression of the cartilage ossification marker type X collagen. The signals improved cartilage homeostasis. In contrast to its report in osteoblasts, r-irisin treatment reduced the phosphorylation levels of p38, Akt, JNK, and NF-κB but not phosphorylated ERK in chondrocytes over a short period of time (Vadala et al., 2020). These findings signify the possible cellular specificity of irisin signaling in osteoblasts and chondrocytes. Irisin inhibited the differentiation of chondrocytes to osteoblasts, reduced the expression of inflammatory factors IL-1 and IL-6, inhibited chondrocyte apoptosis, downregulated the metalloproteinases MMP-1 and MMP-13, maintained the protective role of the extracellular matrix in cartilage, and promoted chondrocyte proliferation (Vadala et al., 2020). Wang et al. also demonstrated that irisin injection improved gait and inhibited IL-1β-mediated loss of the autophagic markers Atg4 and Atg12, as well as p62 in DMM mice. Irisin inhibits chondrocyte apoptosis and promotes extracellular matrix accumulation by improving membrane

potential and mitochondrial biogenesis in chondrocytes to protect articular cartilage and slow the development of OA (Wang et al., 2020).

However, there are conflicting reports on the ability of irisin to promote chondrocyte proliferation. He et al. observed a significant increase in the proportion of hyaline cartilage with reduced calcification of tibial cartilage at the knee joint in an ACLT model mouse. The results showed that there were no changes in the ability of chondrocytes to proliferate after being administered intravenously with irisin that was observed in an *in vitro* pulling assay that simulated exercise. Accordingly, He et al. concluded that the alleviating effect of irisin on osteoarthritis was mainly achieved by reducing the apoptosis of bone cells in subchondral bone and improving the microstructure of subchondral bone (He Z. et al., 2020). To further clarify the role of irisin in cartilage tissue, in 2021, Li et al. cultured and characterized irisin KI with KO in transgenic mice. *In vivo*, irisin knockout mice exhibited more severe osteoarthritic features following DMM modeling, whereas KI mice with intra-articular injection of irisin significantly resisted DMM-induced progression of osteoarthritis. In experiments with primary chondrocytes cultured *in vitro*, cell proliferation in irisin KI mice was significantly increased in both normal and IL-1β-induced inflammatory states, while KO mouse-derived chondrocytes had decreased proliferative capacity, and the addition of r-irisin was able to reverse the proliferative capacity of KO cells. Irisin reduced the gene expression levels of inflammatory factors and inflammatory mediators in chondrocytes and upregulated COL2a1, aggrecan, and SOX9 expression. These experiment results clarify the role of irisin in promoting chondrocyte proliferation Li X. et al. (2021). We speculate that differences in the intensity settings of mechanical pulling *in vitro* and the forms of cell culture in the different studies may have contributed to the differences in the results of the different studies. Primary chondrocytes cultured in 3D can better simulate the effect of irisin *in vivo*. In a recent study, Jia et al. compared the effects of low, moderate, or high-intensity treadmill exercise with the effects on the concentration levels of irisin in the synovial fluid of SD rats (Jia et al., 2022). This study demonstrated that exercise of appropriate intensity maintained high circulating levels of irisin, significantly increased the concentration of irisin in synovial fluid, alleviated inflammation and scorching of chondrocytes, reduced OA cartilage damage in a rat model, and achieved therapeutic effects in osteoarthritis. In contrast, high-intensity exercise may cause excessive mechanical stimulation, resulting in damage that outweighs the therapeutic effect of increased irisin concentrations and therefore exacerbates the progression of OA.

These results suggest that irisin, as an exercise-induced muscle factor, may act directly on cartilage tissue and influence the disease process of knee OA by inhibiting inflammation. The ameliorative effect of irisin on osteoarthritis is mediated by its modulation of subchondral bone mass in conjunction with its direct intervention on cartilage tissue metabolism.

Irisin and cartilage metabolism

High expression of irisin inhibits the activation of chondrocyte Wnt/β-catenin and NF-κB signaling pathways in osteoarthritis. The regulation within chondrocytes is shown in Figure 5. The metabolic imbalance between anabolic and catabolic factors produced by chondrocytes leads to the degradation and destruction of cartilage. This is an important cause of chondrocyte apoptosis, as well as degradation of extrachondral mechanisms, ultimately leading to osteoarthritis (Messina et al., 2019; Oliviero and Ramonda, 2021).

Activation of Wnt/β-catenin and NF-κB signaling pathways in chondrocytes regulates chondrocyte metabolism and plays an important role in OA progression (Zhou et al., 2017; Choi et al., 2019). Among these, the Wnt/β-catenin signaling pathway regulates the development of arthritis and mediates the high expression of downstream effectors, such as mmp family members, adamts, acan, and Col2a1 genes and inflammation-related factors in chondrocytes with osteoarthritis (Zhou et al., 2017). The strong activation of typical Wnt signaling exhibited joint damage due to DMM surgery in chondrocytes. In transgenic mice with stable mutations in β-catenin, the model showed a significant progressive loss of articular cartilage as β-catenin expression in cartilage was upregulated. Inhibition of the activation state of the Wnt pathway in cartilage tissue alleviates OA symptoms and mitigates cartilage loss in a surgically induced mouse model of OA (Lietman et al., 2018). NF-κB is aberrantly activated in OA and the associated signals are involved in a variety of biological processes, including chondrocyte apoptosis, inflammatory factor release, and extracellular matrix degradation (Chen Z. et al., 2020) Tumor necrosis factor-alpha (TNF-α) is an important cytokine (Cao et al., 2021), and studies have shown that IL-1β-induced TNF-α expression is significantly upregulated in chondrocytes and activates the NF-kB pathway by increasing p-IkBa and p-p65 (Li et al., 2019) NF-kB pathway (Li Z. et al., 2021).

Irisin is a myokine that can be upregulated after being induced during exercise. Wang et al.'s (2020) study confirmed that the irisin signaling pathway plays a protective role on the mitochondria of chondrocytes, inhibiting apoptosis and preventing oxidative damage in inflammatory chondrocytes, along with key regulators, including Sirt3, a signaling factor closely associated with the activation of Wnt pathway. Li et al. induced osteosarcoma cells with IL-1β to simulate OA *in vitro*. The results showed that irisin treatment significantly inhibited the protein and mRNA levels of WnT-1 and β-catenin. Irisin intervention also significantly reduced the induction effect of LiCl on β-catenin. Irisin inhibited Wnt/β-catenin pathway in chondrocytes. The expression of MMP-13 and other

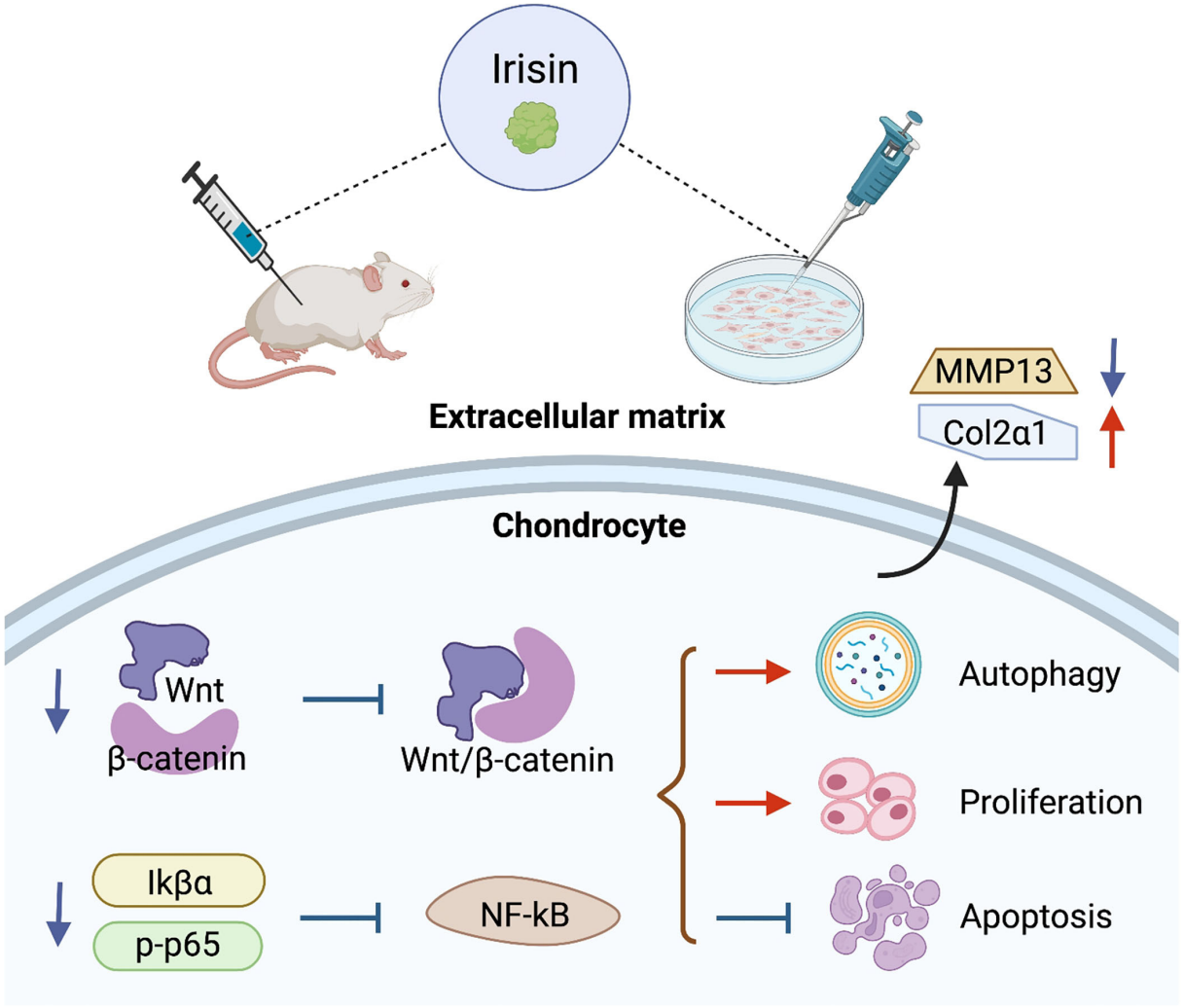


FIGURE 5
Regulatory role of irisin in chondrocyte metabolism. Irisin inhibits the activation of Wnt/β-catenin and NF-κB signaling pathways in osteoarthritic chondrocytes, promotes cell autophagy and proliferation, inhibits apoptosis, and improves the stability of the extracellular matrix.

metal matrix proteases in cartilage tissues was down-regulated, and the protein level of type II collagen in IL-1β-induced osteosarcoma cells was reversed. Irisin showed strong resistance to inflammation (Li et al., 2020). On the other hand, irisin reduced TNF-α expression in chondrocytes cultured *in vitro* (Li X. et al., 2021) demonstrated that irisin reversed IL-1β-induced IkBa expression and p65 phosphorylation levels in osteosarcoma cells. Irisin inhibited cytoplasmic p-p65 and down-regulated NF-κB pathway activity in chondrocytes (Li et al., 2020). *In vitro* morphological observations demonstrated that upregulation of irisin concentrations ameliorated chondrocyte scorch death, an important pro-inflammatory programmed cell death (Jia et al., 2022). In Jia et al.'s study, irisin pretreatment blocked IL-1β-induced NF-κB/p65 nuclear translocation and enhanced chondrocyte-specific collagen II expression, while inhibiting nod-like receptor protein-3 (NLRP3)/caspase-1 activity. The results of both biochemical analysis and biochemical indexes indicated that irisin ameliorated osteoarthritis by inhibiting the activation of PI3K/Akt/NF-κB cascade reaction and suppressing inflammation-induced chondrocyte scorching (Jia et al., 2022).

Irisin exhibited a protective effect on cartilage by inhibiting the activation of Wnt/β-catenin and NF-κB signaling pathways, reducing matrix metalloproteinase expression, enhancing extracellular matrix stability, downregulating inflammatory factors in chondrocytes, inhibiting apoptosis, and promoting chondrocyte proliferation. Notably, the regulation of key factors of the Wnt/β-catenin pathway by irisin in chondrocytes showed opposite characteristics to its promotion of the Wnt/β-catenin pathway in

osteoblastic lineage cells that reflect the cellular specificity of irisin.

Prospect

It is expected that in the future, research on irisin, a muscle factor induced by exercise, will help us to further understand and explain the beneficial effects of exercise in the maintenance of physical health, particularly in the fight against aging and age-related degenerative diseases. As shown in Supplementary Table 1, the effect of different types of exercise on the induction of irisin expression is clearly inconsistent, with resistance exercise being more significant in increasing irisin levels, and a great deal of research has been done to explain the mechanisms underlying this phenomenon. The FITT principle, which includes frequency, intensity, time, and type, is a standard prescription for physical activity programs as newly defined by the American College of Sports Medicine (ACSM) (DeSimone, 2019). Exercise protocols based on the FITT principles hold the promise of resolving the contradictory results that have emerged from past studies of exercise modulation of irisin and will help to further clarify the modulatory effects of exercise on irisin in the future. The roles of irisin in bone and cartilage tissue and the mechanisms that trigger it (as shown in Figures 3–5) have received a great deal of attention in the exercise treatment of osteoarthritis. In the past 2 years, studies involving the roles of irisin in osteoarthritis have increased rapidly, revealing the regulation of bone density (Zhang et al., 2020; Wang et al., 2022), resistance to inflammatory factors (Vadala et al., 2020; Wang et al., 2020), and the protective effects of irisin on articular cartilage (Li X. et al., 2021; Jia et al., 2022). However, the research on related pathways is still not thorough, and many important nodes are missing. For example, what is the receptor of irisin in chondrocytes? Irisin plays different roles in bone and cartilage tissues, and the reasons for its obvious tissue specificity and its role in coordinating the metabolic balance between bone tissue, cartilage tissue, and other body tissues are all problems that need to be solved in the future.

Conclusion

Irisin, a myokine secreted by skeletal muscle in response to exercise stimulation, is involved in resistance to aging and its discovery explains the protective mechanism of exercise in bone and cartilage tissues. Irisin has been shown to promote osteoblast differentiation and proliferation in bone, increase bone density, improve bone quality, and enhance the mechanical support of cartilage by subchondral bone; on the other hand, irisin promotes chondrocyte proliferation, reduces the secretion of inflammatory factors and matrix metalloproteinases in chondrocytes, inhibits chondrocyte apoptosis, and strengthens the stability of the extrachondral matrix, which has great potential in the prevention and treatment of osteoarthritis. In conclusion, this study shows that irisin is a very useful tool in the prevention and treatment of osteoarthritis. In conclusion, this study suggests that irisin may be a new marker signal and therapeutic target in osteoarthritis. Further research into the effects of exercise form and intensity on the induction of irisin expression, as well as the mechanisms regulating the effects of irisin in bone density and cartilage metabolism, will help to implement better prevention and treatment modalities for osteoarthritis.

Author contributions

X-aZ, ZW, and KN designed the research and collected the materials. X-aZ provided conceptual and funding support for this article. X-aZ and ZW reviewed and revised the manuscript. KN wrote and amended the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.934406/full#supplementary-material

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Effects of three modes of physical activity on physical fitness and hematological parameters in older people with sarcopenic obesity: A systematic review and meta-analysis

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Objective: This systematic review and meta-analysis assessed the effects of three modes of physical activity (PA) (aerobic training [AT], resistance training [RT], and aerobic combined with resistance training [MT]) on body composition (body weight [BW], body mass index [BMI] and percentage of body fat [BF%]), muscle mass (skeletal muscle mass [SM], appendicular skeletal muscle mass [ASM] and appendicular skeletal muscle mass index [ASMI]), muscle strength (handgrip strength [HG] and knee extension strength [KES]), physical performance (gait speed [GS]) and hematological parameters (inflammatory markers, insulin-like growth factor 1 [IGF-1] and lipid profiles) in older people with sarcopenic obesity (SO).

Methods: We searched all studies for PA effects in older people with SO from six databases published from January 2010 to November 2021. Two researchers independently screened studies, extracted data according to inclusion and exclusion criteria, and assessed the quality of included studies. Pooled analyses for pre-and post- outcome measures were performed by Review Manager 5.4. We calculated a meta-analysis with a 95% confidence interval (95% CI) and the standardized mean differences (SMD).

Results: 12 studies were analyzed. There were 614 older people (84.9% female) with SO, aged 58.4 to 88.4 years. Compared with a no-PA control group, AT decreased BW (SMD = −0.64, 95% CI: −1.13 to −0.16, $p = 0.009$, $I^2 = 0\%$) and BMI (SMD = −0.69, 95% CI: −1.18 to −0.21, $p = 0.005$, $I^2 = 0\%$); RT improved BF% (SMD = −0.43, 95% CI: −0.63 to −0.22, $p < 0.0001$, $I^2 = 38\%$), ASMI (SMD = 0.72, 95% CI: 0.24 to 1.21, $p = 0.004$, $I^2 = 0\%$), ASM (SMD = −0.94, 95% CI: −1.46 to −0.42, $p = 0.0004$), HG (SMD = 1.06, 95% CI: 0.22 to 1.91, $p = 0.01$, $I^2 = 90\%$) and KES (SMD = 1.06, 95% CI: 0.73 to 1.39, $p < 0.00001$, $I^2 = 14\%$); MT improved BMI (SMD = −0.77, 95% CI: −1.26 to −0.28, $p = 0.002$, $I^2 = 0\%$), BF% (SMD = −0.54, 95% CI: −0.83 to −0.25, $p = 0.0003$, $I^2 = 0\%$), ASMI

(SMD = 0.70, 95% CI: 0.22 to 1.19, p = 0.005, I^2 = 0%) and GS (SMD = 0.71, 95% CI: 0.23 to 1.18, p = 0.004, I^2 = 37%). PA increased IGF-1 (SMD = 0.38, 95% CI: 0.11 to 0.66, p = 0.006, I^2 = 0%), but had no effect on inflammatory markers and lipid profiles.

Conclusion: PA is an effective treatment to improve body composition, muscle mass, muscle strength, physical performance, and IGF-1 in older people with SO.

KEYWORDS

exercise, body composition, muscle mass, muscle strength, physical performance, inflammation, insulin-like growth factor 1, lipids profiles

Introduction

Sarcopenic obesity (SO) refers to the combination of sarcopenia and obesity. Sarcopenia is an age-related decrease of skeletal muscle mass with a decline in muscle strength and reduced physical performance (Chen et al., 2020). Obesity is a risk factor for insulin resistance, dyslipidemia, type 2 diabetes mellitus, and cardiovascular disease (Rosen and Spiegelman, 2006). People with SO are less physically active, intake more calories, and have a higher risk of diabetes or dyslipidemia than nonobese people with and without sarcopenia (Batsis and Villareal, 2018; Lim et al., 2018). A meta-analysis of SO adults showed a 24% increased risk of all-cause mortality, especially in men, compared with adults without SO (Tian and Xu, 2016). Data from World Population Prospects: the 2019 Revision (United Nations, 2019) shows that by 2050, one in six people will be 65 years or older globally, and one in four people in Europe and North America will be 65 years or older. Currently, the global prevalence of SO is 11% in nursing homes, communities, and hospitals (Gao et al., 2021). With the aging population increasing, SO may affect 100–200 million people worldwide in the next 35 years. As SO increases the risk of hospitalization, it also can increase the economic burden on individuals and nations (Janssen et al., 2004; Withrow and Alter, 2011; Lee et al., 2016; Rossi et al., 2017). Accordingly, researchers, clinicians, and policymakers should be aware of SO, its complications, and its impact on society.

Inflammatory markers play a vital role in the progression of SO (Schrager et al., 2007). Obesity causes a chronic inflammatory state, which leads to an increase in inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP) (Sáinz et al., 2010). Elevated IL-6 (>5 Pg/ml) and elevated CRP (>6.1 μg/ml) increase the risk of losing >40% muscle strength by 2 to 3 times more than people with normal IL-6 and CRP levels (Schaap et al., 2006). Upregulation of the inflammatory marker IL-6 leads to a decrease in anabolic actions of insulin-like growth factor 1 (IGF-1) (Batsis and Villareal, 2018), which weakens the maintenance and growth of skeletal muscle (Mak et al., 2011). A low level of IGF-1 also increases the risk of hyperlipidemia (García-Fernández et al., 2008), which increases the risk of cardiovascular disease (CVD) (Nelson, 2013). In people with SO, lipid levels for triglyceride (TG) and total cholesterol (TC) are higher, and high-density lipoprotein (HDL) is lower compared to people without SO (Habib et al., 2020). Increasing IGF-1, decreasing inflammatory markers, and normalizing lipid levels may improve muscle mass and strength and reduce CVD risk in people with SO (Batsis and Villareal, 2018).

At present, there is still a lack of specific pharmacological interventions for SO (Evans et al., 2021). Non-pharmacological interventions are the most commonly used method for the treatment of SO. Many studies have indicated that physical activity (PA) is one of the most effective non-pharmacological interventions for the management of SO (Theodorakopoulos et al., 2017; Hita-Contreras et al., 2018; Hsu et al., 2019). Systematic reviews and meta-analyses in older people with SO demonstrate that PA improves body composition, muscle mass, strength, and physical performance. Changes have been observed in the percentage of body fat [BF%] (Hita-Contreras et al., 2018; Hsu et al., 2019), body weight [BW] (Hsu et al., 2019), body mass index [BMI] (Hsu et al., 2019), appendicular skeletal muscle mass [ASM] (Hita-Contreras et al., 2018), handgrip strength [HG] (Theodorakopoulos et al., 2017; Hita-Contreras et al., 2018; Hsu et al., 2019) and gait speed [GS] (Theodorakopoulos et al., 2017; Hita-Contreras et al., 2018; Hsu et al., 2019). Moreover, compared with other non-pharmacological interventions (e.g., electrical acupuncture, nutritional supplements, and dietary management), older people with SO benefit from PA in reducing BF% and increasing HG and GS (Yin et al., 2020). Studies also have shown that PA in older people with SO can decrease IL-6 (Wang et al., 2019), increase IGF-1 (Chen et al., 2017; Wang et al., 2019), and improve TC and LDL lipid profiles (Park et al., 2017), reducing inflammation and the risk of CVD.

There are some limitations to meta-analysis studies on PA and SO. Firstly, inconsistent diagnostic criteria, measurement indicators, and assessment methods of SO create high heterogeneity in the meta-analysis of SO (Martínez-Amat et al., 2018; Hsu et al., 2019; Yin et al., 2020). For example, the diagnostic criteria used to diagnose sarcopenia differ among the European Working Group on Sarcopenia (EWGSOP-2010)

TABLE 1 Characteristics of included studies.

Study	Sample size (ETG/CG)	Gender (n: Male/female)	Age (ETG/CG)	Sarcopenia diagnostics (indicator, cut-points, Source)	Obesity diagnostics (indicator, cut-points, Source)	Intervention				Control group	Outcome
						Mode	Training movement	Intensity	Duration days/week (weeks)		
Huang et al. (2017)	18/17	0/35	68.89 ± 4.91/ 69.53 ± 5.09	SM/weight^2*100% by BIA<27.6 (Janssen)	BF% by BIA>30% (Liu)	RT: Elastic band	RT: Muscle group training included shoulders, arms, lower limbs, chest, and abdomen	3 sets/10 reps	3 (12)	Education	BW, BMI, BF %, TG, HDL, LDL, TC, CRP
Vasconcelos et al. (2016)	14/14	0/28	72 ± 4.6/ 72 ± 3.6	HG ≤ 21 kg (Fried)	BMI≥30 kg/m^2 (Vasconcelos)	RT: Elastic band	RT: Knee exercises, hip exercises, and mini-squats	2–3 sets/12 reps (40–60% 1RM) for knee exercises; 2–3 sets/12 reps (1–3 kg) for hip exercises; 2–3 sets/ 10 reps (1–3 kg) for mini-squats	2 (10)	Non-exercise	KES, GS
Liao et al. (2018)	33/23	0/56	66.67 ± 4.54/ 68.32 ± 6.05	SM/weight*100% by BIA<27.6% (Janssen)	BF% by BIA>30% (Liu)	RT: Elastic band	RT: Upper body exercises included seated chest press, seated row, seated shoulder press; Lower body exercises included knee extension, knee flexion, hip flexion, and hip extension	3 sets/10 reps; RPE = 13	3 (12)	Non-exercise	BF%, SM, HG, KES, GS
Liao et al. (2017)	25/21	0/46	66.39 ± 4.49/ 68.42 ± 5.86	SM/height^2 by BIA<7.15 kg/m^2 (EWGSOP-2010)	BF% by BIA>30% (Baumgartner)	RT: Elastic band	RT: Seated chest press, seated row, seated shoulder press, concentric–eccentric hip circumduction, leg press, leg curl	3 sets/10–20 repsRPE = 13	3 (12)	Non-exercise	BF%, HG, KES, GS
Chiu et al. (2018)	36/34	35/35	79.64 ± 7.36/ 80.15 ± 8.26	SM/weight*100% by BIA, M: ≤37.15%F: ≤32.26% (Janssen)	BF%, F: ≥29%, M: ≥40% (Ko)	RT: Sandbag and grip ball	RT: Upper extremities training that targeted the biceps, deltoids, grip, and pinch; Lower extremities training included leg extension, leg flexion, calf raises, stepping forward and sideward	3 sets/4–10 reps	2 (12)	Non-exercise	BF%, ASM, HG
Park et al. (2017)	25/25	0/50	73.5 ± 7.1/ 74.7 ± 5.1	ASM/weight*100% by BIA<25.1% (Lim)	BMI≥25.0 kg/ m^2 (Lim)	RT: Elastic band AT: Walking	RT: elbow flexion, wrist flexion, shoulder flexion, lateral raise, front raise, chest press, reverse flies, side band, dead lift, squat, leg press, ankle plantar flexion AT: sideways, backward, forward walking, slow and fast indoor walking	All 50–80 min, RT:2-3sets/ 8–15reps,20–30 min/ session; AT:30–50min/ session with the RPE = 13–17	RT: 3 (24), AT: 5 (24)	Education	BF%, ASM, HG, GS, TG, HDL, LDL, TC, CRP

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TABLE 1 (*Continued*) Characteristics of included studies.

Study	Sample size (ETG/CG)	Gender (n: Male/female)	Age (ETG/CG)	Sarcopenia diagnostics (indicator, cut-points, Source)	Obesity diagnostics (indicator, cut-points, Source)	Intervention				Control group	Outcome
						Mode	Training movement	Intensity	Duration days/week (weeks)		
Chen et al. (2017)	RT:15, AT: 15, RT + AT:15, CG:15	10/50	RT:68.9 ± 4.4, AT:69.3 ± 3.0, RT + AT: 68.5 ± 2.7, CG: 68.6 ± 3.1	ASM/Weight*100%, M: ≤32.5%, F: ≤25.7% (Chung)	BMI≥ 25 kg/m^2 (WHO); VFA≥ 100 cm^2 (Lu)	RT: Weight-training equipment, AT: dance steps class	RT: shoulder presses, bicep curls, triceps curls, bench presses, deadlifts, leg swings, squats, standing rows, unilateral rows, and split front squats. AT: stepping on the spot, knee lifts, high knee running, rowing arm swings, arm swings, twist steps, arm raises, squats, V steps, mambo steps, diamond steps, and point step jumps	RT: 3 sets/8–12 reps. AT: moderate intensity (>3 metabolic equivalents)	RT: 2 (8), AT: 2 (8), RT + AT: 1 (8)	Non-exercise	BW, BMI, BF %, ASMI, SM, HG, KES, IGF-1
Kim et al. (2016)	RT + AT: 35, CG:34	0/69	81.4 ± 4.3/ 81.1 ± 5.1	SM/height^2 by DXA<5.67 kg/m^2 or HG < 17.0 kg, or GS < 1.0 m/s (Kim-2016)	BF% by DXA≥32% (Kim-2016)	RT: Weight machines, Elastic band. AT: Stationary bicycle	RT: toe raises, heel raises, knee lifts, and knee extension, hip flexion, seated row, leg press, abduction, leg extension, and abdominal crunch. AT: Stationary bicycle	RT: 1–3/10 reps, AT: 12 min	RT:2 (12), AT: 2 (12)	Education	BW, BF%, ASM, HG, KES, GS, TG, TC, IL-6, CRP
Wang et al. (2019)	RT:20, AT: 20, RT + AT:20, CG:20	43/37	RT:65.1 ± 3.4, AT:64.2 ± 3.0, RT + AT: 63.6 ± 5.2, CG: 64.1 ± 2.8	ASM by DXA, M: <7 kg/m^2, F:<5.4 kg/m^2; HG, M: <26kg, F: <18 kg	BMI, M: < 0.789, F: < 0.512 (FNIH)	—	RT: Hands, feet, abdomen, pelvis and back muscle training, AT: Stepping, knee lift, leg lift, arm swing, arm lift, diamond step and dot step jump	RT:3-5sets/10–15reps, AT: 40%–60%, VO_2max, RT + AT: RT for 10 min, AT for 20 min	RT: 2 (8), AT: 2 (8), RT + AT: 2 (8)	Non-exercise	BW, BMI, BF %, ASMI, HG, KES, IL-6, IGF-1
Li et al. (2020)	RT + AT: 15, CG:15	—	RT + AT: 63.87 ± 3.56, CG: 64.93±3.84	ASM/height^2 by DXA, M: ≤7.0 kg/m^2, F: ≤5.4 kg/m^2 (AGWS-2013)	BF% by DXA, M: ≥25%, F: ≥35% (WHO)	RT: Elastic band, AT: Speed walking	RT: Major muscle groups training of limbs and trunk, AT: Speed walking	RT:1-3sets/10reps, RPE = 5–6/10, RPE = 5–6/10, AT: 60%–80% HRmax	RT: 3 (12), AT: 5 (12)	Non-exercise	BF%, ASM
Banitalebi et al. (2021)	RT:32, CG:31	0/63	RT:64.11± 3.81,CG: 64.05± 3.35	SM/Weight*100% by DXA≤ 28% or SM/ height^2 by DXA ≤28% or ≤7.76 kg/m^2; GS ≤ 1 m/s (Newman)	BF% by DXA≥32%; BMI by DXA >30 kg/ m^2 (ASBP)	RT: Elastic band	RT: major muscle groups training (legs, back, abdomen, chest, shoulders, and arms)	RT: 1–2/12 reps	RT: 3 (12)	Non-exercise	BW, BMI, BF%
Lee et al. (2021)	RT: 15,CG:12	0/27	RT:70.13 ± 4.41, CG: 71.82 ± 5.23	ASM/height^2 by DXA <5.67 kg/m^2 and HG < 20 kg or GS < 0.8 m/s (EWGSOP-2010)	BF% by DXA,>35% (Li)	RT: Elastic band	RT: major muscle groups training (shoulders, arms, lower limbs, chest, and abdomen)	RT: 3 set/10 reps	RT: 3 (12)	Non-exercise	BF%, SM, HG, GS

ETG, exercise training group; CG, control group; RT, resistance training; AT, aerobic training; reps, repetition; RPE, rated perceived exercise; 1RM, one repetition maximum; W, week; BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; BW, body weight; BMI, body mass index; BF%, percentage body fat; SM, skeletal muscle mass; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; HG, handgrip strength; GS, gait speed; KES, knee extension strength; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; IL-6, interleukin-6; CRP, C-reactive protein; IGF-1, insulin-like growth factor 1; HRmax, maximal heart rate; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; AWGS, Asian Working Group for Sarcopenia; ASBP, the American Society of Bariatric Physicians; Age is expressed as mean ± standard deviation;

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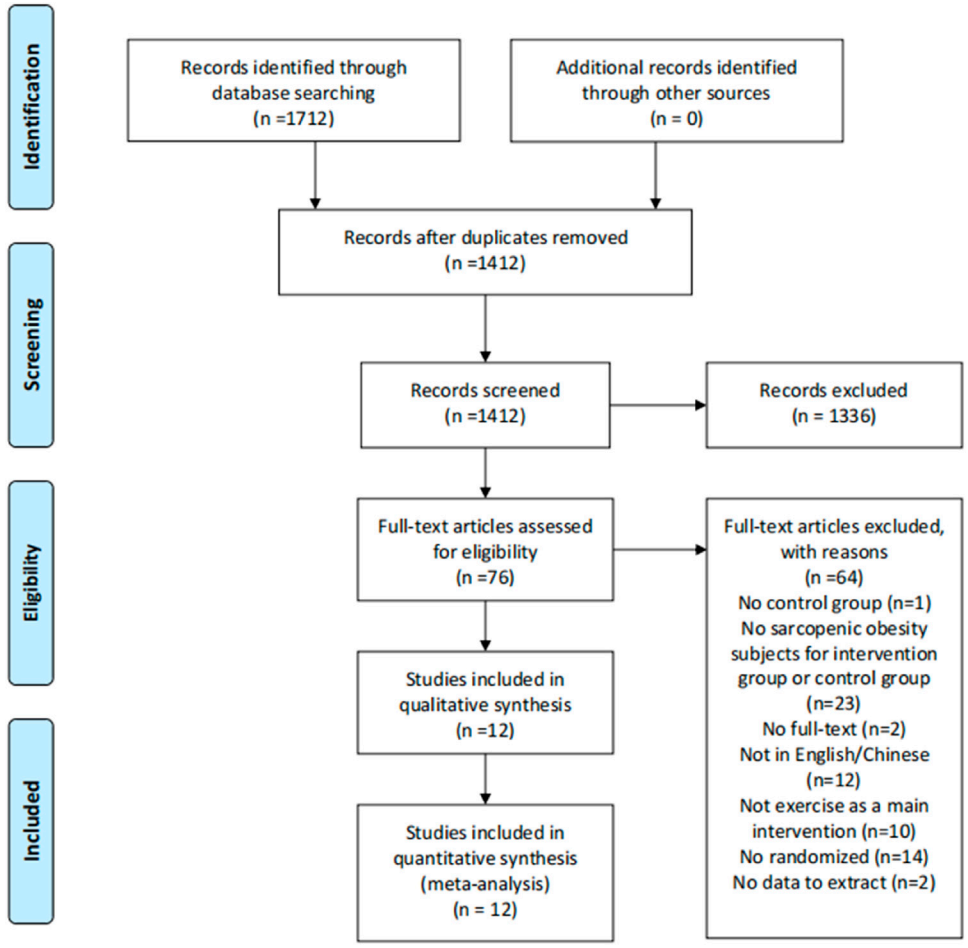


FIGURE 1
Flow of screening and selecting process according to preferred reporting items for systematic reviews and meta-analysis (PRISMA).

(Liao et al., 2017), the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (Wang et al., 2019) and others (Kim et al., 2016; Vasconcelos et al., 2016; Chen et al., 2017; Huang et al., 2017; Park et al., 2017; Liao et al., 2018). The cut-off points for measurement indicators differ for ASM, HG, and GS. Diagnosis of obesity status also was inconsistent. For example, studies used different methods to measure body fat [i.e., bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA)]. They also based the diagnosis of obesity on different measures of body fat [e.g., BF%, BMI, visceral fat area (VFA)]. Due to different diagnostic criteria, assessment methods, and cut-off points of sarcopenia and obesity, there are differences in the identification of SO in the included articles (Kim et al., 2016; Vasconcelos et al., 2016; Chen et al., 2017; Huang et al., 2017; Liao et al., 2017; Park et al., 2017; Chiu et al., 2018; Liao et al., 2018; Wang et al., 2019; Li et al., 2020; Banitalebi et al., 2021; Lee et al., 2021). Secondly, PA mainly included aerobic training (AT), resistance training (RT), and mixed training (MT), of which the most used is aerobic combined with resistance training. There is currently a lack of studies on the effects of AT on people with SO. In people without SO, regular AT prevents loss of skeletal muscle mass and strength (Gielen et al., 2003), increases maximal oxygen uptake (VO_2max) (Katzmarzyk et al., 2001), decreases body fat mass (Katzmarzyk et al., 2001), improves physical performance (Bull et al., 2020), and reduces the risk of CVD (Fiuza-Luces et al., 2018). The International Exercise Recommendations in Older Adults (ICFSR): Expert Consensus Guidelines 2021 (Izquierdo et al., 2021) recommends that older people perform AT 3–7 times per week at 55%–70% of heart rate reserve. In the current meta-analysis of SO, only Hsu et al. (Hsu et al., 2019) investigated the effects of AT on older people with SO. Although they indicated that older people with SO could get benefits from RT and MT, there was not enough evidence showing AT's effects on older people with SO. Many studies have proved the benefits of AT for healthy older people or older

TABLE 2 Different indicators and cut-off points in defining sarcopenia.

Diagnosis criteria	Target district	Cut-off points		
		Muscle mass	Muscle strength	Muscle performance
EWGSOP-2010 Cruz-Jentoft et al. (2010)	countries from Europe	ASM/height^2 by DXA: (M:<7.26 kg/m^2, F:<5.50 kg/m^2); or SM/height^2 by BIA: (M:≤8.87 kg/m^2, F:≤6.42 kg/m^2)	HG: (M:<30 kg, F: <20 kg)	GS (4 m): <0.8 m/s; or GS (6 m): < 1 m/s, or SPPB: ≤ 8
AWGS-2013 Chen et al. (2014)	countries from Asia	ASM/height^2 by DXA: (M:≤7.0 kg/m^2, F:≤5.4 kg/m^2); or ASM/height^2 by BIA: (M: ≤7.0 kg/m^2, F: ≤5.7 kg/m^2)	HG: (M:<26 kg, F: <18 kg)	GS (6 m): <0.8 m/s
FNIH Studenski et al. (2014)	United States	ASM/BMI by DXA: (M < 0.789, F < 0.512)	HG: (M < 26kg, F < 16 kg)	—
Janssen et al. (2002)	United States	[(height^2/BIA-resistance * 0.401) + 3.825 (gender)+ 0.071 (age)+ 5.102]/body mass * 100] <1 standard deviations of a young reference population	—	—
Chung et al. (2013)	Korea	ASM/weight * 100% by DXA, M: ≤32.5%, F: ≤25.7%	—	—
Newman et al. (2003)	United States	F:ALM (kg) = −13.19 + 14.75*height (m) + 0.23 * total fat mass (kg). M:ALM (kg) = −22.48 + 24.14 * height(m) + 0.21 * total fat mass (kg),the 20th percentile of the distribution of residuals	—	—
Lim et al. (2010)	Korea	ASM/height^2 by DXA: (M < 7.09 kg/m^2,F < 5.27 kg/m^2); or ASM/weight * 100% by DXA: (M<29.9%, F<25.1%)	—	—
Kim et al. (2016)	Japan	SM/height^2 by DXA <5.67 kg/m^2	HG: <17.0 kg	GS (5 m): <1.0 m/s
Fried et al. (2001)	United States	weight loss>10 poundsor ≥5% of body weight of the previous year	HG: lowest 20% (by gender, BMI)	GS: slowest 20% (by gender, height)

BIA: bioelectrical impedance analysis; DXA: dual energy X-ray absorptiometry; BMI: body mass index; SM: skeletal muscle mass (kg); ASM: appendicular skeletal muscle mass; ALM: appendicular lean mass; HG: handgrip strength; GS: gait speed; SPPB: the short physical performance battery; TUG: time up and go test; EWGSOP: European Working Group on Sarcopenia in Older People; FNIH: Foundation for the National Institutes of Health; AWGS: Asian Working Group for Sarcopenia; M: male; F: female.

TABLE 3 Different indicators and cut-off points in defining obesity.

Diagnosis criteria	Target district	Cut-off points
Deurenberg et al. (1998)	America, Caucasia, China, Ethiopia, Indonesia, Polynesia and Thailand	BF% by BIA>30%
Ko et al. (2001)	China	BF% by BIA,F: ≥29%,M: ≥40%
Vasconcelos et al. (2016)	Brazil	BMI≥30 kg/m^2
Baumgartner. (2000)	New Mexico	BF% by BIA>30%
Lim et al. (2010)	Korea	VFA by abdominal CT > 100 cm^2
FNIH Studenski et al. (2014)	—	BMI, M:<0.789, F:< 0.512
Kim et al. (2016)	Japan	BF% by DXA, ≥ 32%
WHO Use and Anthropometry. (1995)	Asia	BF% by DXA, M: ≥ 25%, F: ≥ 35%; BMI ≥25 kg/m^2
Li et al. (2012)	China	BF% by BIA, M: ≥ 25%, F: ≥ 35%
ASBP Ilich et al. (2016)	United States	BF% by DXA ≥32%

BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; BF%, body fat percentage; VFA, visceral fat area; CT, computed tomography; BMI, body mass index; M, male; F, female; FNIH, foundation for the national institutes of health; WHO, world health organization; ASBP, american society of bariatric physicians.

people with chronic diseases (Chodzko-Zajko et al., 2009; Bull et al., 2020; Izquierdo et al., 2021); however, there is insufficient evidence if AT is beneficial in the progression of SO. Thirdly, IGF-1 plays a vital role in the mechanism of SO and is closely related to CVD. Currently, among the meta-analyses of SO, only Hsu et al. (Hsu et al., 2019) explored the effects of different forms of PA on hematological parameters (IL-6, CRP, TC, TG, HDL, and LDL) in older people with SO. There is no meta-analysis of PA and IGF-1. Finally, up to now, few studies have investigated the effects of different modes of PA in older people with SO. It is necessary to integrate more individual studies in a meta-analysis to explore the effects of different modes of PA on the progression of SO to provide an effective intervention for the prevention and treatment of SO.

To the best of our knowledge, this is the first meta-analysis to comprehensively explore the effects of different modes of PA

TABLE 4 PEDro criteria and scores of included studies.

Study	Eligibility criteria	Random allocation	Concealed allocation	Baseline similar	Blinding (subject)	Blinding (therapists)	Blinding (assessor)	Measure for>85%	Intention-to-treat analysis	Group comparison	Point measures	Total score (0–10)
Huang et al. (2017)	yes	1	1	1	0	0	1	1	1	1	1	8
Vasconcelos et al. (2016)	yes	1	1	1	0	0	1	1	1	1	1	8
Liao et al. (2018)	yes	1	1	1	0	0	1	1	1	1	1	8
Liao et al. (2017)	yes	1	1	1	1	1	1	1	1	1	1	10
Chiu et al. (2018)	yes	0	0	1	1	1	0	0	0	1	1	5
Park et al. (2017)	yes	1	0	1	0	0	1	1	1	1	1	7
Chen et al. (2017)	yes	1	0	1	0	0	1	0	0	1	1	5
Kim et al. (2016)	yes	1	1	1	0	0	0	1	0	1	1	6
Wang et al. (2019)	yes	1	1	1	0	0	0	1	0	1	1	6
Li et al. (2020)	yes	1	1	1	0	0	0	1	1	1	1	7
Banitalebi et al. (2021)	yes	1	1	1	0	0	0	1	1	1	1	7
Lee et al. (2021)	yes	1	1	1	0	0	1	1	1	1	1	8

PEDro, Physiotherapy Evidence Database; 1, meet the standard; 0, not meet the standard.

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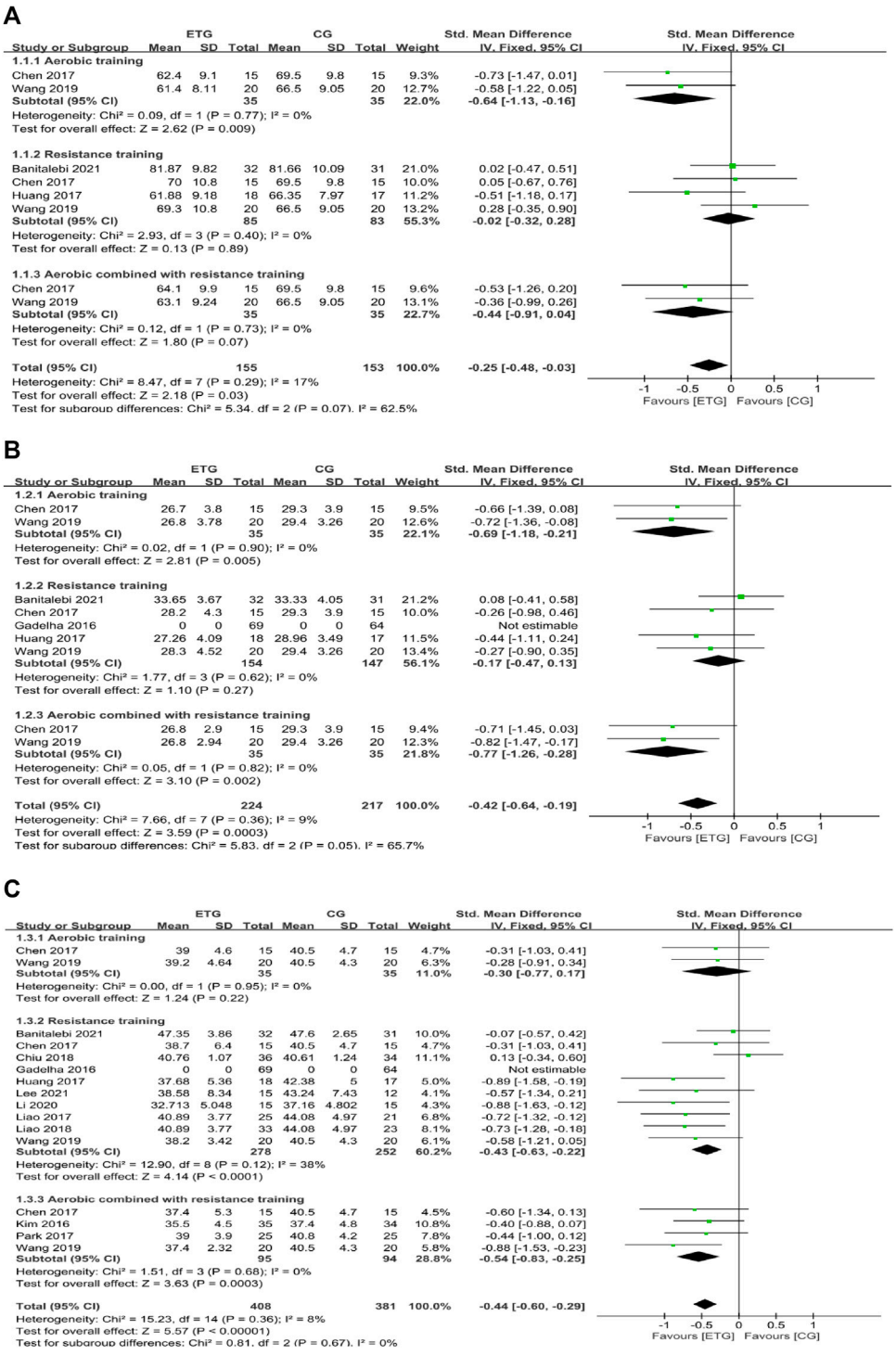


FIGURE 2
Forest plots of the comparison of the exercise training group (ETG) versus the control group (CG) on **(A)** body weight (BW); **(B)** body mass index (BMI); **(C)** percentage of body fat (BF%); CI: confidence interval; SD: standard deviation.

on physical fitness and performance outcomes in older people with SO. This meta-analysis aims to investigate the effects of three types of PA (AT, RT, and MT) on measures of body composition, muscle mass, muscle strength, physical performance, and hematological parameters in older people with SO.

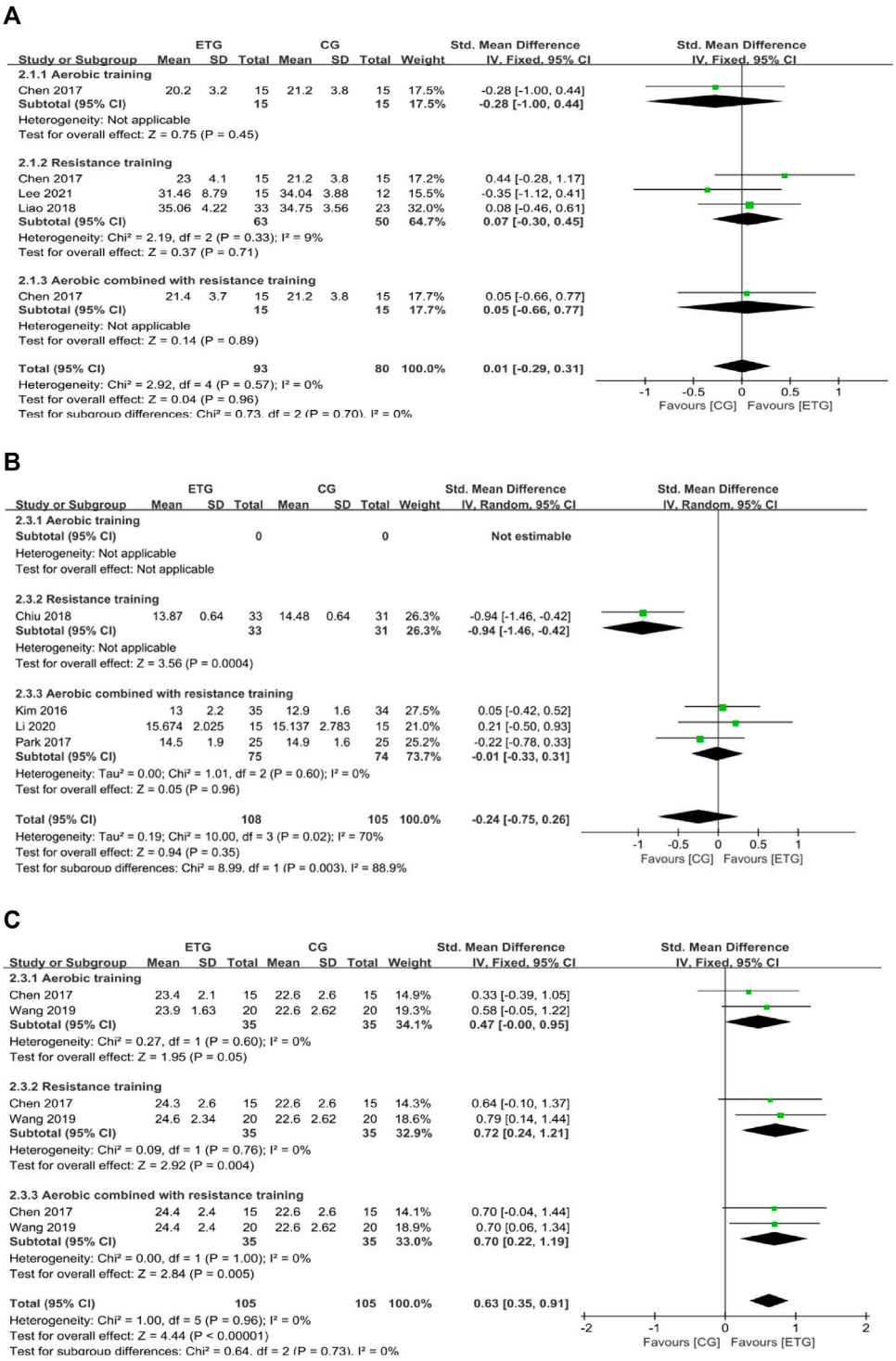


FIGURE 3
Forest plots of the comparison of the exercise training group (ETG) versus the control group (CG) on **(A)** skeletal muscle mass (SM); **(B)** appendicular skeletal muscle mass (ASM); and **(C)** appendicular skeletal muscle mass index (ASMI); CI, confidence interval; SD, standard deviation.

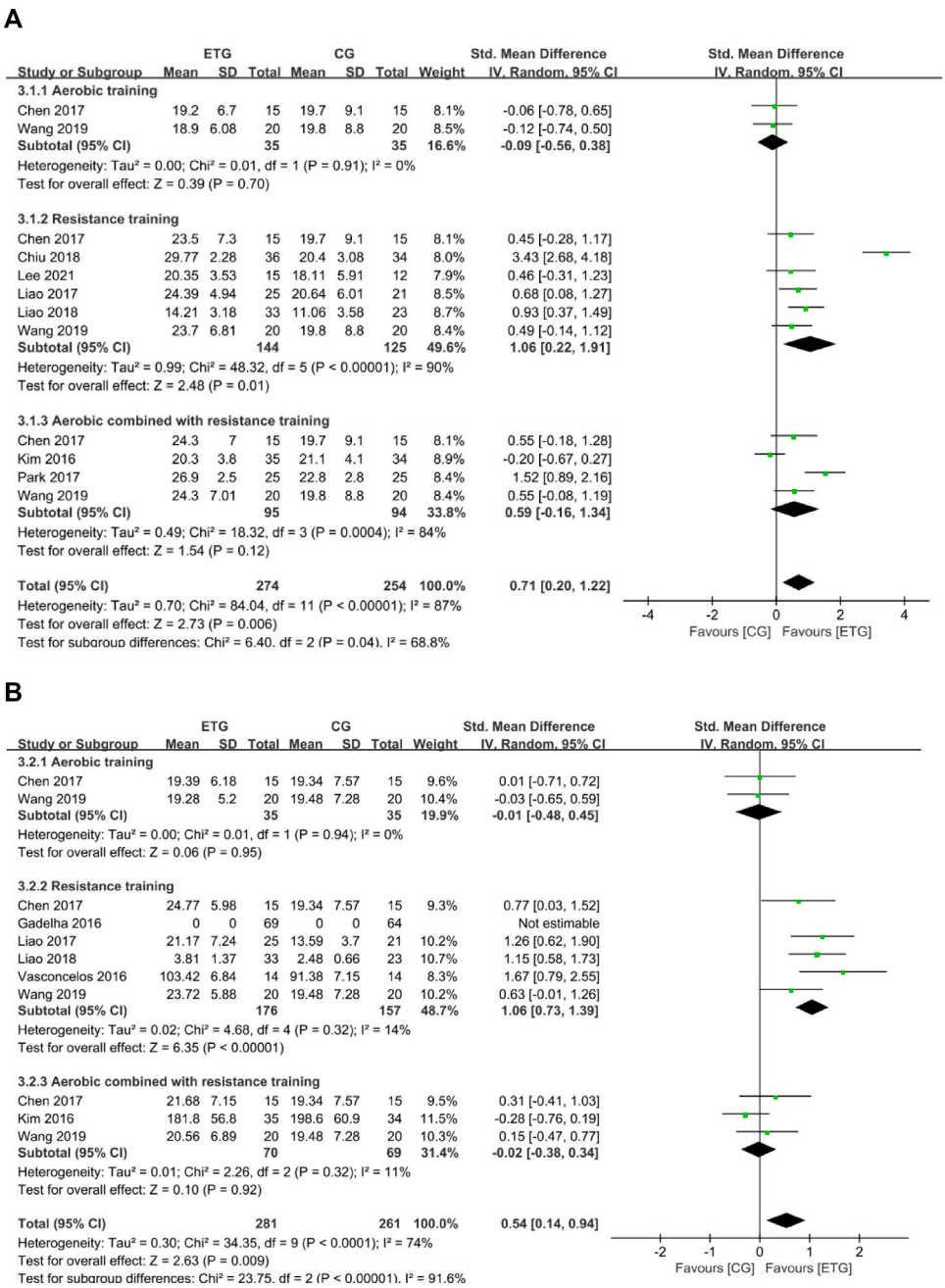


FIGURE 4
Forest plots of the comparison of the exercise training group (ETG) versus the control group (CG) on **(A)** handgrip strength (HG); **(B)** knee extension strength (KES); CI, confidence interval; SD, standard deviation.

Material and methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Vrabel, 2015) and is registered in the PROSPERO (CRD42022301883). We searched the following six databases: PubMed, Embase, the Cochrane Library Database, Web of Science, the China National Knowledge Infrastructure (CNKI), and Wanfang Data for studies published from January 2010 to November 2021. The Mesh terms and the synonyms were used as follows: "aging," "aged," "aged, 80 and over," "cognitive aging," "frail elderly," "sarcopenia," "sarcopenias," "sarcopenic," "muscle

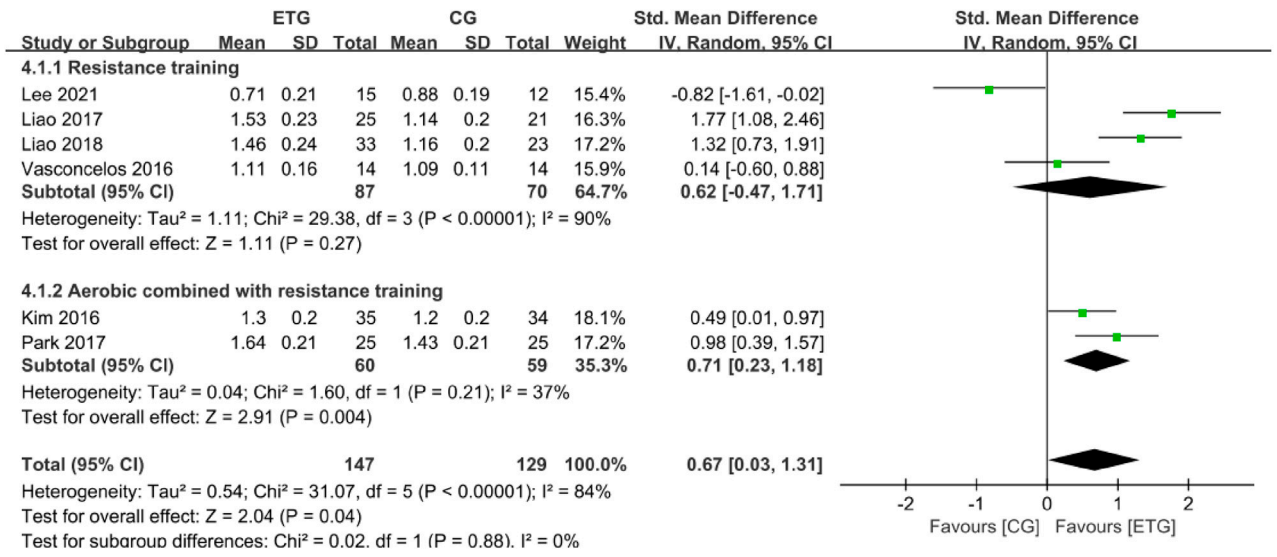


FIGURE 5
Forest plots of the comparison of the exercise training group (ETG) versus the control group (CG) on gait speed (GS); CI, confidence interval; SD, standard deviation.

loss," "muscle wasting," "muscular atrophy," "age-related muscle loss," "muscle insufficiency," "muscle depletion," "skeletal muscle depletion," "obesity," "obese," "overweight," "sarcopenic obesity," "exercise," "motor activity," "movement," "movements," "kinesiotherapy," "physiotherapy," "exercise therapy," "training," "physical therapy," "physical therapy modalities," "endurance training" and "resistance training." All search strategies are shown in Supplementary Table S1.

Inclusion criteria

The inclusion criteria were as follows:

1) All subjects met the definition of sarcopenic obesity (according to a working group or clinical research);
2) Aged 60 and above;
3) Without diagnosed chronic diseases, such as cardiovascular disease, metabolic disease, chronic obstructive pulmonary disease (COPD), cancer, and stroke;
4) Had at least one PA intervention group;
5) the control group did not receive any PA intervention but could receive education intervention.

Exclusion criteria

The exclusion criteria were as follows:

1) The full text was unavailable;
2) Not in English or Chinese;
3) The studies failed to provide extractable data;
4) the intervention group received intervention combined with nutritional supplementation.

Data extraction

According to the inclusion and exclusion criteria, two authors (MZ and MJ) independently screened the title and abstract of all studies. Then the two authors (MZ and MJ) screened the remaining full text according to inclusion and exclusion criteria. If there were disagreements about the studies, the third author (NC) participated in the discussion to resolve it. The two authors (MZ and MJ) recorded the following information in Microsoft Excel 2019: 1) the study's first author and year of publication; 2) the characteristics of the subjects, for example, sample size, gender, and age; 3) the diagnostic criteria for sarcopenic obesity; 4) the characteristics of the intervention group, such as mode, training movement, intensity, and duration days/weeks; 4) control group intervention; 5) outcomes (e.g., body composition, muscle mass, muscle strength, physical performance, and hematological parameters). One author (MZ) was responsible for extracting the data, while the other (MJ) was responsible for checking the accuracy of the data. If the study was a multi-arm intervention, the two authors (MZ and MJ) extracted only data related to the exercise and the control group. When raw data was missing, we contacted the authors by email to request the data. We excluded the article data if the author failed to reply or would not share the raw data.

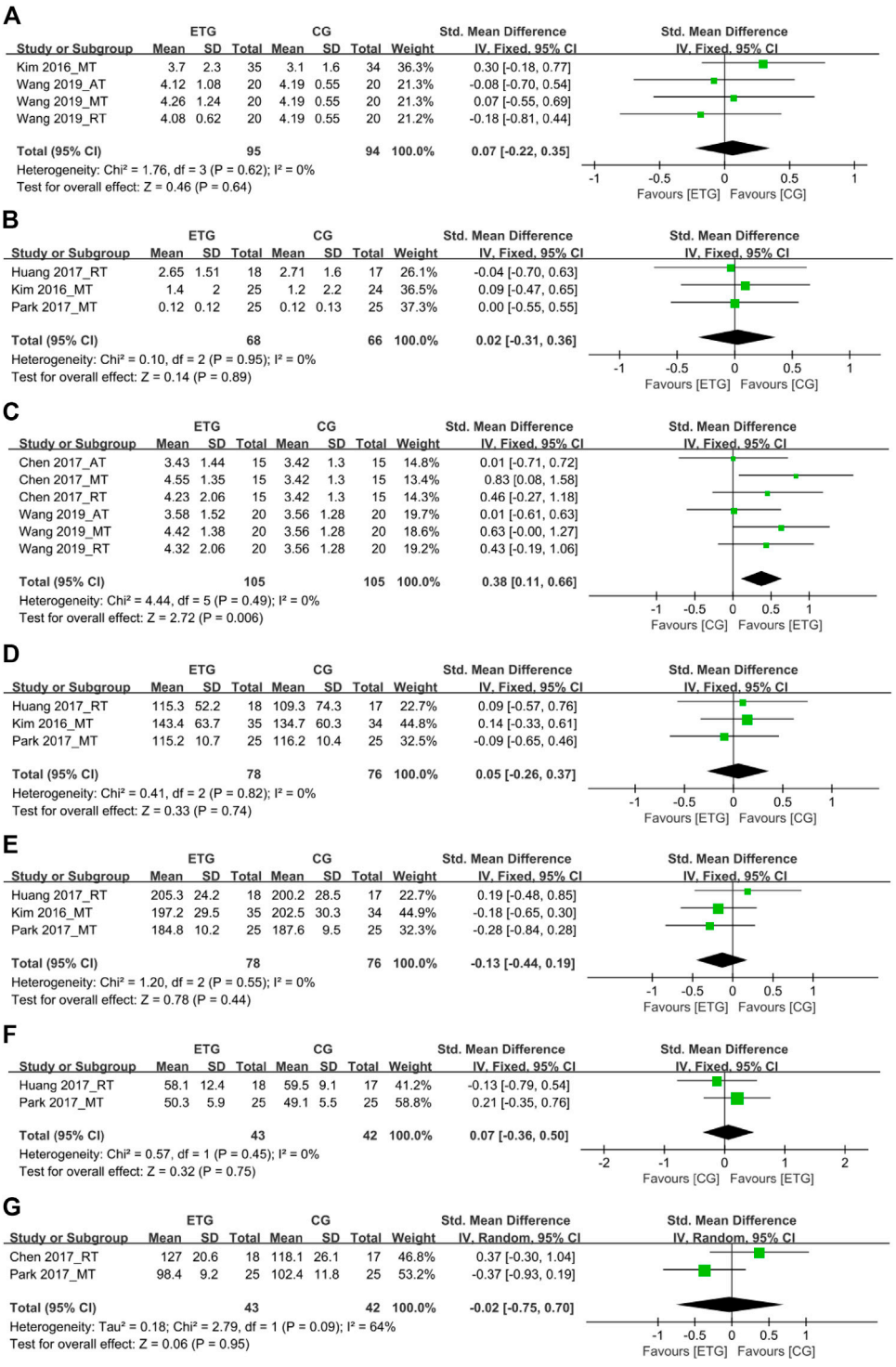


FIGURE 6
Forest plots of the comparison of the exercise training group (ETG) versus the control group (CG) on **(A)** interleukin-6 (IL-6); **(B)** C-reactive protein (CRP); **(C)** insulin-like growth factor 1 (IGF-1); **(D)** triglyceride (TG); **(E)** total cholesterol (TC); **(F)** high-density lipoprotein (HDL); **(G)** low-density lipoprotein (LDL); AT, aerobic training; RT, resistance training; MT, aerobic combined with resistance training; CI, confidence interval; SD, standard deviation.

TABLE 5 Influence of moderator variables in the effect of physical activity on inflammatory markers, lipid profiles, BMD and muscle mass.

Variable	Subgroup	Studies	n	Effect size with 95% confidence interval	Heterogeneity			Test overall effects. Z(p)	Test for subgroup Difference.Chi^2(p)
					Chi^2	P	I^2		
Inflammatory markers (IL-6 and CRP)									
Age (years)	<70	4	155	−0.06 [−0.37, 0.26]	0.33	0.95	0	0.36 (0.72)	0.86 (0.35)
	≥70	3	188	0.14 [−0.14, 0.43]	0.71	0.70	0	0.98 (0.33)	
Intervention duration (weeks)	<12	3	120	−0.06 [−0.42, 0.29]	0.33	0.85	0	0.35 (0.73)	0.62 (0.43)
	≥12	4	223	0.11 [−0.15, 0.38]	0.95	0.81	0	0.86 (0.39)	
Frequency (days/week)	<3	5	258	0.07 [−0.17, 0.32]	1.77	0.78	0	0.60 (0.55)	0.13 (0.72)
	≥3	2	85	−0.02 [−0.44, 0.41]	0.01	0.93	0	0.07 (0.94)	
Sarcopenia Assessment method	BIA	2	85	−0.02 [−0.44, 0.41]	0.01	0.93	0	0.07 (0.94)	0.13 (0.72)
	DXA	5	258	0.07 [−0.17, 0.32]	1.77	0.78	0	0.60 (0.55)	
Sarcopenia diagnostic indicator	SM	3	173	0.15 [−0.15, 0.45]	0.74	0.69	0	0.97 (0.33)	0.80 (0.37)
	ASM	4	170	−0.05 [−0.35, 0.26]	0.37	0.95	0	0.29 (0.77)	
Obesity diagnostic indicator	BF%	3	173	0.15 [−0.15, 0.45]	0.74	0.69	0	0.97 (0.33)	0.80 (0.37)
	BMI	4	170	−0.05 [−0.35, 0.26]	0.37	0.95	0	0.29 (0.77)	
Lipid profiles (TC, TG, HDL LDL)									
Age (years)	<70	4	140	0.13 [−0.20, 0.46]	1.11	0.77	0	0.77 (0.44)	1.16 (0.28)
	≥70	6	338	−0.09 [−0.30, 0.13]	3.54	0.62	0	0.79 (0.43)	
Sarcopenia assessment method	BIA	8	340	−0.02 [−0.24, 0.19]	4.96	0.66	0	0.23 (0.82)	0.00 (0.97)
	DXA	2	138	−0.02 [−0.35, 0.32]	0.85	0.36	0	0.11 (0.91)	
Sarcopenia diagnostic indicator	SM	6	278	0.06 [−0.18, 0.29]	2.34	0.80	0	0.47 (0.64)	1.04 (0.31)
	ASM	4	200	−0.13 [−0.41, 0.14]	2.42	0.49	0	0.94 (0.35)	
Obesity diagnostic indicator	BF%	5	243	0.08 [−0.17, 0.34]	2.01	0.73	0	0.64 (0.52)	2.51 (0.11)
	BMI	3	150	−0.25 [−0.57, 0.07]	0.50	0.78	0	1.51 (0.13)	
Intervention duration (weeks)	≤12	6	278	0.06 [−0.18, 0.29]	2.34	0.80	0	0.47 (0.64)	1.04 (0.31)
	>12	4	200	−0.13 [−0.41, 0.14]	2.42	0.49	0	0.94 (0.35)	
Frequency (days/week)	≤3	6	278	0.06 [−0.18, 0.29]	2.34	0.80	0	0.47 (0.64)	1.04 (0.31)
	>3	4	200	−0.13 [−0.41, 0.14]	2.42	0.49	0	0.94 (0.35)	
BMD									
T-score	>-1 SD	12	530	−0.52 [−0.70, −0.35]	13.81	0.24	20	5.84 (<0.00001)	0.51 (0.48)
	≤-1 SD	3	119	−0.37 [−0.74, -0.01]	3.35	0.19	40	2.00 (0.05)	

Variable	Subgroup	Studies	n	Effect size with 95% confidence interval	Heterogeneity				Test overall effects Z(p)	Test for subgroup Difference.Chi^2(p)
					Tau^2	Chi^2	P	I^2		
SM, ASM and ASMI										
Age (years)	<65	3	110	0.52 [0.14, 0.90]	0.00	1.04	0.59	0	2.68 (0.007)	3.15 (0.08)
	≥65	12	486	0.08 [−0.22, 0.38]	0.17	28.96	0.002	62	0.54 (0.59)	
Sarcopenia Assessment method	BIA	13	539	0.20 [−0.09, 0.49]	0.18	33.50	0.0008	64	1.33 (0.18)	0.62 (0.43)
	DXA	2	57	−0.05 [−0.61, 0.50]	0.02	1.13	0.29	11	0.19 (0.85)	
Obesity diagnostic indicator	BF%	5	246	−0.20 [−0.64, 0.24]	0.16	11.42	0.02	65	0.88 (0.38)	4.67 (0.03)
	BMI	10	350	0.36 [0.11, 0.62]	0.05	12.64	0.18	29	2.80 (0.005)	
BMI levels	<27 kg/m^2	10	390	0.09 [−0.26, 0.44]	0.21	26.36	0.002	66	0.51 (0.61)	0.64 (0.42)
	≥27 kg/m^2	5	206	0.30 [−0.08, 0.68]	0.08	7.19	0.13	44	1.57 (0.12)	
Intervention duration (weeks)	<12	9	300	0.46 [0.23, 0.69]	0.00	7.72	0.46	0	3.87 (0.0001)	9.28 (0.002)
	≥12	6	296	−0.20 [−0.56, 0.15]	0.11	11.43	0.04	56	1.12 (0.26)	
Frequency (days/week)	<3	11	433	0.26 [−0.09, 0.61]	0.23	31.48	0.0005	68	1.46 (0.14)	1.82 (0.18)
	≥3	4	163	−0.06 [−0.37, 0.25]	0.00	1.72	0.63	0	0.39 (0.70)	

IL-6, interleukin-6; CRP, C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; SM, skeletal muscle mass; BMI, body mass index; BF%, percentage of body fat; BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; n, the number of participants; BMD, bone mineral density; SD, standard deviation.

Quality assessment

The two authors (MZ and MJ) assessed the methodological quality of each included study independently, using the Physiotherapy Evidence Database (PEDro) Scale (Maher et al., 2003), which assesses the following 11 categories: 1) eligibility criteria and source; 2) random allocation; 3) concealed allocation; 4) baseline comparability; 5) blinding of subjects; 6) blinding of therapists; 7) blinding of assessors; 8) adequate follow-up (>85%); 9) intention-to-treat analysis; 10) between-group statistical comparisons; 11) reporting of point measures and measures of variability.

If the item met the criteria, it was rated one point, and if it did not meet the criteria, it was rated 0 points. An overall score of less than four points was considered poor, and 9–10 was considered excellent. Two authors (MZ and MJ) evaluated each study independently, and if there were disagreements, the third author (YL) participated in the discussion and resolved it.

Outcome variables

Five categories of outcome variables were extracted. Body composition was measured as body weight (BW), body mass index (BMI), and body fat percent (BF%). Muscle mass was measured as appendicular skeletal muscle mass (ASM), skeletal muscle mass (SM), and appendicular skeletal muscle mass index (ASMI). Upper and lower muscle strength was measured as handgrip (HG) and knee extension strength (KES). Physical performance was measured as gait speed (GS). Hematological parameters were measured as Interleukin-6 (IL-6), c-reactive protein (CRP), Insulin-like growth factor 1 (IGF-1), and lipids for serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Statistical analysis

All data included in the studies were analyzed using Review Manager (RevMan 5.4; Cochrane, Lindon, United Kingdom). We used the I^2 statistic to assess the heterogeneity of the outcomes of the studies. When $I^2 < 50\%$, we used the fixed-effects model, and when $I^2 > 50\%$, we used the random-effects model. We calculated the pooled effect sizes using the inverse variances, the 95% confidence interval (95% CI), and the standardized mean differences (SMD). A p-value < 0.05 was considered statistically significant.

Results

Study selection

Figure 1 illustrates a flow chart of the study selection process and reasons for excluding studies. According to the Mesh and the synonyms published between 1 January 2010, and 30 November 2021, we identified 1712 studies from the databases. After removing 300 duplicates, 1412 studies remained. Screening the title and abstract resulted in the exclusion of 1336 studies. Of the remaining 76 studies, we excluded 64 following a full-text review according to the inclusion and exclusion criteria. The final sample included 12 studies.

Study characteristics

Table 1 summarizes the characteristics, diagnostic criteria for SO, intervention and control group details, and the study outcomes. Subjects included 614 older people with sarcopenic obesity, aged from 58.4 to 88.4 years. Among them, 496 were female (84.93%). Eight studies (Kim et al., 2016; Vasconcelos et al., 2016; Huang et al., 2017; Liao et al., 2017; Park et al., 2017; Liao et al., 2018; Banitalebi et al., 2021; Lee et al., 2021) included women only, and none included men only. Four studies (Chen et al., 2017; Chiu et al., 2018; Wang et al., 2019; Li et al., 2020) included women and men. Diagnostic criteria for sarcopenia and obesity, the intervention and control group methods, and outcomes varied among the studies.

Diagnostic criteria for sarcopenia

Table 2 shows the diagnostic criteria for sarcopenia among studies in the meta-analysis. The diagnostic criteria came from the 2010 version of the European Working Group on Sarcopenia in Older People [EWGSOP-2010 (Cruz-Jentoft et al., 2010)], the 2013 version of the Asian Working Group for Sarcopenia criteria [AGWS-2013 (Chen et al., 2014)], the Foundation for the National Institutes of Health [FNIH (Studenski et al., 2014)], and diagnostic criteria from specific research groups [Janssen (Janssen et al., 2002), Chung (Chung et al., 2013), Newman (Newman et al., 2003), Lim (Lim et al., 2010), Kim (Kim et al., 2016), and Fried (Fried et al., 2001)]. The diagnostic criteria reflect the region-specific cut-off points for muscle mass consisting of Europe [EWGSOP-2010 (Cruz-Jentoft et al., 2010)], Asia [AWGS-2013 (Chen et al., 2014)], the United States [FNIH (Studenski et al., 2014), Janssen (Janssen et al., 2002), Newman (Newman et al., 2003) and Fried (Fried et al., 2001)], Korea [Chung (Chung et al., 2013) and Lim (Lim et al., 2010)] and Japan [Kim (Kim et al., 2016)].

The studies used various criteria to measure sarcopenia. Two studies used EWGSOP-2010 (Liao et al., 2017; Lee et al., 2021), one study used AGWS-2013 (Li et al., 2020), three studies used Janssen (Huang et al., 2017; Chiu et al., 2018; Liao et al., 2018), and one study each used criteria from FNIH (Wang et al., 2019), Chung (Chen et al., 2017), Newman (Banitalebi et al., 2021), Lim (Park et al., 2017), Kim (Kim et al., 2016), and Fried (Vasconcelos et al., 2016).

Diagnostic criteria for obesity

Table 3 shows the methods and cut-off points used to classify obesity, including the names of people and organizations creating the cut-off points to classify obesity in international locations. The methods included BF% measured by bioelectrical impedance analysis (BIA) and Dual Energy X-ray Absorptiometry (DXA), visceral fat area (VFA) measured by computed tomography (CT), and BMI calculated as weight kilogram/height meter^2.

Seven studies measured obesity with BF% (Kim et al., 2016; Huang et al., 2017; Liao et al., 2017; Chiu et al., 2018; Liao et al., 2018; Li et al., 2020; Lee et al., 2021) three studies used BMI (Vasconcelos et al., 2016; Park et al., 2017; Wang et al., 2019), one study used BMI and VFA (Chen et al., 2017), and one study used BF% and BMI (Banitalebi et al., 2021). No studies only used VFA. Sources for the diagnostic criteria for obesity used in studies were Deurenberg (Huang et al., 2017; Liao et al., 2018), Ko (Chiu et al., 2018), Vasconcelos (Vasconcelos et al., 2016), Baumgartner (Liao et al., 2017), Lim (Park et al., 2017), World Health Organization (WHO) (Chen et al., 2017; Li et al., 2020), FNIH (Wang et al., 2019), Kim (Kim et al., 2016), American Society of Bariatric Physicians (ASBP) (Banitalebi et al., 2021) and Li (Lee et al., 2021). The diagnostic criteria for obesity vary, and the applications and cut-off points used to classify obesity may be regional. In general, most studies use the cut-off points for obesity of BF% ≥ 25% and BMI ≥30 kg/m^2.

Quality assessment

Table 4 shows the PEDro scores of the 12 studies. One was rated 10, considered "excellent." Nine were rated six to eight, considered "good." Two were rated 5, considered "fair." All studies met eligibility criteria for group comparison, point measures reporting, and measures of variability. Eleven studies were allocated randomly. Nine studies had concealed allocation. The baselines were similar for the 12 studies. Ten studies had adequate follow-up (>85%). Two studies blinded both participants and therapists. Seven studies blinded the assessors.

Outcomes

Effects of different exercise modes for sarcopenic obesity on body composition

Eleven of the 12 studies assessed the effects of different exercise modes on body composition (BW, BMI, and BF%). Four explored the effects of different exercise modes on BW (Chen et al., 2017; Huang et al., 2017; Wang et al., 2019; Banitalebi et al., 2021) (Figure 2). Two studies included all three exercise modes (Chen et al., 2017; Wang et al., 2019). AT improved BW compared with the control group (SMD = −0.64, 95% CI: −1.13 to −0.16, p = 0.009, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). RT showed no significant difference in BW compared with the control group (SMD = −0.02, 95% CI: −0.32 to 0.28, p = 0.89, I^2 = 0%) (Chen et al., 2017; Huang et al., 2017; Wang et al., 2019; Banitalebi et al., 2021). MT showed no significant difference in BW compared with the control group (SMD = −0.44, 95% CI: −0.91 to 0.04, p = 0.07, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). Collectively, the three exercise modes showed a significant decrease in BW compared with the control group (SMD = −0.25, 95% CI: −0.48 to −0.03, p = 0.03, I^2 = 17%).

Four of the 12 studies explored the effects of different exercise modes on BMI (Chen et al., 2017; Huang et al., 2017; Wang et al., 2019; Banitalebi et al., 2021). Two studies included all three exercise modes (Chen et al., 2017; Wang et al., 2019). AT improved BMI compared with the control group (SMD = −0.69, 95% CI: −1.18 to −0.21, p = 0.005, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). RT showed no significant difference in BMI compared with the control group (SMD = −0.17, 95% CI: −0.47 to 0.13, p = 0.27, I^2 = 0%) (Chen et al., 2017; Huang et al., 2017; Wang et al., 2019; Banitalebi et al., 2021). MT improved BMI compared with the control group (SMD = −0.77, 95% CI: −1.26 to −0.28, p = 0.002, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). Collectively, all exercise modes showed a significant decrease in BMI compared with the control group (SMD = −0.42, 95% CI: −0.64 to −0.19, p = 0.0003, I^2 = 9%).

Eleven of the 12 studies explored the effects of different exercise modes on BF% (Kim et al., 2016; Chen et al., 2017; Huang et al., 2017; Liao et al., 2017; Park et al., 2017; Chiu et al., 2018; Liao et al., 2018; Wang et al., 2019; Li et al., 2020; Banitalebi et al., 2021; Lee et al., 2021). Two studies included all three exercise modes (Chen et al., 2017; Wang et al., 2019). AT showed no significant difference in BF% compared with the control group (SMD = −0.30, 95% CI: −0.77 to 0.17, p = 0.22, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). RT improved BF% compared with the control group (SMD = −0.43, 95% CI: −0.63 to −0.22, p < 0.0001, I^2 = 38%) (Chen et al., 2017; Huang et al., 2017; Liao et al., 2017; Chiu et al., 2018; Liao et al., 2018; Wang et al., 2019; Li et al., 2020; Banitalebi et al., 2021; Lee et al., 2021). MT improved BF% compared with the control group (SMD = −0.54, 95% CI: −0.83 to −0.25, p = 0.0003, I^2 = 0%) (Kim et al., 2016; Chen et al., 2017; Park et al., 2017; Wang et al., 2019). Collectively, different exercise modes showed a significant decrease in BF% compared with the control group (SMD = −0.44, 95% CI: −0.60 to −0.29, p < 0.00001, I^2 = 8%).

Effects of different exercise modes on muscle mass

There were three outcomes of muscle mass: SM, ASM, and ASMI.

Three of the 12 studies explored the effects of different exercise modes on SM (Chen et al., 2017; Liao et al., 2018; Lee et al., 2021) (Figure 3). One study included all three exercise

modes (Chen et al., 2017) and two studies included only RT (Liao et al., 2018; Lee et al., 2021). Results showed no significant difference between exercise groups and control group (AT, SMD = −0.28, 95% CI: −1.00 to 0.44, p = 0.45; RT, SMD = 0.07, 95% CI: −0.30 to 0.45, p = 0.71, I^2 = 9%; MT, SMD = 0.05, 95% CI: −0.66 to 0.77, p = 0.89). Collectively, different exercise modes showed no significant difference in SM compared with the control group (SMD = 0.01, 95% CI: −0.29 to 0.31, p = 0.96, I^2 = 0%).

Four of the 12 studies explored the effects of different exercise modes on ASM (Kim et al., 2016; Park et al., 2017; Chiu et al., 2018; Li et al., 2020). RT improved ASM compared with the control group (SMD = −0.94, 95% CI: −1.46 to −0.42, p = 0.0004) (Chiu et al., 2018). MT showed no significant differences between exercise modes with the control groups (SMD = −0.01, 95% CI: −0.33 to 0.31, p = 0.96, I^2 = 0%) (Kim et al., 2016; Park et al., 2017; Li et al., 2020). Collectively, the different exercise modes showed no significant difference in ASM compared with the control group (SMD = −0.24, 95% CI: −0.75 to 0.26, p = 0.35, I^2 = 70%).

Two of the 12 studies explored the effects of different exercise modes on ASMI (Chen et al., 2017; Wang et al., 2019). Two studies included all three exercise modes (Chen et al., 2017; Wang et al., 2019). AT showed no significant difference in ASMI compared with the control group (SMD = 0.47, 95% CI: −0.00 to 0.95, p = 0.05, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). RT showed a significant increase in ASMI compared with the control group (SMD = 0.72, 95% CI: 0.24 to 1.21, p = 0.004, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). MT showed a significant increase in ASMI compared with the control group (SMD = 0.70, 95% CI: 0.22 to 1.19, p = 0.005, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). Collectively, different exercise modes showed a significant increase in ASMI compared with the control group (SMD = 0.63, 95% CI: 0.35 to 0.91, p < 0.00001, I^2 = 0%).

Effects of different exercise modes on muscle strength

There were two outcomes of muscle strength: HG and KES. Eight of the 12 studies explored the effects of different exercise modes on HG (Kim et al., 2016; Chen et al., 2017; Liao et al., 2017; Park et al., 2017; Chiu et al., 2018; Liao et al., 2018; Wang et al., 2019; Lee et al., 2021) (Figure 4). AT showed no significant difference in HG compared with the control group (SMD = −0.09, 95% CI: −0.56 to 0.38, p = 0.70, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). RT showed a significant increase in HG compared with the control group (SMD = 1.06, 95% CI: 0.22 to 1.91, p = 0.01, I^2 = 90%) (Chen et al., 2017; Liao et al., 2017; Chiu et al., 2018; Liao et al., 2018; Wang et al., 2019; Lee et al., 2021). MT showed no significant difference in HG compared with the control group (SMD = 0.59, 95% CI: -0.16 to 1.34, p = 0.12, I^2 = 84%) (Kim et al., 2016; Chen et al., 2017; Park et al., 2017; Wang et al., 2019). Collectively, different exercise modes showed a significant increase in HG compared with the control group (SMD = 0.71, 95% CI: 0.20 to 1.22, p = 0.006, I^2 = 87%).

Six of the twelve studies explored the effects of different exercise modes on KES (Kim et al., 2016; Vasconcelos et al., 2016; Chen et al., 2017; Liao et al., 2017; Liao et al., 2018; Wang et al., 2019). Two studies included all three exercise modes (Chen et al., 2017; Wang et al., 2019). AT showed no significant difference in KES compared with the control group (SMD = -0.01, 95% CI: −0.48 to 0.45, p = 0.95, I^2 = 0%) (Chen et al., 2017; Wang et al., 2019). RT showed a significant increase in KES compared with the control group (SMD = 1.06, 95% CI: 0.73 to 1.39, p < 0.00001, I^2 = 14%) (Vasconcelos et al., 2016; Chen et al., 2017; Liao et al., 2017; Liao et al., 2018; Wang et al., 2019). MT showed no significant difference in KES compared with the control group (SMD = -0.02, 95% CI: −0.38 to 0.34, p = 0.92, I^2 = 11%) (Kim et al., 2016; Chen et al., 2017; Wang et al., 2019). Collectively, different exercise modes showed a significant increase in KES compared with the control group (SMD = 0.54, 95% CI: 0.14 to 0.94, p = 0.009, I^2 = 74%).

Effects of different exercise modes for sarcopenic obesity on the physical performance

Six of the 12 studies explored the effects of different exercise modes on GS (Kim et al., 2016; Vasconcelos et al., 2016; Liao et al., 2017; Park et al., 2017; Liao et al., 2018; Lee et al., 2021) (Figure 5). No studies explored the effect of AT on GS. RT showed no significant difference in GS compared with the control group (SMD = 0.62, 95% CI: −0.47 to 1.71, p = 0.27, I^2 = 90%) (Vasconcelos et al., 2016; Liao et al., 2017; Liao et al., 2018; Lee et al., 2021). MT showed a significant increase in GS compared with the control group (SMD = 0.71, 95% CI: 0.23 to 1.18, p = 0.004, I^2 = 37%) (Kim et al., 2016; Park et al., 2017). Collectively, different exercise modes showed a significant increase in GS compared with the control group (SMD = 0.67, 95% CI: 0.03 to 1.31, p = 0.04, I^2 = 84%).

Effects of different exercise modes on hematological parameters

Seven outcomes of hematological parameters included inflammatory markers (IL-6 and CRP), IGF-1, and lipid profile measures (TG, TC, HDL, and LDL). For the inflammatory markers, two of the studies explored the effects of different exercise modes on IL-6 (Kim et al., 2016; Wang et al., 2019) (Figure 6). One study included all three exercise modes (Wang et al., 2019). The other study explored the effect of MT on IL-6 (Kim et al., 2016). None of the exercise modes showed a significant difference in IL-6 compared with the control group (SMD = 0.07, 95% CI: −0.22 to 0.35, p = 0.64, I^2 = 0%). Three studies explored the effects of different exercise modes on CRP (Kim et al., 2016; Huang et al., 2017; Park et al., 2017). One study explored the effect of RT on CRP (Huang et al., 2017). Two studies explored the effect of MT on CRP (Kim et al., 2016; Park

et al., 2017). No studies explored the effect of AT on CRP. None of the exercise modes showed a significant difference in CRP compared with the control group (SMD = 0.02, 95% CI: -0.31 to 0.36, p = 0.89, I^2 = 0%).

Two studies explored the effects of different exercise modes on IGF-1 (Chen et al., 2017; Wang et al., 2019). Both studies included all three exercise modes (Chen et al., 2017; Wang et al., 2019). In total, all three exercise modes showed a significant increase in IGF-1 compared with the control group (SMD = 0.38, 95% CI: 0.11 to 0.66, p = 0.006, I^2 = 0%).

Among the lipid profile markers, three studies explored the effects of RT and MT on TG (Kim et al., 2016; Huang et al., 2017; Park et al., 2017). One of the three studies explored the RT on TG (Huang et al., 2017). The other two studies explored the effect of MT on TG (Kim et al., 2016; Park et al., 2017). No studies explored the effect of AT on TG. None of the two exercise modes showed a significant difference in TG compared with the control group (SMD = 0.05, 95% CI: −0.26 to 0.37, p = 0.74, I^2 = 0%). Three studies explored the effects of different exercise modes for SO on TC (Kim et al., 2016; Huang et al., 2017; Park et al., 2017). One of the three studies explored the RT on TC (Huang et al., 2017). The other two studies explored the effect of MT on TC (Kim et al., 2016; Park et al., 2017). No studies explored the effect of AT on TC. None of the two exercise modes showed a significant difference in TC compared with the control group (SMD = −0.13, 95% CI: −0.44 to 0.19, p = 0.44, I^2 = 0%).

Two studies explored the effects of RT and MT for SO on HDL, respectively (Huang et al., 2017; Park et al., 2017). None of the exercise modes showed a significant difference in HDL compared with the control group (SMD = 0.07, 95% CI: −0.36 to 0.50, p = 0.75, I^2 = 0%). Two studies explored the effects of RT and MT for SO on LDL, respectively (Chen et al., 2017; Park et al., 2017). None of the exercise modes showed a significant difference in LDL compared with the control group (SMD = −0.02, 95% CI: −0.75 to 0.70, p = 0.95, I^2 = 64%).

Moderator variables

To explore the influence of different exercise modes on muscle mass, inflammatory markers, and lipid profiles, we performed subgroup analyses to assess the potential effects of different moderators on the outcomes. Table 5 illustrates the influence of moderator variables on muscle mass, inflammatory markers, and lipid profiles. The subgroup analysis included the moderator variables of sarcopenia and obesity diagnostic indicators (e.g., EWGSOP-2010, BF%), intervention duration, and intervention frequency.

Inflammatory markers: There were no significant relationships between inflammatory markers and age, intervention duration, intervention frequency, sarcopenia and obesity diagnostic indicators, and sarcopenia assessment methods.

Lipid profiles: There were no significant relationships between lipid profiles and age, intervention duration, intervention frequency, sarcopenia assessment methods, and sarcopenia and obesity diagnostic indicators.

Muscle mass: Muscle mass increased significantly in people <65 years (SMD = 0.52, 95% CI: 0.14 to 0.90, p = 0.007, I^2 = 0%). Muscle mass increased significantly when the obesity diagnostic indicator was BMI (SMD = 0.36, 95% CI: 0.11 to 0.62, p = 0.005, I^2 = 29%). Concerning the training protocol, a greater effect on muscle mass was observed when intervention duration was less than 12 weeks as compared with longer durations (SMD = 0.46, 95% CI: 0.23 to 0.69, p = 0.0001, I^2 = 0%).

Discussion

In this systematic review and meta-analysis, we analyzed 12 studies (including 11 randomized controlled trials and one non-randomized controlled trial) to compare the effects of three exercise modes (AT, RT, and MT) on body composition, muscle mass, muscle strength, physical performance and hematological parameters in older people with SO. Our results found that AT could significantly decrease BW and BMI. RT could improve BF%, ASMI, ASM, HG, and KES, and, MT could improve BMI, BF%, ASMI, and GS in older people with SO. PA could significantly increase IGF-1, but all exercise modes (AT, RT, and MT) had no effects on other inflammatory markers and lipids profile markers in older people with SO.

An epidemiological study showed that the decrease of skeletal muscle mass in middle-aged and elderly women over 50 years old was greater than that in men. The decrease in estrogen level was the most important physiological characteristic of postmenopausal women. This change would lead to secondary body composition changes (Wang et al., 2016). The fat mass of the human body would increase significantly after the age of 45, especially in the elderly stage of women, due to the influence of physiological factors and the reduction of physical activity, fat mass was easier to accumulate, and abdominal fat increases obviously, resulting in obesity (Bahrami et al., 2006). Therefore, it was recommended that older people with SO, especially women, improve their body composition and health through gradual and regular PA.

BW, BF%, and BMI are obesity-related indicators associated with insulin resistance (Kurniawan et al., 2018). Progression of SO is often accompanied by changes in body composition. Obesity accompanies a chronic inflammatory state and plays a negative role in SO progression (Wijesinghe et al., 2021). Therefore, improving body composition is crucial for older people with SO. Also, studies indicated that PA is an effective intervention component to ameliorate the adverse effects caused by aging and obesity (Vincent et al., 2012). Consistent with our

results, previous studies have shown that AT decreases BW while RT and MT improve BF% in older people with SO (Hsu et al., 2019). Wang et al. (2019) and Chen et al. (2017) also showed that MT (aerobic combined with resistance training for 8 weeks, once or twice a week) significantly improved BMI and BF% in older people with SO.

SM and ASM are measures of lean muscle mass measured by BIA or DXA. Our findings agreed with Hsu et al. (2019) and Hita-Contreras et al. (2018), showing that none of the exercise modes changed the SM values. In our study, other exercise modes had no effect on ASM except RT. Although AT, RT, and MT may not completely reverse the loss of SM and ASM, regular PA helps slow down many age-related mitochondrial markers of muscle, potentially delaying the process of muscle loss (Koltai et al., 2012).

ASMI personalizes measures of muscle mass in older people with SO, adjusting ASM by height or weight. Our results found that RT and MT significantly improved ASMI. RT improves muscle strength, mass, and neuromuscular function (Cadore et al., 2014). Chelly et al. (2009) observed that the first 8 weeks of RT usually improves neural adaptation rather than changing muscle structure in novice weight lifters. Thus, we speculate that different training protocols might effect muscle mass differently. We found improved muscle mass of SO people when intervention duration lasted less than 12 weeks in a subsample of people aged <65 with obesity status determined by BMI. This finding persisted regardless of the sarcopenia assessment method, BMI levels, and intervention frequency. This finding was inconsistent with the study by Chen et al. (2021) found that RT 1–2 times per week for ≥12 weeks could improve muscle mass . Contrary to Chen et al. (2021) study, we speculated that duplicate inclusion of the subgroup analysis less than 12 weeks would affect the final results of the meta-analysis. We extracted subgroup data for different modes of PA and different indicators. For example, two studies with fewer than 12 weeks of exercise duration contained nine subgroup combinations (Chen et al., 2017; Wang et al., 2019). Six studies with more than 12 weeks duration (Kim et al., 2016; Park et al., 2017; Chiu et al., 2018; Liao et al., 2018; Li et al., 2020; Lee et al., 2021) contained six subgroup combinations. Eleven studies had an exercise frequency of fewer than three times per week, and four studies had more than three times per week. A significant imbalance in the number of studies analyzed by subgroups may affect the final results. Therefore, we suggest future studies of PA in older people with SO last longer than 12 weeks and with an exercise frequency of three or more times per week.

Muscle strength declines with age at an average rate of 2%–4% per year, 2–5 times faster than muscle mass loss (Mitchell et al., 2012). Muscle strength and physical performance are predictors of disability and hospitalization in older people (Legrand et al., 2014). Lu et al. (2020) showed that HG strength correlates with arm and leg strength and represents whole-body muscle strength. KES is a method for assessing lower limb strength and predicting falling risk (Bobowik and Wiszomirska, 2020). Consistent with Hsu et al. (2019), our study showed that RT significantly improved both HG and KES, and MT improved GS. MT combines the dual advantages of AT and RT and should have a better effect on muscle strength than RT in improving muscle strength. However, our results did not find that MT significantly improved the subjects' muscle strength, which was inconsistent with previous studies. A meta-analysis by Lu et al. (2021) indicated that RT and MT had the same effect on muscle strength in people with sarcopenia. This increase in muscle strength may be due to the complex training in Lu et al.(2021) study was aerobic combined resistance exercise and balance and gait training. However, no studies have explored the comparison of RT and MT on muscle strength in older people with SO. Thus, researchers should conduct more research to compare these two modes of exercise in people with SO. Consistent with Lu et al.(2021) results, MT could improve GS, but inconsistent with our study, they also pointed out that RT could improve GS. This difference may be that the longest training time for RT on GS in Lu et al.(2021) study was 24 weeks, while in our study, the longest RT time for GS was 12 weeks. Increased neural activity in areas of the brain associated with cognition and memory was one of the potential mechanisms for action (Hansen, 2014). Therefore, we hypothesized that with longer training durations, the proficiency of the movement increases, and the training difficulty of MT becomes more complex than that of AT and RT. This effect causes the whole body to promote increases in GS.

IGF-1 positively effects the body as it mediates growth hormone and anabolic responses in many cells and tissues. Conversely, chronic inflammation and hyperlipidemia have adverse effects on various tissues and cellular functions, including CVD progression. Our study indicated that PA significantly improved IGF-1, and none of the exercise modes changed inflammatory markers and lipid profiles. As shown by Li et al. (2021), exercise induced the secretion of large amounts of IGF-1 from liver and skeletal muscle and triggered a series of downstream responses, such as activation of skeletal muscle satellite cells to promote myogenic cell proliferation and differentiation, and inhibition of cell expression of collagen to reduce skeletal muscle fibrosis. In conclusion, skeletal muscle cells could produce IGF-1 in response to exercise stimuli, which played a protective role in maintaining muscle mass and function. Wang et al. (2019) demonstrated that in older people with SO, 8-weeks of RT could reduce IL-6, and 8-weeks of RT and MT increased IGF-1. Park et al. (2017) found that 24 weeks of MT significantly improved TC and LDL in older people with SO. By contrast, Hsu et al. (2019) showed that PA, regardless of exercise mode, did not affect CRP, TC, TG, and HDL in older people with SO. Therefore, the effect of PA on inflammatory markers and lipids profiles in people with

SO is equivocal. We speculate that differences in subject characteristics and training protocols are responsible for these findings. In subgroup analyses, we expected to see the positive effects of different moderators on inflammatory markers and lipid profiles.

Contrary to expectations, we did not find a significant relationship between moderators, inflammatory markers, and lipid profiles. We infer that this may be related to the limited number of studies included in the meta-analyses reviewed. Thus, more research should explore different exercise modes on inflammatory markers and lipid profiles in older people with SO.

In the subgroup analysis, some of the results showed high heterogeneity. The reasons for this may be composed of the following points. First, the diagnostic criteria for SO varied by region, race, age, and measurement tools, and the diagnostic criteria for SO were a combination of diagnostic criteria for sarcopenia and diagnostic criteria for obesity, but the prevalence of the SO varied widely using different combinations. Second, the inconsistent baseline characteristics of the older people with SO in the included studies may have led to differences in the improvement effect of different exercise modes on various indicators. Finally, the diversity of exercise intervention protocols and the inconsistency of quality monitoring during the intervention resulted in high heterogeneity.

Strengths and limitations

This systematic review and meta-analysis comprehensively assessed the effects of different modes of PA (AT, RT, and MT) in older people with SO. The strength of this study is the rigorous screening where we excluded studies of subjects without SO, studies where SO subjects were treated with nutritional supplements, and studies where SO subjects were diagnosed with chronic diseases. Our findings were comprehensive and consisted of the changes in body composition, muscle mass, muscle strength, physical performance, and hematological parameters, including the effect of PA on IGF-1 in older people with SO.

This study also had some limitations. We included studies that recruited older people with osteosarcopenic obesity. However, researchers know little about how osteoporosis may affect PA in older people with SO. In our subgroup analysis, after PA intervention, people without osteoporosis significantly decreased BF% compared with older people with osteoporosis. Postmenopausal women lost the protective effect of estrogen, osteoclasts, and bone absorption were enhanced, resulting in sparse trabecular bone and reduced bone mass, which increased the difficulty of PA intervention when co-occurring with SO (Li et al., 2020). Therefore, osteoporosis can affect the effect of exercise on SO. Limited to the number of included studies, we only explored the influence of the efficacy of exercise on BF%. More RCTs are needed to study this relationship in the future. The intervention duration for studies in this systematic review and meta-analysis was shorter than 24 weeks, which may limit changes in muscle mass and hematological parameters. More studies are needed to investigate the effects of long-term PA on SO. Based on strict inclusion and exclusion criteria, the number of eligible studies was small, and the subjects were predominantly female, limiting the general applicability of the meta-analysis results.

Conclusion

Our results illustrated the importance of PA in the management of SO in older people. Different modes of exercise selectively improve body composition (BW, BMI, and BF%), muscle mass (ASMI and ASM), muscle strength (HG and KES), physical performance (GS), and hematological parameters (IGF-1) in older people with SO. In particular, AT decreases BW and BMI; RT improves BF%, ASMI, ASM, HG, and KES; and MT improves BMI, BF%, ASMI, and GS. PA increased IGF-1. These findings require additional high-quality RCTs with longer intervention duration to confirm these benefits of PA in older people with SO.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

MZ, MJ, and TL participated in protocol design, data extraction, quality assessment, statistical analyses, and manuscript preparation. LL and BA participated in manuscript revision. NC and YL participated in protocol design, quality assessment, and manuscript revision. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Effects of vibration training vs. conventional resistance training among community-dwelling older people with sarcopenia: three-arm randomized controlled trial protocol

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Introduction: Sarcopenia is a chronic and progressive disease, which is accompanied by the decline in muscle mass, muscle strength, and physical performance with aging, and it can lead to falls, fracture, and premature death. The prevention and treatment of sarcopenia mainly include exercise therapy and nutritional supplement. Exercise therapy is one of the most potential interventions to prevent and/or delay the progression of sarcopenia. Resistance training (RT), one of the most commonly used exercise types, is widely used in the treatment of sarcopenia, while vibration training (VT) is a prospective strategy for improving sarcopenia in older people. The aim of our study is to compare the effect of VT and RT in older people with sarcopenia on muscle mass, muscle strength, physical performance, blood biomarkers, and quality of life.

Methods and analysis: Our study is a 12-week, three-arm randomized controlled trial with assessor-blinded. The diagnosis criteria for subject recruitment adopt the guidelines for the Asian Working Group for Sarcopenia. A total of 54 subjects who met the criteria were randomized into one of the following three groups: VT group, RT group, and control group. The VT group and RT group received a 12-week whole-body vibration training and a resistance training program three times every week, respectively. The primary outcome is lower limb muscle strength, and the secondary outcomes include muscle mass, upper limb muscle strength, physical performance, blood biomarkers, and quality of life. We then performed assessments three times, at baseline (0 week), after intervention (12 weeks), and follow-up (24 weeks). The adverse events were also be reported. All outcome measurements were performed by the same researchers. Data were saved in the unified database, and the collected data of all subjects were analyzed by intention-to-treat analysis.

Ethics and dissemination: This study was reviewed and approved by the Ethical Committee of Xinhua Hospital Chongming Branch. The findings of the study were authorized in peer-reviewed journals with online access; meanwhile, it will be presented at domestic or international academic congresses.

Clinical trial registration: Chinese Clinical Trial Registry (ChiCTR2100051178), registered on 15 September 2021.

KEYWORDS

sarcopenia, vibration training, resistance training, muscle mass, muscle strength, physical performance, blood biomarkers

Introduction

Sarcopenia is a progressive disease associated with aging, characterized by low skeletal muscle mass, decreased muscle strength, and/or poor physical performance (Chen et al., 2020). In China, the prevalence of sarcopenia in older people aged 60 years and above in the suburb-dwelling population was 9.3%, with 6.4% in men and 11.5% in women according to the guideline for the Asian Working Group for Sarcopenia (AWGS) (Han et al., 2016). Several adverse outcomes, such as accidental falls (Zhang et al., 2020), fractures of upper and lower limbs (Zhang et al., 2018), physical disability (Janssen et al., 2002), cognitive impairment (Peng et al., 2020), poor quality of life (Tsekoura et al., 2017), or even death (Nascimento et al., 2019), are associated with the progression of sarcopenia. The changes of older people with sarcopenia are not only reflected in clinical outcomes (Chen et al., 2020) and physiological outcomes, such as age-related inflammation (Tournadre et al., 2019), metabolic abnormalities (Hunter et al., 2019), and endocrine changes (McKee et al., 2017). The pathophysiological mechanisms of sarcopenia are complexly associated with the following blood biomarkers: inflammatory factors {i.e., hypersensitive C-reactive protein [hs-CRP] (Shokri-Mashhadi et al., 2021), tumor necrosis factor-α cytokines [TNF-α] (Bian et al., 2017), and interleukin-6 [IL-6] (Rong et al., 2018)}, hormones {i.e., insulin growth factor-1 [IGF-1] (Ascenzi et al., 2019), growth hormone [GH] (Bian et al., 2020), testosterone (Colla et al., 2015), and 25(OH)D (Remelli et al., 2019; Abiri and Vafa, 2020)}, growth factors {i.e., myostatin [MSTN] (White and LeBrasseur, 2014) and follistatin [FST] (Echeverria et al., 2021)}, and muscular injury biomarkers such as creatine kinase (CK) (Kurita et al., 2021). The adverse outcomes of sarcopenia inflict a huge economic burden to patients and their families (Bruyère et al., 2019). Therefore, some measures should be taken to prevent and/or delay the development of the sarcopenia.

Until now, there is no particularly effective pharmacological treatment for sarcopenia (Cruz-Jentoft and Sayer, 2019), and many studies have indicated that non-pharmacological treatment is the most potential treatment, especially exercise training, and results in significant improvements in muscle function and physical fitness in older people with sarcopenia (Lo et al., 2020). Currently, one of the most commonly used exercise trainings for older people with sarcopenia is resistance training (RT) (Beckwée et al., 2019). Vibration training (VT), a prospective strategy for improving sarcopenia in older people (Wu et al., 2020), is a training method that uses the vibration platform with different vibration frequencies and amplitudes in different positions (Nordlund and Thorstensson, 2010). In recent years, the application of VT has been more widely used to delay the loss of muscle functions in older people with sarcopenia (Wei and Ng, 2018; Camacho-Cardenosa et al., 2019; Zhu et al., 2019). A meta-analysis demonstrated that VT can change the declining trend of muscle mass, muscle strength, and physical performance (Wu et al., 2020); meanwhile, several studies have confirmed that VT has positive effects on sarcopenia (Wei et al., 2016, 2017; Chang et al., 2018; Wei and Ng, 2018). Thus, VT may be a potential alternative training method to improve sarcopenia compared with conventional resistance training (CRT), which is generally a high-intensity RT. Although

Abbreviations: AWGS, Asian Working Group for Sarcopenia; ACSM, American College of Sports Medicine; M, male; F, female; BH, body height; BW, body weight; CC, calf circumference; BIA, bioelectrical impedance analyzer; SMM, skeletal muscle mass; SMI, skeletal muscle mass index; ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; 1RM, one repetition maximum; HGS, handgrip strength; KES, knee extension strength; 6-MW test, 6-meter walk test; 5-CS test, 5-chair stand test; GS, gait speed; SPPB, Short Physical Performance Battery; TUG test, Timed Up and Go test; hs-CRP, hypersensitive C-reactive protein; TNF-α, tumor necrosis factor-α cytokines; IL-6, interleukin-6; MSTN, myostatin; FST, follistatin; IGF-1, insulin growth factor-1; GH, growth hormone; CK, creatine kinase; SF-36, Short-Form Health Survey; RT, resistance training; CRT, conventional resistance training; VT, vibration training; WBVT, whole-body vibration training.

a large number of studies have confirmed the benefits of VT on muscle function, there is still a lack of comparison of the effects between VT and CRT in older people with sarcopenia. For VT to replace CRT, it is necessary to compare the effects of the two training methods on sarcopenia in older people.

RT is the most effective method to improve muscle function and physical performance in older people. The American College of Sports Medicine (ACSM) (Nelson et al., 2007) and the World Health Organization (World Health Organization, 2018) recommend 2–3 times of RT (60–80% of one repetition maximum [1RM]) per week. The intensity of RT recommended by the ACSM is $\geq$ 70% 1RM to achieve significant muscle hypertrophy among older people (American College of Sports Medicine, 2009). Similarly, it is demonstrated that high-intensity RT (60–70% 1RM) can produce significant effects on muscle conditions and physical performance in older people (Chen et al., 2017; Guizelini et al., 2018; Sahin et al., 2018) compared to low-intensity RT (40% 1RM) (Lixandrão et al., 2017; Sahin et al., 2018). However, RT needs high-technology requirements for older people (Wernbom et al., 2008; Thiebaud et al., 2014) and it is easy to produce muscle fatigue (Jacko et al., 2018). These may reduce the compliance of older people, especially for frail older people, and are difficult to generally conduct in the clinical setting.

Thus, the aims of our study are to (1) evaluate the effects of 12-week VT and RT on muscle mass, muscle strength, physical performance, blood biomarkers, and quality of life in older people with sarcopenia; (2) compare the effects of VT and RT on sarcopenia; and (3) explore the mechanisms of VT and RT on the improvement of sarcopenia.

Methods and analysis

Study design

This study is a three-arm, assessor-blinded, randomized control trial. The experimental flowchart is given in Figure 1. The schedule of enrollment, interventions, and assessments for our study is shown in Table 1.

Study setting

We selected subjects for our study from four communities in Chongming district of Shanghai, China, who met the inclusion and exclusion criteria. This study was conducted in May 2022 at Xinhua Hospital Chongming Branch. A total of 54 older people met the eligibility criteria and were enrolled in the study. The subjects were stratified by sex and then randomized into one of three groups (18 in each group): VT group, RT group, and control group. The assessments were performed three times: at baseline (0 week), after intervention (12 weeks), and follow-up (24 weeks).

Inclusion criteria

1. People aged between 65 and 80 years;
2. Older people diagnosed with sarcopenia according to the criteria for AWGS: appendicular skeletal muscle mass index (ASMI) < 7.0 kg/m^2 for male (M) and < 5.7 kg/m^2 for female (F) using a bioelectrical impedance analyzer (BIA); handgrip strength (HGS), M: < 28 kg, F: < 18 kg; and/or gait speed (GS) < 1.0 m/s in the 6-m walk (6-MW) test;
3. The participants without serious diseases, such as uncontrolled hypertension, hyperlipidemia, hyperglycemia, and diabetes;
4. The participants without untreated diseases, such as gallstones or kidney stones, and infectious diseases;
5. The participants with no regular exercise habit for more than 3 months.

Exclusion criteria

1. People with absolute contraindication for exercising, such as deep venous thrombosis and/or blood clotting disorders;
2. People with serious cognitive impairments that have impact on the assessments and communication with researchers, such as dementia and mental illness;
3. Individuals suffering from serious diseases that affect the assessments and interventions, such as musculoskeletal diseases (e.g., fracture, dislocation, osteoporosis, and rheumatoid arthritis) and disability (e.g., loss of hands, feet, or limbs);
4. Individuals with serious spinal diseases or a surgical history, such as vertebral fracture, inflammatory joint disease, ankylosing spondylitis, spondylolisthesis, rheumatism, cauda equina syndrome, and tumor;
5. Individuals who have taken the following drugs regularly in past 3 months: antiplatelet agents (e.g., aspirin, Aggrenox, cilostazol, eptifibatide, ticlopidine, and tirofiban), anticoagulant drugs, and analgesic drugs;
6. Patients with other diseases whose participation in this study is not recommended by doctors;
7. Patients who did not sign the informed consent before the beginning of study.

Termination criteria

1. The participants having serious adverse events or complications during the intervention period and cannot continue to participate in the study;
2. The participants who proposed that they were unwilling to continue to participate in the study;
3. Lost contact with subjects during the experiment and/or follow-up.

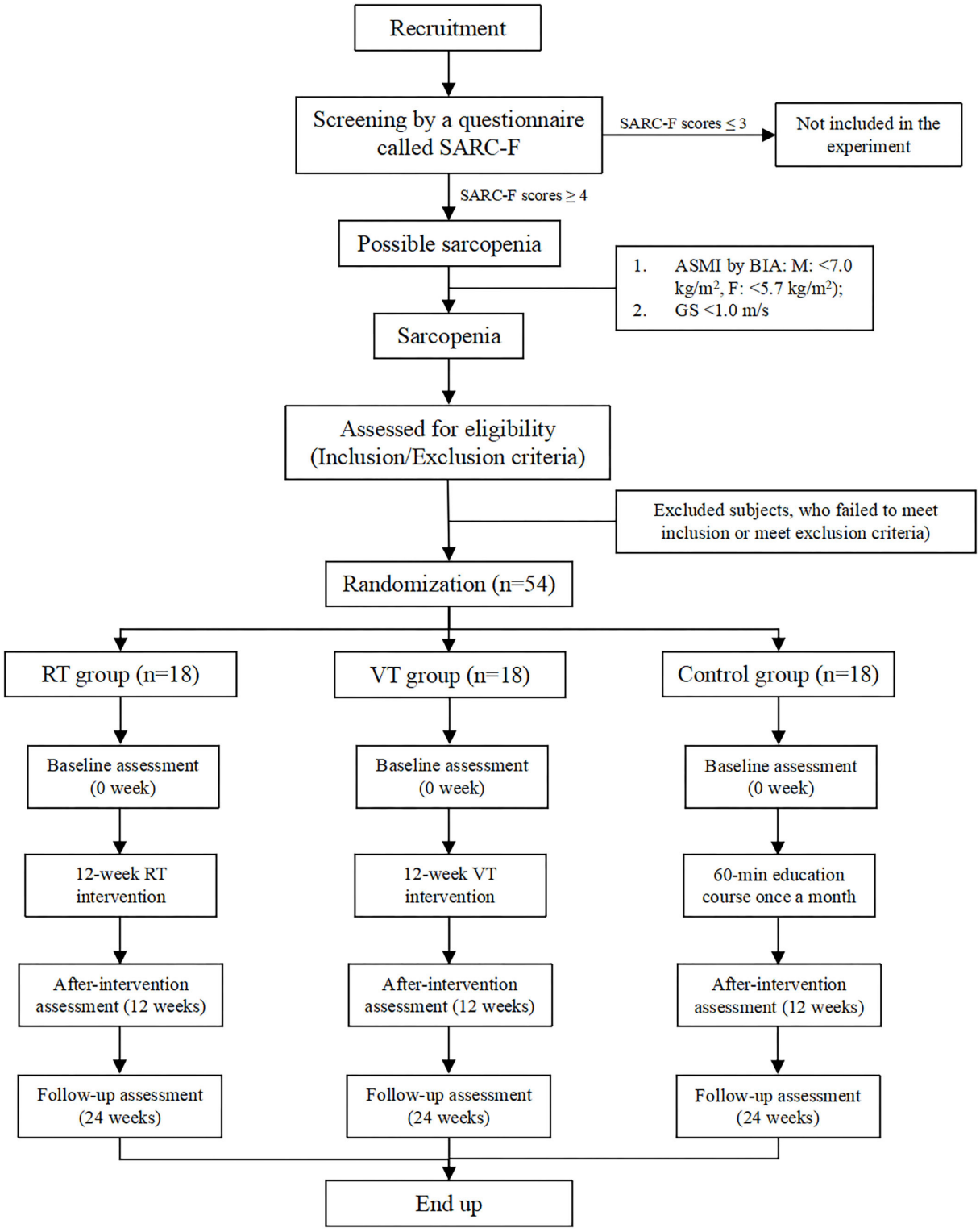


FIGURE 1
Experimental flowchart showing the patient recruitment, intervention, and assessment process.

TABLE 1 Schedule of enrollment, interventions, and assessments.

Study period

Timepoint		Before week 0	Week 0	Week 1–12	Week 12	Week 24
Screening	Eligibility screening	X				
Allocation	Informed consent	X				
Intervention	VT			X		
	RT			X		
	Education (No intervention)			X		
Assessment	Muscle mass		X		X	X
	Muscle strength		X		X	X
	Physical performance		X		X	X
	Blood biomarkers		X		X	X
	Quality of life		X		X	X
Others	Subjects' compliance		X	X	X	X
	Adverse events		X	X	X	X
	Dropout reasons			X		

VT, vibration training; RT, resistance training.

Recruitment

The subjects were recruited using three approaches: (1) the annual community physical examination in four communities in Chongming district; (2) educational lectures and talks about sarcopenia at community centers; (3) home visits in cooperation with workers in the community, and the physical examination of older people who do not participate in community activities regularly for a long time.

Screening

The subjects were screened by a screening questionnaire called SARC-F, which assesses five aspects in older people: strength, assistance in walking, rising from a chair, climbing stairs, and falls (Malmstrom and Morley, 2013; Malmstrom et al., 2016). The SARC-F questionnaire has a score range (0 [best] to 10 [worst]) for the initial diagnosis of sarcopenia, and older people with scores $\geq$ 4 points were considered as having a risk of sarcopenia (Chen et al., 2020). Then, the older people with a score $\geq$ 4 points underwent a further screening in accordance with the AWGS standard: (1) the assessment of HGS using a hand dynamometer (Jamar Plus+ Digital Hand Dynamometer; IL, USA), M: $<$ 28 kg, F: $<$ 18 kg; or (2) and five-time chair stand (5-CS) test, the time of the 5-CS test $\geq$ 12 s. If the results of the measurements meet the aforementioned standards, older people were considered "possible sarcopenia". A formal assessment of sarcopenia was performed using the ASMI with a portable BIA system (Inbody, S10, Korean), M: $<$ 7.0 kg/m^2, F: $<$ 5.7 kg/m^2, and the assessment of the 6-MW test, the result of GS $<$ 1.0 m/s.

Randomization and blinding

The subjects were informed of the purpose of the study and the safety risks that may happen in the study, and if they were willing to participate in the study, informed consent was required to sign before the subjects were screened. A stratified randomization method by sex was performed on the subjects meeting the eligibility criteria for a balanced distribution so that each group will have the same number of males and females. The stratified randomization sampling was performed by a researcher, who did not participate in our experiment, by a computer program (Research Randomizer Form www.randomizer.org). The subjects were then randomized into three groups: VT group, RT group, or control group at a 1:1:1 ratio. The randomized number and group assignments were sent to a researcher, who also did not participate in our study, as an electronic file with encryption to store the experimental information. The therapists for different intervention groups conducted the intervention according to the group assignments. Only the therapists will not be blinded to the group assignments, and other research staff (including the assessors, data managers, and data statisticians) will be blinded to the group assignments.

Interventions

Group protocols

A pre-training for the VT group and RT group were performed three times to familiarize them with the

corresponding training courses. Formal training was conducted after pre-training. In two intervention groups (VT ang RT groups), 5-min warm-up and cool-down training were conducted before and after intervention. All training sessions were carried out by physical therapists. During the whole training period, the researchers recorded the participants' attendance and compliance. If a subject could not participate in the training on time due to some reasons, training was performed at other times in that week. All subjects were asked not to perform additional physical activity and/or change their daily lifestyle during the experimental period.

Vibration training program

The VT group received a 30-min whole-body vibration training (WBVT) three times a week for 12 weeks. For the WBVT, a vibration platform generating vertical vibrations (Siehe Typenschild, Wellengang excellence, Germany) was used. Each training lasted about 30 min, which included a 5-min warm-up, 20-min vibration training, and 5-min cool-down. The vibration frequency was progressively increased to 20–25 Hz and the peak-to-peak amplitude of 4 mm. During the WBVT, the subjects was asked to stand barefoot on the vibration platform with knees flexion at 30°, and a vibration rope, if needed, were held by the subjects with both hands to maintain balance. And the movement in WBVT should maintain 1 min, and repeat 10 groups with 1-min resting between groups in each training day.

Resistance training program

The RT group received a 12-week resistance exercise program for three times every week. Each exercise session included three parts: (1) a 5-min warm-up (mainly stretching) of the neck, shoulders, lower back, hips, knees, and ankles; (2) a resistance exercise training, which consisted of three sets/10 reps of each exercise session, and the subjects had a 1-min rest between sets. The TheraBand elastic band is used for the resistance exercise training. Before beginning the intervention, each subject should complete the 1RM test to evaluate muscle strength and determine the intensity of resistance exercise training. According to the results of the 1RM test, the intensity of resistance exercise training was specified according to the individual's 1RM. The intensity was 60% 1RM in the first 4 weeks, 65% 1RM in the second 4 weeks, and 70% 1RM in the third 4 weeks. Resistance exercise movements include upper limb exercises (elbow flexion, shoulder extension, and abduction), lower limb exercises (hip abduction, knee flexion, and extension), and trunk exercises (chest press); and (3) a 5-min cool-down was performed after the aforementioned exercise training, which is similar to the warm-up exercise.

Control group with education courses

The subjects in the control group received a 60-min education course two times a month at the community center. The education course was taught by the invited experts, and the topics of courses were aging, health, and sarcopenia, including the definition of sarcopenia, cause of disease, pathology, clinical performance, and adverse consequences for older people.

Nutritional intake control

During a 12-week intervention period and a 12-week follow-up period, all subjects were required to maintain their dietary habits. The study staff and community workers supervised and recorded the nutritional intakes, and the record content on the specific notebook includes the diet of three meals a day for protein, fat, etc. The frequency of dietary recording should be maintained at two times a week on weekdays and once on weekends.

Outcome measurements

The outcome was measured at baseline (0 week), after invention (12 weeks), and follow-up (24 weeks).

Primary outcome

Lower limb muscle strength was assessed by an estimated 1RM of knee extension strength (KES) (Abdalla et al., 2020). The 1RM test was the most popular method used for measuring muscular strength, but the standard 1RM test was too difficult for frail older people with sarcopenia and can even cause the injury to subjects (Rontu et al., 2010); therefore, our study chose the estimated 1RM test, which is more suitable to assess muscle strength for frail older people. The calculation is as follows: Estimated 1RM (kg) = submaximal weight (kg)/(1.0278–0.0278 × maximal number of repetitions) (Brzycki, 1993). The subjects should sit on the extensor chair and the weight plates of extensor chair are in kilograms (Brzycki, 1993). In the beginning, the weight was set at M: 64% of the body mass and F: 45% of the body mass (Kuramoto and Payne, 1995; Abdalla et al., 2020). If a subject can perform knee extension 10 times under the initial weight, the weight was increased, and the repetitions of the maximal weight was recorded. Conversely, if the subject repeated 10 times or less, the weight was considered the submaximal weight. The maximal number of repetitions performed and the submaximal weight were used to calculate the estimated 1RM.

Secondary outcomes

Anthropometric measurements

Body height (BH) and body weight (BW) were measured by researchers. BH measurement requires the subjects to stand barefoot on the floor with the standard posture for measuring height. When measuring BW, the subjects were required to wear minimal clothes and stand barefoot on the digital weight scale. In addition, the calf circumference (CC) or other basic physical indicators of the subjects were measured and recorded.

Muscle mass

Muscle mass includes skeletal muscle mass (SMM), skeletal muscle mass index (SMI), appendicular skeletal muscle mass (ASM), and ASMI. These indicators were measured using the BIA (Inbody, S10, Korean). The SMI and ASMI were calculated (SMI= SMM/height^2, kg/m^2; ASMI= ASM/height^2, kg/m^2).

Upper limb muscle strength

HGS as an indicator of upper limb muscle strength was assessed by a Jamar® hand dynamometer (Jamar Plus+ Digital Hand Dynamometer; IL, USA). The measurement process is as follows: in a standing position, the subjects were instructed to hold a dynamometer with the upper limb abducted at 30° from the body. The maximum HGS of each hand was measured and recorded continuously for three times, and the maximum value was considered as the final HGS value.

Physical performance

Physical performance was assessed using the Short Physical Performance Battery (SPPB) test, 6-MW test, and the Timed Up and Go (TUG) test.

The SPPB test includes a progressive standing balance test, a walk test, and a chair sit-to-stand test (Welch et al., 2020). In the balance test, the subjects were asked to stand in a side-by-side, semitandem and full-tandem positions, respectively. The subjects must stand at each position for at least 10 s. In the walk test, the subjects were asked to take a 4-m usual walk at the preferred GS from the standing position, and the tests were repeated two times, and the fastest time was selected. In the chair sit-to-stand test, the subjects were asked to fold their arms across the chest (without using one's arms) and try to complete five-time chair sit-to-stand tests as rapidly as possible.

Using the 6-MW test to assess GS, the subjects must walk 6 m at their usual speed. The test was repeated two times with the 2- to 3-min resting time, and the average value was calculated as the final GS.

The procedure of the TUG test is as follows: the subject should initially sit in the chair, stand up from the armchair (with the arms crossing in front of the chest), walk ahead 3 meters (at normal speed and as fast as possible), bypass the obstacle, walk back, and then sit down again (Podsiadlo and Richardson, 1991). The test was performed two times with a 2- to 3-min resting time, and the mean value was recorded as the final record.

Blood biomarkers

For each participant, the fasting venous blood sample after 12-h overnight fasting was collected by nurses in the morning about 08:00 for baseline (0 week), after intervention (12 weeks), and follow-up (24 weeks). The blood sample was sent to the laboratory for an automatic enzyme-linked immunosorbent assay to determine the level of blood biomarkers. The blood biomarkers include inflammatory factors (hs-CRP, TNF-α, and IL-6), hormones [IGF-1, GH, testosterone, and 25(OH)D], growth factor (MSTN and FST), and a muscular injury biomarker (CK).

Quality of life

Quality of life in older people was assessed using the validated Chinese version of the 36-item Short-Form Health Survey (SF-36). The SF-36 consists of 36 items and eight health scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, and reported health transition) assessing function and wellbeing of older people. The total score ranges from 0 to 100, and a higher score represents better quality of life.

Sample size

In our study, we used G-Power software version 3.1 to calculated the simple size. A previous study showed that lower limb muscle strength can directly reflect the effect of exercise training on sarcopenia (Eckardt, 2016; Floreani et al., 2018). Thus, lower limb muscle strength was used as the primary outcome for the calculation of simple size. A power of 0.80 with an alpha of 0.05 was obtained in the calculation of simple size of each group, and the effect size was 0.48, which was reported in a previous meta-analysis study (Rogan et al., 2015). Our study adopted this effect size for calculating the sample size. We used above parameters in G-Power software and produced the total simple size as 45 subjects (15 subjects per group). Considering that there is a potential 20% drop rate of subjects, the total sample size should be 54 subjects (18 per group) in our study.

Statistical analysis

The results in the study took the questionnaire result and five components of the outcome measurements into account. All results were analyzed by IBM SPSS Statistics version 24 (SPSS, Inc., USA) with a statistical significant difference as $p < 0.05$. Continuous variables were represented by mean ± standard deviation or median. The chi-square test was used for categorical variables. For baseline characteristics data of between-group comparisons, we used the one-way analysis of variance (for parametric continuous data) or Kruskal–Wallis tests (for non-parametric continuous data).

The linear mixed model was used to analyze the differences in the outcome variables between the three intervention groups, which change over time following the principle of intention-to-treat. Missing data were assumed at random and then were processed by using the linear mixed model and maximum likelihood method.

Safety monitoring

The occurrence of adverse events during the experiment was recorded. Serious adverse events were reported to the superior unit and recorded, and then the best solution was sought for subjects by researchers. Medical treatments and appropriate medical compensation were provided to the subjects, if necessary. If the subjects thought the next intervention would cause safety problems to them, they had the rights not to continue to participate in the experiment.

Data management and monitoring

All data in this study were recorded and managed by data management software in Microsoft Excel 365 at baseline (0 week), after intervention (12 weeks), and follow-up (24 weeks), and adverse events and solutions during the experiment were also recorded. In order to ensure the confidentiality of the study, the name of the subjects was not uploaded in the database, but an identifiable number. All researchers used the encrypted computer when recording and saving data to ensure the security of data, with back up data to avoid data loss.

The data monitoring committee (DMC), which is independent of the competing interests and sponsor, regularly monitored and tested the data to ensure the authenticity and reliability of the data. This committee comprises trial experts, clinical experts, investigators, and statisticians.

Ethics and dissemination

Ethics approval

This study was reviewed and approved by the Ethical Review Committee of the Xinhua Hospital Chongming Branch in November 2020 (approval no. CMEC-2020-KT-42) and was registered in the China Clinical Trial Registry on 15 September 2021 (ChiCTR2100051178).

In the study, researchers collected demographic data (including name, age, gender, marital status, occupation, lifestyles, usual physical activity, drug use, and disease history), all questionnaire results, outcome results, and signed informed consent from the subjects. The electronic data were stored in an encrypted computer, and the paper data were be stored in the project office of Xinhua Hospital Chongming Branch.

Dissemination

We will authorize the publication of our study in peer-reviewed journals, and also will be performed at domestic or international academic congresses. The individual results will be reported to the subjects of this study by the researcher after publishing. Any changes or additions to the study protocol will be documented at www.chictr.org.cn.

Discussion

This is the first study comparing the effects of VT and RT in older people with sarcopenia. In addition, we comprehensively discussed the effects of VT and RT on outcomes related to sarcopenia, including anthropometric measurements (BH, BW, and CC), muscle mass (SMM, SMI, ASM, and ASMI), muscle strength (HGS and KES), physical performance (TUG test, GS, and SPPB), blood biomarkers [hs-CRP, TNF-α, IL-6, IGF-1, GH, testosterone, 25(OH)D, MSTN, FST, and CK], and quality of life (SF-36), between two intervention groups and a control group. At the present stage, a sharply increasing proportion of older people are suffering from sarcopenia, causing many adverse outcomes [e.g., falls (Woo and Kim, 2014), fractures (Harris et al., 2017), and other secondary health problems] to older people. Increasing studies have indicated that WBVT is a potential alternative method to delay the progression of sarcopenia in older people, and RT is one of the most effective exercise training methods for sarcopenia in older people. Therefore, we aimed to find an effective, simple training method to prevent and treat sarcopenia.

Our study has the following advantages: First, our study used two training methods (VT and RT) to provide suitable treatment for older people with sarcopenia. However, CRT has the risk of increasing injury like musculoskeletal problems for older people (Keogh and Winwood, 2017). It may be that CRT is too difficult to be implemented for older people, especially for frail older people, which could lead to low participation, low adherence, and perception difficulty (Fisher et al., 2017). The practical application of the research shows that compared with CRT, VT requires less technical abilities, less space, and less time to perform training (Marín and Rhea, 2010). Compared with physically strong older people with sarcopenia, frail older people may be more appropriate for VT, rather than RT. Therefore, we used VT and RT methods for older people with sarcopenia in our study.

Second, our study compared the effects of the two training methods (VT vs. RT) in older people with sarcopenia, rather than focusing on only one training method. For example, previous studies only explored the effects of different protocols of vibration training in older people with sarcopenia (Wei et al., 2016, 2017). A systematic review and meta-analysis by Wu

et al. also pointed out that current studies did not explore the efficacy of WBVT compared with other exercise training methods, and recommended more in-depth studies should be carried out in future on the comparison on WBVT with CRT (Wu et al., 2020). Therefore, our study aimed to solve this problem and provide a simple, effective alternative training method for older people with sarcopenia with difficulty to carry out the CRT.

Third, our study selected 20–25 Hz as the relatively appropriate vibration frequency. Previous studies on vibration were limited to comparing the efficacy of different vibration protocols in older people with sarcopenia. Wei et al. found that the most effective frequency of VT to improve muscle performance in older people with sarcopenia ranged between 20 and 40 Hz (Wei et al., 2016, 2017). Daniel et al. also demonstrated that the vibration frequency of about 6–26 Hz can improve GS and decrease the time of the TUG test in frail older people (Wadsworth and Lark, 2020). Stengel et al. found that VT with a frequency of 25–35 Hz produced positive effects on body composition and muscle strength in older people aged $\geq$ 65 years (von Stengel et al., 2012). Thus, we selected 20–25 Hz as the vibration frequency in our study. In addition, too long vibration exposure time may reduce subjectivity and compliance of older people with sarcopenia during the intervention period (Silva-Grigoletto et al., 2011). Therefore, we adopted a shorter vibration exposure time and increased the number of vibration repetitions.

Fourth, previous studies mostly focused on the acute effect of VT on sarcopenia (Giombini et al., 2013; Perchthaler et al., 2015) and less on the long-term effect of VT on sarcopenia. Thus, our study aimed to explore the long-term effects of VT and RT in older people with sarcopenia. Therefore, we set the intervention period as 3 months, and after intervention for 3 months, we performed the follow-up assessment to explore the remaining effects of VT and RT on sarcopenia in subjects.

Fifth, the subjects of our study are older people with sarcopenia but without other serious diseases. Previous studies mostly focused on young people [such as athletes (Gómez-Bruton et al., 2017; Takanashi et al., 2019; Chang et al., 2021)] and older people suffering from various diseases [such as knee osteoarthritis (Lai et al., 2019; Zhang et al., 2021), Parkinson's disease (Ribot-Ciscar et al., 2017), chronic low-back pain (Kaeding et al., 2017)], or healthy elderly (Camacho-Cardenosa et al., 2019; Jaime et al., 2019; Pérez-Gómez et al., 2020; Cheng et al., 2021). There are relatively few studies on the effects of VT on frail older people (especially for sarcopenia).

Sixth, the indicators measured in our study not only include three primary outcomes of sarcopenia (i.e., muscle mass, muscle strength, and physical performance) but also the outcomes of blood biomarkers (including inflammatory factors, hormones, growth factors, and muscular injury biomarkers) and quality of life. For the measurement of muscle strength, we measured both upper and lower limb muscle strength. In previous studies, only upper limb muscle strength (Chang et al., 2018; Miller et al., 2018) or lower limb muscle strength (Wei et al., 2016; Wei and Ng, 2018; Camacho-Cardenosa et al., 2019) was assessed. But studies have demonstrated that sarcopenia is associated with the decline of whole-body muscle, so it is not enough to only study upper/lower muscle strength (Cruz-Jentoft and Sayer, 2019). Therefore, our study evaluated both upper and lower limb muscle strength for the included subjects. For the measurement of blood biomarkers, our study explored the effects of different training methods on the physiological mechanism of the progression of sarcopenia. However, there is a lack of studies focusing on the change in the blood biomarker level in older people with sarcopenia using VT. Thus, we speculated that VT can also improve the blood biomarkers related to sarcopenia so as to prevent and/or delay sarcopenia in older people. In addition, we aimed to explore the mechanism of sarcopenia by exploring the changes of the blood biomarker level caused by VT and RT in the subjects.

Our study also has a limitation: in the VT group, we reduced each vibration exposure time and increased the number of vibration repetitions. A study found that longer time at each vibration increases muscle fatigue of the subjects and decreases subjects' compliance (Silva-Grigoletto et al., 2011). Therefore, we reduced the vibration exposure time of each vibration and increased the number of vibration repetitions. But we are not sure whether this will also lead to muscle fatigue in older people with sarcopenia. Hence, in future experiments, we will increase the monitoring of subjects' movements and make timely adjustments.

Trial status

On 15 September 2021, this study was registered in the Chinese Clinical Trial Registry with the number ChiCTR2100051178. The recruitment of subjects began in October 2021 and ended in February 2022. The formal study is expected to start in May 2022 and end in November 2022.

Strengths and limitations of this study

1. The findings of this study provide a convenient, safe, and effective method for older people to prevent and/or treat sarcopenia.
2. To the best of our knowledge, this study is the first to compare the effects of vibration training (VT)

and resistance training (RT) on muscle mass, muscle strength, physical performance, blood biomarkers (e.g., inflammatory factors, hormones, growth factors, and muscular injury biomarkers), and quality of life in older people with sarcopenia.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee of the Xinhua Hospital Chongming Branch. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LL, XH, LM, and NC designed the study. XH and NC provided advice and improved the details about the vibration training and resistance training program. LL, XH, and LM drafted the manuscript. YL and NC contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content, approved the final version of the manuscript, and the study guarantors. XH and LM contributed to data acquisition, analysis, and manuscript revision. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Research trends and frontiers in exercise for movement disorders: A bibliometric analysis of global research from 2010 to 2021

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Objective: To conduct a bibliometric analysis of trends and frontiers on exercise-based non-pharmacological treatments for movement disorders published between 2010 and 2021.

Methods: The Web of Science (WOS) Core Collection database was searched for articles published between 2010 and 2021. The CiteSpace software was used for in-depth analysis of the countries, institutions, journals, and collaboration networks among authors and their types of articles, developmental directions, references, and hot keywords of published articles.

Results: A total of 2,626 published articles were retrieved by search formula and included in the analysis. The number of publications fluctuated during this period, with 96 countries, 3,058 institutions, and 886 academic journals having published articles in this area, with subject classifications that focused on Clinical Neurology and Neurosciences. The United States has maintained its dominant and most influential position in exercise-based non-pharmacological research on movement disorders. Among research institutions and journals, the League of European Research Universities and *Movement Disorders* journals published the highest number of academic articles. In the last five years, the hot research topics by burst keyword analysis, are focused on treatments, research advances, and clinical treatments.

Conclusion: Research on exercise-based non-pharmacological treatments for movement disorders is generally on the rise from 2010 to 2021. The bibliometric analysis of this area will help provide potential collaborations among researchers, frontiers, and directions for development.

KEYWORDS

exercise, non-pharmacological treatment, movement disorders, bibliometrics, visualization, frontier hotspots

Introduction

Movement disorders belong to a diverse group of neurological disorders that manifest as neurological disabilities represented by degeneration of motor function or motor dysfunction and other disorders related to motor control. In recent years, it has received increasing attention in the field related to movement disorders (Fox et al., 2018). Symptoms of movement disorders include non-subjective conscious movements: tics, chorea, stereotypes, myoclonus, dystonia, tremor, etc. (Blackburn and Parnes, 2021). Idiopathic tremor is the most common movement disorder, with a prevalence rate of 14 and 21% in older adults over 65 years of age and in children and adolescents (Moghal et al., 1994; Kurlan et al., 2002), respectively. However, movement disorders are not only a major area of Neurology but also play an equally large role in geriatrics and related fields (Haunton, 2019). Parkinson's disease is a neurological disorder and according to the statistics of The Global Burden of Disease Study, there is currently a considerable increase in the number of patients manifesting Parkinson's disease, which is projected to reach more than 14.2 million by 2040 (Pringsheim et al., 2014; Dorsey and Bloem, 2018).

Clinical manifestations of movement disorders are complicated. Different types of movement disorders require the application of different pharmacological treatments, for example, in patients with dystonia who also have symptoms of mild ataxia, greater attention should be paid to hereditary causes, and in patients with chorea whose symptom cause is unknown, genetic testing for Huntington disease should be performed after appropriate consultation for the initial diagnosis and then other diagnostic and therapeutic workups (Abdo et al., 2010). Pharmacological treatment is currently the main focus on movement disorders in neurological disorders, such as Parkinson's disease, and to some extent relieves its symptoms using pharmacological treatment. However, movement-based movement disorders often do not respond well to pharmacological treatments (Poewe et al., 2017) and the therapeutic window narrows as treatment progresses. Exercise helps improve the brain's ability to repair itself and neuroplasticity, influence motor function recovery after brain injury, and prevent various neurodegenerative diseases (Smith and Zigmond, 2003; van der Kolk et al., 2018).

Bibliometric analysis used econometric research methods to study a body of literature and quantify the past published pieces of literature (Döbrössy and Dunnett, 2003). In recent years, there has been a gradual increase in research on non-pharmacological-based exercise therapy, however, no studies for bibliometric analysis were conducted in this field. Therefore, this study is a systematic bibliometric analysis of the field. The CiteSpace software was used to analyze the current state of research on exercise-based non-pharmacological treatments for movement disorders between 2010 and 2021, including annual publication volume, countries, institutions, journals, authors, keywords, and research directions, to provide future researchers guide of hot spots and directions. The New Horizons expressed in their article an encouragement of the development of new research and therapies and is of great value to the therapeutic and the multidisciplinary cross-learning fields (Wang et al., 2020).

Materials and methods

The flow chart of this research is shown in **Figure 1**.

Search strategy

All literature was obtained from the Web of Science (WOS). The current study showed that the WOS database provides more detailed data in analyzing published articles (Yeung, 2019), and it is more accurate than the Scopus database in terms of criteria based on cited literature, journal classification (Wang and Waltman, 2016), etc. The search formula was determined using Medical Subject Headings (MeSH), which provides a more comprehensive biomedical vocabulary and is a good resource for interpreting biomedical data (Yu, 2018). After determining the search formula, Topic, Title, and Abstract searches were conducted on the WOS (Donthu et al., 2021), and Title searches were selected to ensure the validity of the data source because of the large number of non-relevant literature under Topic and Abstract searches. The search strategy was set to all titles, as follows: (TI = [movement disorder OR dyskinesia syndrome OR myopathies OR myotonic OR myopathy OR paramyotonia congenita OR eulenburg disease OR tremor OR quiver OR rigidity OR rigidities OR gegenhalten OR hypodynamia OR bradykinesia OR myoclonus OR myoclonic OR ataxia OR ataxy OR coordination impairment OR dyssynergia]) AND TI = (exercise OR activity OR activities OR physical OR activity OR water sports OR motor control OR isometric OR aerobic OR train OR sport OR strength OR athletic OR movement OR endurance OR walk OR yoga OR stretch OR kinesiotherapy OR resistance OR pilates OR hydrotherapy OR stability OR tai chi OR core control OR swim OR Sprint OR martial art OR dance OR run). English articles accounted for 96% of all articles retrieved, and both Average per item (20.58) and h-index (92) for English articles were substantially higher than Average per item (2.84) and h-index (8) for non-English articles. English articles were selected to ensure the quality of the included data sources. The language of the articles in the search was set to English, the type of articles was set to "articles and review articles," and the time was set to from January 1, 2010 to December 31, 2021. Data were cleaned to ensure the quality of the included literature, as WOS is not a database dedicated to bibliometric analysis (Donthu et al., 2021). CiteSpace was

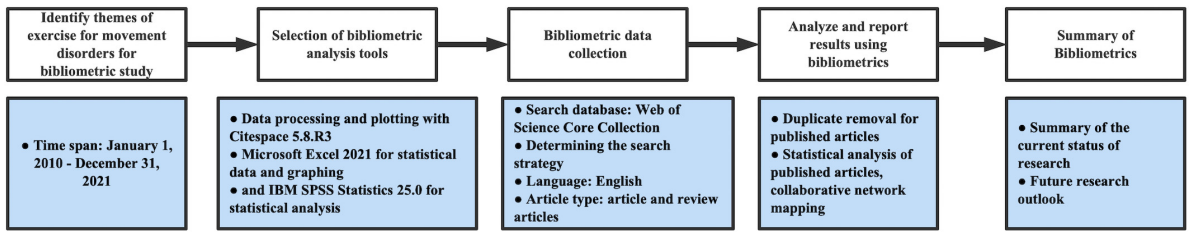


FIGURE 1
Research flow chart.

used to de-duplicate all retrieved literature and remove invalid literature, resulting in the inclusion of a total of 2,626 papers. In bibliometric analysis, the amount of data incorporated should be sufficiently large, e.g., greater than 500 articles, otherwise the use of bibliometric analysis is not required (Donthu et al., 2021). The final search and download date was May 20, 2022.

Analysis tools

The CiteSpace 5.8.R3, Microsoft Excel 2021, and IBM SPSS Statistics 25.0 software were used for plotting and statistical analysis. The CiteSpace 5.8.R3 software is based on the Java platform. The Java platform is a flexible tool for data analysis and it allows data visualization. The software has a unique ability in analyzing the generation of the country, institution, author, keyword, clustering analysis, etc. The visualization mapping function can detect the trends and hotspots of visualization literature through systematic search. It analyzed the association and cooperation networks among countries, institutions, authors, explore the trends of keywords, and clustering analysis, subsequently presenting them through visualization mapping (Synnestvedt et al., 2005). CiteSpace can be analyzed and made into 8 different visualizations. The researcher can set different time periods, nodes, and thresholds in the interface and select different nodes for analysis, nodes such as countries, institutions, journals, authors, etc. (Fang et al., 2018). The visual graph mainly consists of nodes and links and represents different elements such as countries, institutions, etc. Link acts as the main bridge among nodes and interconnects them to form a network relationship. The shades of node and link colors represent the number of references, with darker colors representing the increased number of references. Centrality represents the degree of connection among unrelated nodes, therefore, nodes with higher centrality are recognized as important nodes or key turning points in a domain (Pei et al., 2019), meanwhile, nodes with centrality values greater than 0.1 are considered as key nodes. The CiteSpace software also allows geospatial visualization mapping of the literature (Chen, 2017). The analysis of co-cited journals, authors, references, and keywords can provide clues to the development of the field of expertise (Fang et al., 2018), and is more rigorous and convincing in terms of the development and analysis of trends in the field of study than the analysis of citations alone (Mustafee et al., 2014).

The Microsoft Excel 2021 was used to count and make tables and pictures of literature data, make line graphs of annual publications of literature, and make statistical analyses of countries, institutions, and authors.

Pearson's correlation analysis between the year of publication and the number of published articles was performed using the IBM SPSS Statistics 25.0 software.

Data extraction

The bibliometric indicators of published articles were extracted using the search strategy of the WOS Core Collection database. These include Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI). The number of publications, co-citations, open access, and h-index of countries, institutions, and research directions was extracted using the CiteSpace with Microsoft Excel software, the keyword trends were analyzed, and relevant visualization plots were produced.

This study explains the current status and outlook of research on exercise-based non-pharmacological treatments for movement disorders through the following sections.

- Analysis of the distribution and trends of countries, institutions, journals, authors, and disciplines.
- Assess the collaboration network among countries, institutions, and authors.
- Citation, open access, and h-index analysis. Citation frequency analysis reflects the quality of publications. The higher the citation frequency, the better the quality. The h-index evaluates the academic level and assesses the number and output levels of researchers' academic outputs. The higher the h-index, the greater the influence (Hirsch, 2005). Open access reflects the chance of the article being cited. The higher the open access, the more beneficial it

is to promote the dissemination and communication of research results.
- The analysis of keyword highlighting, clustering, and citation literature.

Results

Annual publication volume and growth trend analysis

The annual publication volume is shown in **Figure 2**. A total of 2,626 articles were included, with a fluctuating growth trend from 2010 to 2017, a gradual growth trend from 2017 to 2021, and a peak in the number of articles published in 2021 (332). The trend of publication volume from 2010 to 2021 shows that exercise-based non-pharmacological treatment for movement disorders is gradually increasing. The American College of Sports Medicine launched the Exercise is Medicine program as early as 2007. It emphasizes on encouraging physicians to promote the treatment and prevention of chronic diseases through scientific exercise when treating their patients, and this program is globally available. The promotion of exercise as a treatment of chronic diseases had a tremendous effect globally (Sallis, 2009), contributing to the rapid growth in publication after 2010. According to a 2015 article, maintaining physical activity is necessary to prevent non-communicable diseases and should increase the role and status of exercise in the medical field (Eijsvogels and Thompson, 2015). The highest number of publications in a single year was reached in 2021, and the development trend in recent years indicates that it is currently in a period of rapid development, in which the movement form is expected to become an important modality in the treatment of movement disorders in the coming years, becoming a mainstream alternative to pharmacological treatment modalities and receiving focused attention from research teams. According to the correlation analysis, the volume of publication was positively correlated with the year ($r = 0.928$, $p < 0.001$).

Analysis of review articles and articles

The analysis of the types of literature only included theses and reviews. Of the 2,626 articles, 2079 articles (79.17%) and 547 reviews (20.83%) were cited. "Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series (Schenck et al., 2013)" was published in the Journal of *Sleep Medicine* and was one of the top five most cited articles (455) of all articles. As shown in the text, 38% of patients with idiopathic rapid eye movement (REM) sleep behavior disorder are transformed into a Parkinson's disease after several years. Studies recommended that patients with Parkinson's disease undergo an annual neurological examination focusing on their cognitive and motor function, and these research advances have significant potential clinical value in the field of multidisciplinary integration (Schenck et al., 2013). The main aspect of diagnosing and treating REM sleep behavior disorder is still medication (Schenck and Mahowald, 2012), and resistance training and self-weight interval training can improve sleep disorders in patients with Parkinson's disease (Amara et al., 2020). The top three among the review articles (373) in terms of frequency of citations were "The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Motor Symptoms of Parkinson's Disease (Fox et al., 2011)," Published in *Movement Disorders*. The article's research illustrates that the training format can reduce the risk of falls, balance, gait, and other abilities in people with Parkinson's disease. It has a positive effect on the rehabilitation process in moderate-to-high intensity training in patients with Parkinson's disease. According to past clinical studies, this will be a research trend in the future proving exercise therapy as a treatment for the disease (Fox et al., 2011).

Analysis of countries and institutions

The CiteSpace and Microsoft Excel software was used to analyze the countries and institutions that published articles in the field, generating plots of countries (**Figures 3A**, **4A**), and institutions (**Figures 3B**, **4B**). In total, 96 countries and 3,058 institutions have published articles in this field in 2,626 articles. According to the number of published articles, the top three countries and regions were the United States (854), the England (325) and Italy (293). According to CiteSpace statistical centrality, the three highest values are in the United States (0.14), Argentina (0.12), and Canada (0.07). In addition to Spain being the highest in average per item (47.84), the United States maintains its lead in the analysis of citations (20,588), open access (486), and h-index (74), based on the combination of publication volume, centrality, citations, average per item, open access, and h-index combined. It showed that the United States maintained its dominant and most influential position in exercise-based non-pharmacological research on movement disorders. The ability of the United States to become a central country in this field of research is closely related to the rapid development of the exercise related non-pharmacological treatment field in the United States, which started early and has received more attention from researchers and has a strong academic research background. Moreover, the United States, Argentina, Canada, Spain, England, and Germany have a strong collaboration with other countries and regions. In the institutional analysis of the published literature, the top three institutions by publication volume

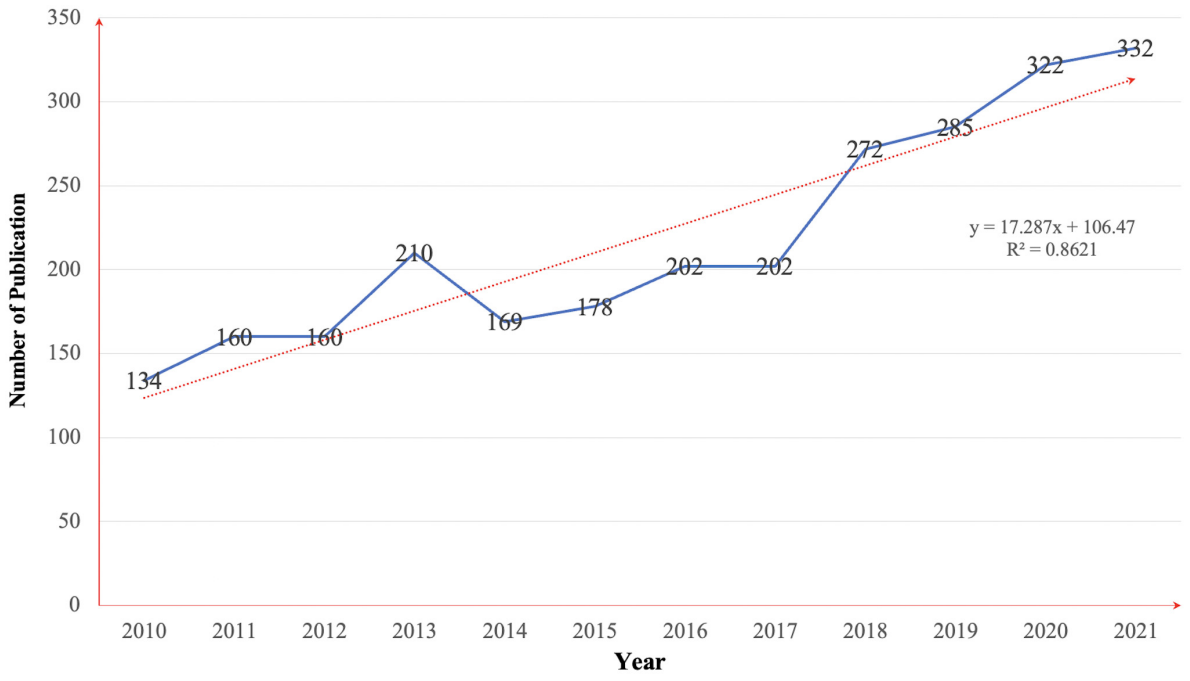


FIGURE 2
Annual publication volume of published articles.

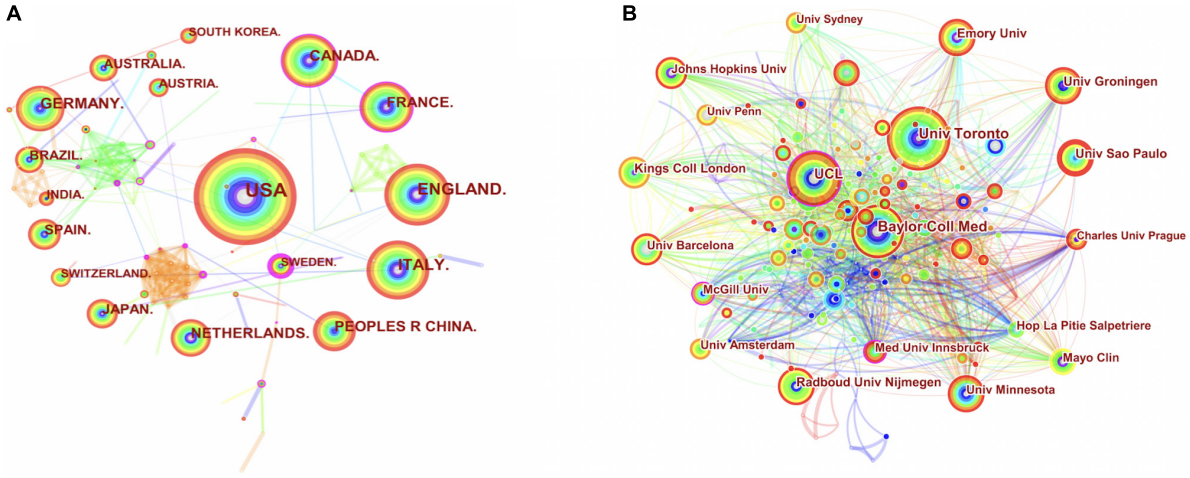


FIGURE 3
Map of collaborative relationships between countries **(A)** and institutions **(B)** that have published articles. PEOPLES R CHINA, People's Republic of China; Univ, university.

are the League of European Research Universities (354), University of London (167), and Udice French Research Universities (124). The top three institutions with the highest centrality values are the University College London (0.15), McGill University (0.12), and Pitie Salpetriere (0.11). The University of California System (55.73) ranked highest in average per item statistics, meanwhile, the League of European Research Universities ranked highest and stayed ahead in publications (354), citations (10,269), open access (220), and h-index (54). Based on the combined analysis of publication volume, centrality, citations, average per item, open access, and h-index, the League of European Research Universities, University College London, and the University of London are the major research institutions. Although the United States is the central country in this field of research, University College London and the University of London, which are

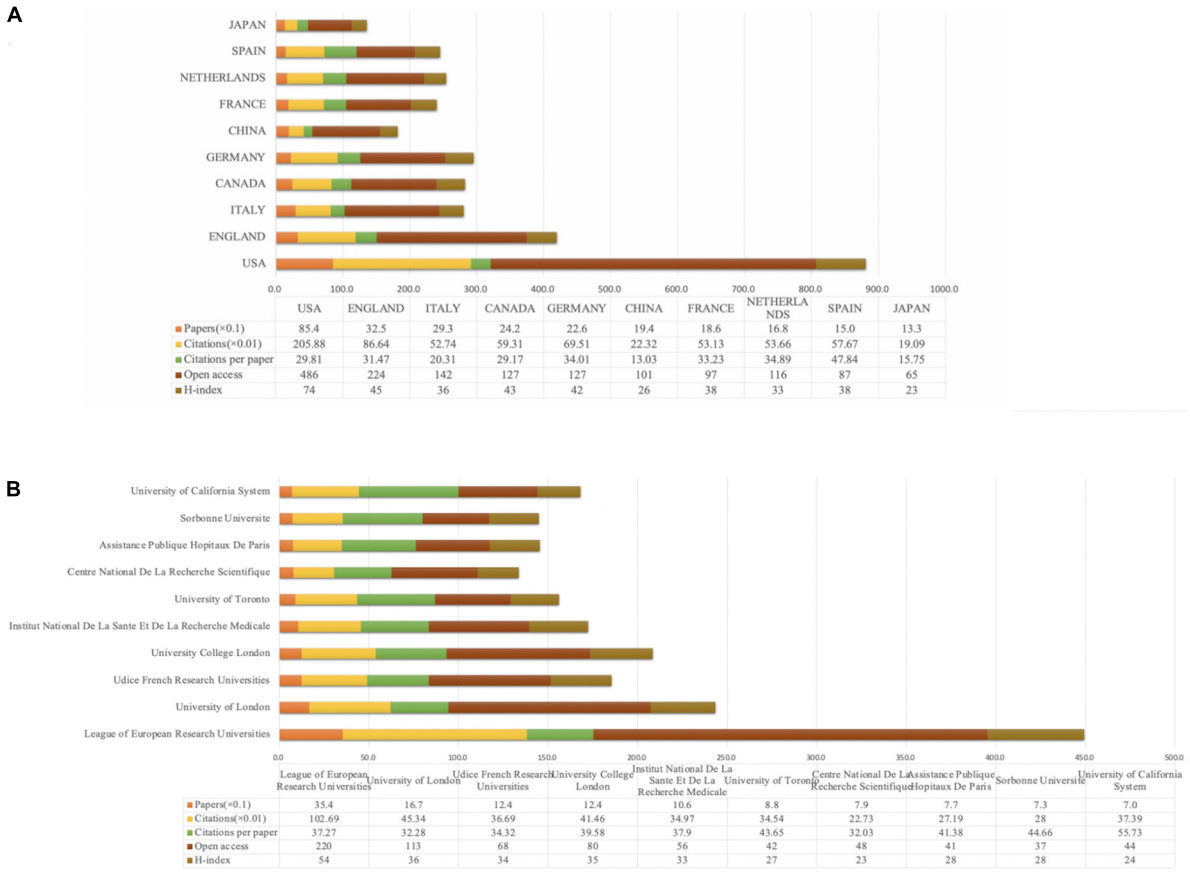


FIGURE 4
Exercise on the number of publications, citations, average per item, open access, and h-index for countries **(A)** and institutions **(B)** that publish articles in the field of movement disorders.

TABLE 1 The top 10 journals in the field of exercise for movement disorders.

Journal	Articles	Times cited (WoS)	Average per item	Open access	WoS sort	IF (2021)	Quartile	H-index
Movement Disorders	152	9,435	62.07	49	Clinical Neurology	9.698	Q1	41
Parkinsonism & Related Disorders	85	1,463	17.21	27	Clinical Neurology	4.402	Q2	22
Sleep Medicine	67	1,989	29.69	12	Clinical Neurology	4.842	Q2	23
Frontiers In Neurology	52	447	8.6	52	Clinical Neurology; Neurosciences	4.086	Q2	13
Movement Disorders Clinical Practice	40	266	6.65	32	Clinical Neurology	4.514	Q2	8
Sleep	36	843	23.42	14	Clinical Neurology; Neurosciences	6.313	Q1	32
Plos One	33	581	17.61	33	Multidisciplinary Sciences	3.752	Q2	14
Journal Of Neurology	32	804	25.13	6	Clinical Neurology	6.682	Q1	18
Current Neurology And Neuroscience Reports	27	371	13.74	9	Clinical Neurology; Neurosciences	6.03	Q1	12
European Journal Of Neurology	26	342	13.15	8	Clinical Neurology; Neurosciences	6.288	Q1	10

WoS, Web of Science; IF, impact factor.

major research institutions, are located in the United Kingdom, indicating that in addition to the United States, England in this field of research also maintains a high international influence. Meanwhile, the University of London is second only to the League of European Research Universities in the statistics in terms of the number of publications (167), citations (4,534), open access (113), and h-index (36). The University College London, McGill University, Pitie Salpetriere, University of Toronto, and Baylor College of Medicine have extensive collaborations with other institutions.

Analysis of journals and co-cited journals

A total of 886 academic journals have been published among the 2,626 articles. A table was created for the top ten journals in terms of the number of articles published (**Table 1**). The top three journals in terms of the number of articles published were *Movement Disorders* (152), *Parkinsonism & Related Disorders* (85), and *Sleep Medicine* (67). In addition to the *Frontiers in Neurology* journal, which had the highest number of publications in the open access statistics (52).

Movement Disorders journals maintained their lead and dominated in terms of publication volume (152), citation frequency (9,435), per-page citation frequency (62.07), impact factor (9.698), and h-index (41). Of the top ten journals, five were located in the first quarter (Q1) of the WOS database classification, and the other five journals are all in the second quarter (Q2), with an average impact factor of 5.6607. The quarterly and impact factors show that all included articles are highly referenced.

Co-cited journals were made into a graph by CiteSpace software (**Figure 5**). The top three journals in terms of the number of co-citations were *Neurology* (1,455), *Movement Disorders* (1,408), and *Brain* (1,121). The top three journals according to centrality were *Archives of Physical Medicine and Rehabilitation* (0.04), *Psychopharmacology* (0.04), and *Journal of Pharmacology and Experimental Therapeutics* (0.04). *Movement Disorders* journals are the leading journals in the field of exercise-based non-pharmacological research based on publication volume, co-citations, and centrality on movement disorders and provide important contributions to research in the field. The top three journals ranked according to their centrality and have values of less than 0.1 are not considered journals with a key role.

Authors and co-cited authors

To fully explore the influential authors in the field and show the collaborative networks among authors, the authors and co-cited authors of the published literature were made into a map using the CiteSpace software (**Figure 6**). A total of 486 nodes and 1,206 connections appeared in the analysis of authors (**Figure 6A**), meanwhile, 744 nodes and 4,599 connections appeared in the analysis of co-cited authors (**Figure 6B**). The larger nodes represent greater roles in the overall network mapping. Authors of published articles are summarized and co-citation frequency and centrality are displayed (**Supplementary Table 1**). The top ten authors, co-cited authors, and co-cited literature were indicated in **Table 2**. The top three authors with the most published articles were Jankovic, Joseph (45), Bhatia, Kailash P. (40), and Hoegl, Birgit (32). Baylor College of Medicine's Professor Jankovic, Joseph has the highest number of publications and his research interests are focused on Neurosciences Neurology, particularly on neurological disorders of the elderly. Among his cited articles, the top five of which are four on the Parkinson's disease (Hong et al., 2010; Marks et al., 2010; Marek et al., 2011; Nalls et al., 2019) and one on the movement disorders (Albanese et al., 2013). A close collaboration has been established among authors such as Fidel Baizabal-Carvallo, Jose, Hallett, Mark, Mehanna, and Raja. According to the CiteSpace analysis, the top three authors with the highest centrality ranking were Bhatia, Kailash P. (0.08), Postuma, Ronald B. (0.05), and Dauvilliers, Yves (0.05), all with centrality values of less than 0.1, which is insufficient as a critical node, indicating that the intensity of collaboration among researchers was not high.

The top three authors in terms of co-citations were Postuma, Ronald B. (257), Iranzo, Alex (243), and Fahn, Stanley (233). Professor Postuma, Ronald B. of McGill University has the highest number of co-citations, with a research interest in Neurosciences Neurology. The top three authors according to centrality are Postuma, Ronald B. (0.12), Iranzo, Alex (0.04), and Fahn Prof. Postuma, Ronald B. Professor Postuma, Ronald B. is the key author of the co-citation and has also established close collaboration with authors such as Gagnon, Jean-Francois, and Montplaisir, Jacques Y.

Analysis of subject categories of Web of Science

In the analysis of 2,626 articles on the study of movement disorders with exercise-based non-pharmacological treatments, a total of 145 disciplinary categories were classified, and the top 20 disciplinary categories with the highest number of publications were charted (**Figure 7**). Clinical Neurology (1,221) and Neurosciences (769) accounted for 75.781% of the total number of publications, making them the two leading disciplines in this field of research. Clinical Neurology is leading in the number of publications (1,221), citations (20,012), average per item (25.15), open access (515), and h-index (76). There are 90 research directions in 145 subject categories, mainly in Neurosciences Neurology, Psychiatry, and

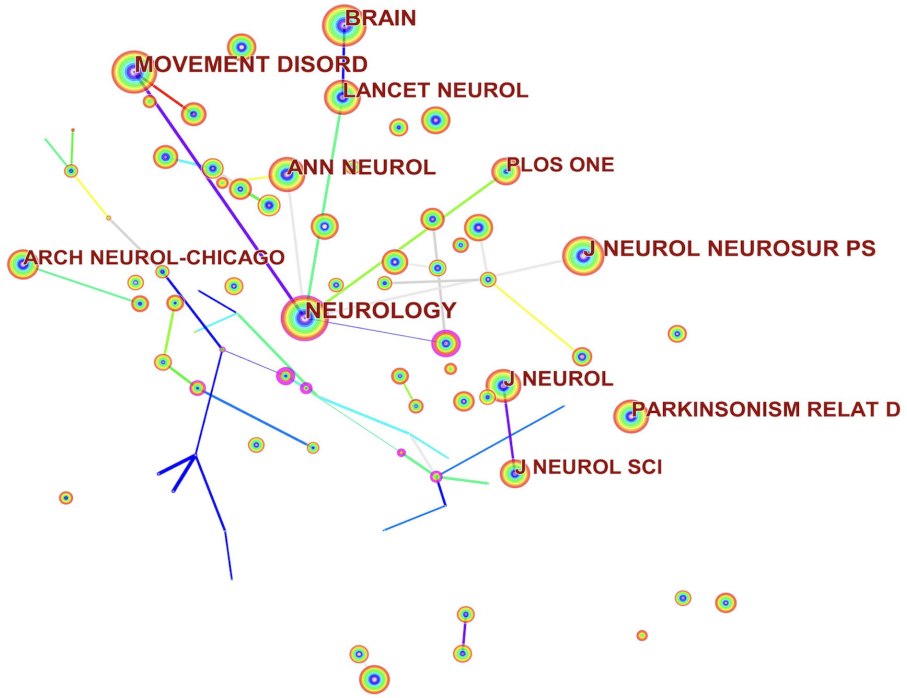


FIGURE 5
Journal co-citation maps in the field of exercise for movement disorders research.

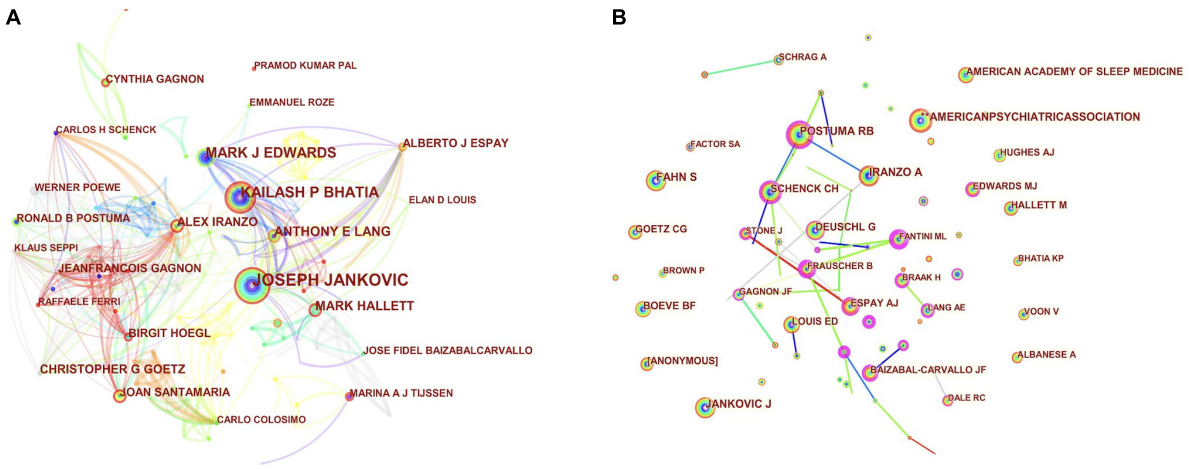


FIGURE 6
Collaborative network map of authors **(A)** and co-cited authors **(B)** of exercise for movement disorders.

Psychology. The Neurosciences Neurology research directions accounted for 58.72% of the publication volume (1,542). The disciplinary classification is dominated in the field of neurological related research, but also forms a multidisciplinary network of intersectional relationships, including pediatrics, rehabilitation, and surgery. It provides a background of one-discipline dominated multidisciplinary intersection for research in the field of exercise to movement disorders.

Analysis of co-cited and cited references

Statistical analysis of co-cited references is an important indicator for correlation analysis in the literature. The higher the number of co-cited references, the higher the correlation among documents. Figure 8 shows a timeline plot of co-cited references, which shows 12 clusters, all of which were extracted

TABLE 2 The top 10 authors, co-cited authors, and co-cited references on exercise for movement disorders.

Author	Published articles	Co-cited author	Cited times	Co-cited reference	Cited times
Jankovic, Joseph	45	Postuma, Ronald B.	257	Idiopathic REM sleep behavior disorder and neurodegeneration—an update	41
Bhatia, Kailash P.	40	Iranzo, Alex	243	Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series	40
Hoegl, Birgit	32	Fahn, Stanley	233	Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behavior disorder: an observational cohort study	39
Edwards, Mark J.	31	American Psychiatric Association	232	Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder	35
Iranzo, Alex	31	Jankovic, Joseph	200	MDS clinical diagnostic criteria for Parkinson's disease	30
Postuma, Ronald B.	30	Schenck, Carlos H.	197	Phenomenology and classification of dystonia: A consensus update	29
Hallett, Mark	28	American Academy of Sleep Medicine	169	Idiopathic rapid eye movement sleep behavior disorder: diagnosis, management, and the need for neuroprotective interventions	29
Santamaria, Joan	28	Boeve, Bradley F.	167	Neurodegenerative Disorder Risk in Idiopathic REM Sleep Behavior Disorder: Study in 174 Patients	29
Gagnon, Jean-Francois	27	Deuschl, Guenther	150	Parkinson risk in idiopathic REM sleep behavior disorder Preparing for neuroprotective trials	27
Mirelman A	20	[Anonymous]	134	Polysomnographic diagnosis of idiopathic REM sleep behavior disorder	25

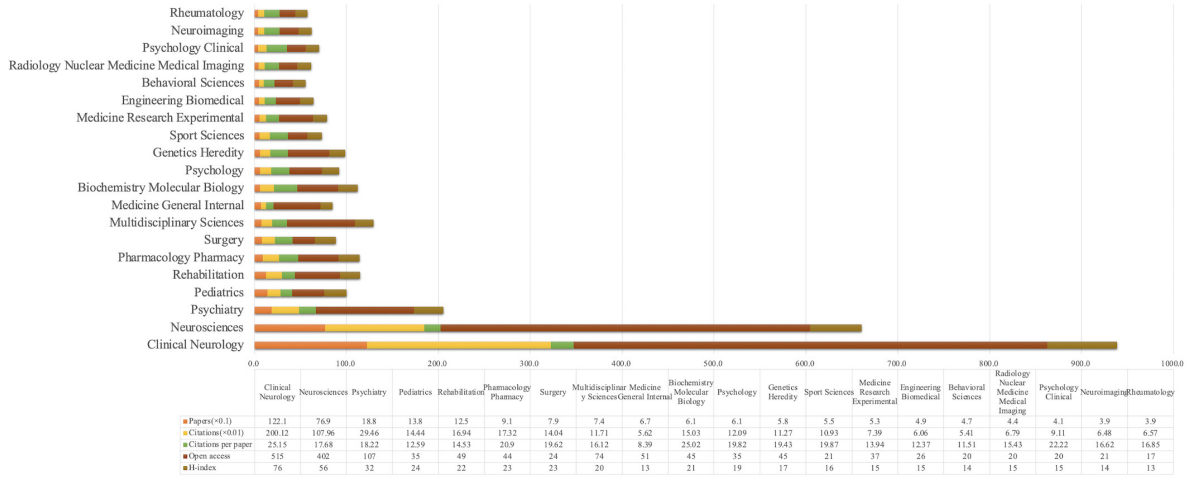


FIGURE 7
Analysis of the number of publications, citations, average per item, open access, and h-index for exercise for subject categories in the field of movement disorders.

by keywords of co-cited references. Dystonia, narcolepsy, and gnao1 were labeled as the first cluster #0, second cluster #1, and third cluster #2, respectively. In the analysis of co-cited literature (Table 2), "Idiopathic REM sleep behavior disorder and neurodegeneration-an update (Högl et al., 2018)" had the highest number of co-citations (41), meanwhile, "The spectrum of movement disorders in children with anti-NMDA receptor encephalitis (Baizabal-Carvallo et al., 2013)" had the highest centrality value (0.15).

The top ten most cited articles are shown in Table 3. The "Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines (Litvan et al., 2012)" had the highest number of citations (1,365), however, all citations were in the

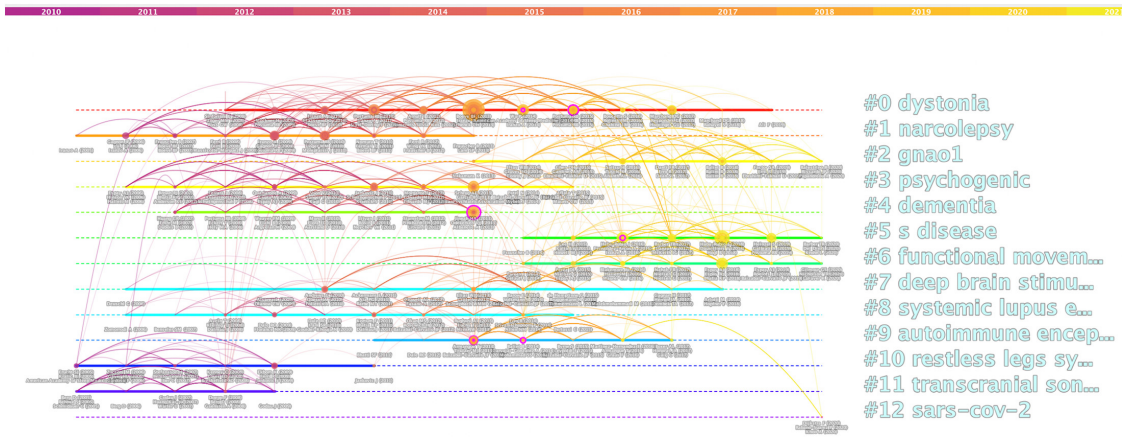


FIGURE 8
Timeline view map of exercise for movement disorders.

TABLE 3 The top 10 articles with the most citations on exercise for movement disorders.

Title	First Author	Journal	IF (2021)	Year	Citations (WoS)	WoS Sort
Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines	Litvan, Irene	*Movement Disorders*	9.698	2012	1365	Clinical Neurology
Multifunctional wearable devices for diagnosis and therapy of movement disorders	Son, Donghee	*Nature Nanotechnology*	40.523	2014	980	Materials Science
Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria	Hoeglinger, Guenter U.	*Movement Disorders*	9.698	2017	762	Clinical Neurology
The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease	Seppi, Klaus	*Movement Disorders*	9.698	2011	539	Clinical Neurology
How Common Is the Most Common Adult Movement Disorder? Update on the Worldwide Prevalence of Essential Tremor	Louis, Elan D.	*Movement Disorders*	9.698	2010	514	Clinical Neurology
Consensus Statement on the Classification of Tremors. From the Task Force on Tremor of the International Parkinson and Movement Disorder Society	Bhatia, Kailash P.	*Movement Disorders*	9.698	2018	474	Clinical Neurology
Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series	Schenck, Carlos H.	*Sleep Medicine*	4.842	2013	455	Neurosciences Neurology
Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behavior disorder: an observational cohort study	Iranzo, Alex	*Lancet Neurology*	59.935	2013	400	Neurosciences Neurology
How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale	Stebbins, Glenn T.	*Movement Disorders*	9.698	2013	379	Clinical Neurology
The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Motor Symptoms of Parkinson's Disease	Fox, Susan H.	*Movement Disorders*	9.698	2011	373	Clinical Neurology

Clinical Neurology disciplinary classification, meanwhile, in the Neurosciences as the second most cited disciplinary classification, "The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults-An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses (Aurora et al., 2012)" holds

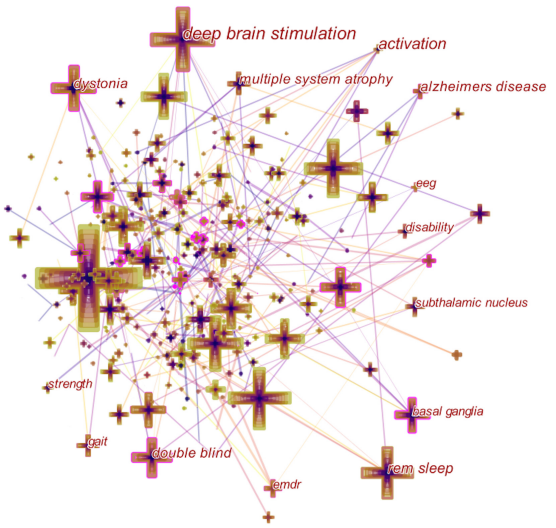


FIGURE 9
Keyword map of exercise for movement disorders.

the highest citation frequency (209). "Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria (Höglinger et al., 2017)" ranked first in citations in each of the last two years with the highest annual average of citation frequency (127.83).

Analysis of co-citation keywords and emergent keywords

The intensity values of co-cited keywords, emergent keywords, and the intensive time of emergent keywords reflect the research frontiers and development trends and uncover emerging research frontiers and development directions. The co-cited keywords were analyzed using the CiteSpace software and created a keyword network map (**Figure 9**), which generated 488 nodes and 3,996 connections. All keywords were summarized and co-citation frequency and centrality were shown (**Supplementary Table 2**). The top five keywords in terms of co-citation frequency were Parkinson's disease (557), movement disorder (355), deep brain stimulation (166), diagnosis (156), and REM sleep (145). The top five keywords with centrality values were brain (0.07), performance (0.06), clinical feature (0.06), movement disorder (0.05), and restless legs syndrome (0.05), all of which had centrality values of less than 0.1 and were not used as important references. Parkinson's disease, movement disorder, deep brain stimulation, diagnosis, and REM sleep were hot keywords in terms of co-citation frequency and centrality analysis, indicates widespread interest in the study of movement therapy for movement disorders.

For a more in-depth analysis of the keywords, the burst value and burst time of keywords were analyzed using the CiteSpace software (**Figure 10**). The burst value of a keyword represents that it has received special attention at a certain time and represents the research hotspot in that research area at a certain time (Lin et al., 2020). **Figure 10** shows the 25 keywords with the highest intensity of burst values, with the red nodes representing the aggregation of time. The three keywords with the highest burst value intensity from 2010 to 2016 are neurodegenerative diseases (7.74), delayed movement disorders (4.74), and muscle disorders (4.69). The top three keywords with the highest burst values from 2017 to 2021 shifted to efficacy (5.49), progression (4.57), and *in vivo* (4.32), however, these three keywords are mainly focused on 2019, keywords indicating that the frontiers in the last five years were focused on therapeutic approaches, research progress, and clinical treatment.

Discussion

Global research trends and frontiers in exercise for movement disorders

The present analysis was performed on articles studying exercise therapy for movement disorders published between 2010 and 2021. A total of 2,626 articles were retrieved and these data were entered into the CiteSpace software with various bibliometric indicators extracted for countries, institutions, journals, authors, references, and keywords. Using the CiteSpace and Microsoft Excel software, the data were analyzed and processed and their corresponding graphs and plots were produced.

In the analysis of publication volume, the results show that there is an overall upward trend with increasing years, with a total of 52,888 citations from 2012 to 2021, with an average citation frequency of 20.14 per article, open access 1290, and h-index 91. In 2021, the highest publication volume and citation frequency were 332 and 10,032, respectively. The publication volume rapidly increased from 2016 to 2021, with an increase of 159.7% compared to the volume from 2010 to 2015. However, a sudden increase in the number of publications over a certain time does not guarantee an increase in the quality of research in the field. It is because the data extracted from published articles only counts the number of publications of research in the field and does not analyze the quality of research articles. The frequency of citations of the published articles only represents the size of the attention that researchers give to the articles. In the analysis of the countries and institutions that have published articles, there are 96 and 3,058 that have published articles in this field, respectively. The United States is the leading influential country in this field, with the League of European Research Universities, University College London, and University of London as the main research institutions. In the analysis of journals that published articles, 886 academic journals have published articles in the field, with

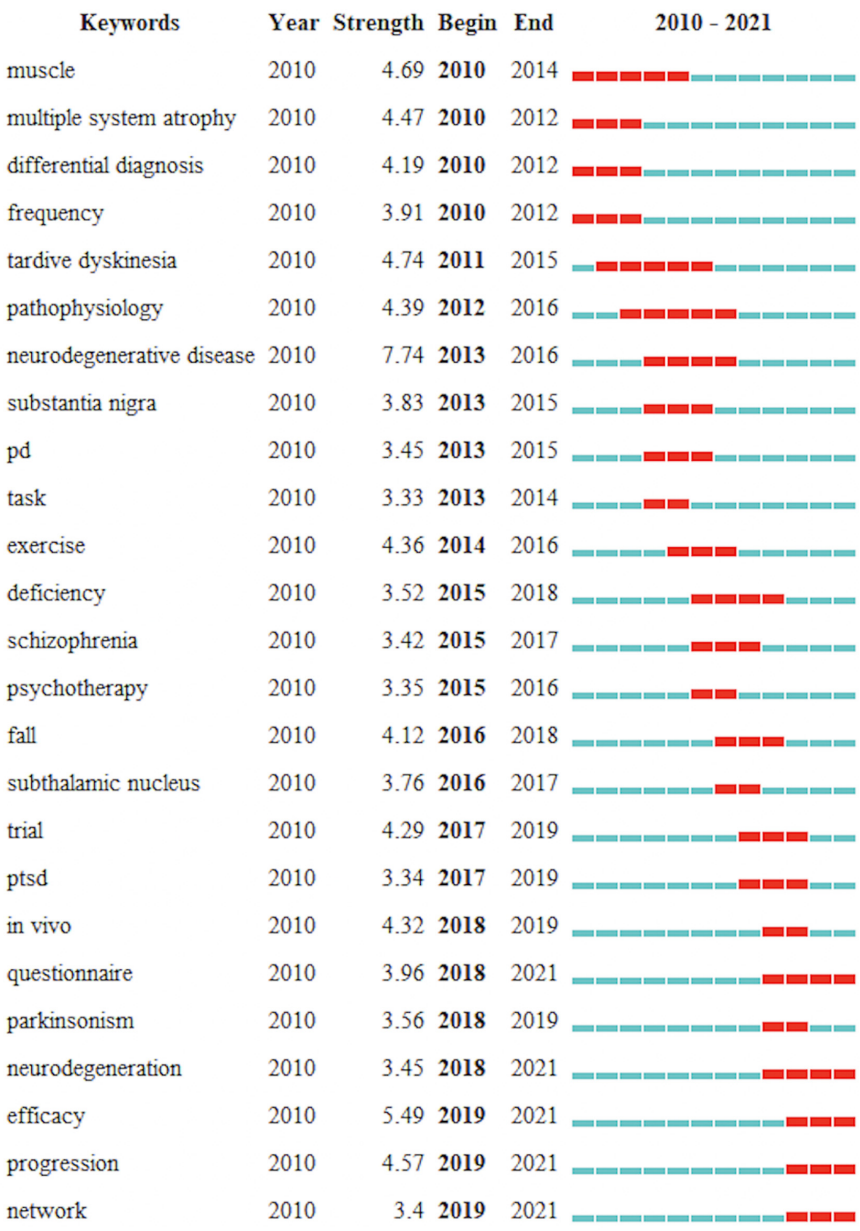


FIGURE 10
The top 25 keywords with the strongest burst value. Red bar represents keywords with higher co-citation in the time period.

the *Movement Disorders* journals dominating all journals that published articles. The number of publications of the *Movement Disorders* journals rapidly increased from 2017 to 2020, reaching the highest single-year publication volume in 2019 and 2020 (18) and the highest single-year citation frequency in 2021 (1,898), indicating that the *Movement Disorders* journals have received certain attention and influence in the field in recent years. In previous studies, great progress has been made in diagnosing movement disorders (Sharma, 2020). A growing number of studies have demonstrated that improvement in movement disorders positively affects the patients' quality of life, however, surgical treatment can have certain side effects, such as residual motor symptoms after surgery (Rowland et al., 2017). Parkinson's disease is mostly treated with pharmacological and surgical interventions, although they can improve and relieve symptoms, they also produce certain side effects (Ventura et al., 2015). In addition, avoiding surgery in patients and trying to uncover better strategies for the treatment of movement disorders is today's important long-term goal (Rowland et al., 2017). In the analysis of the authors of the published articles, Prof. Jankovic, Joseph had the highest number of publications (45) and Prof. Postuma, Ronald B. had the highest number of

co-citations (257). Both authors have the same research interest in Neurosciences Neurology.

In an analysis of the WOS disciplinary classification, the most heavily concentrated research on exercise for movement disorders is in the Neurosciences Neurology research area of the Clinical Neurology discipline, and this is dominated by the United States and England. The American Medical Association and the American College of Sports Medicine jointly organized the "Exercise is Medicine" advocacy campaign in 2007 to strongly advocate the importance of exercise for health. It was implemented nationwide in the United States, encouraging people of all ages, genders, and ethnicities to maintain good exercise habits. The project established the importance of exercise in health care (Lobelo et al., 2014). The British Journal of Sports Medicine, ranked number one in sports science and has a major influence in the field of sports medicine. The 2,014 article showed that the Exercise is Medicine campaign has now partnered with 39 countries worldwide and in the future exercise therapy will be integrated into the global development strategy of healthcare, making a significant contribution to the global sports medicine field (Lobelo et al., 2014). Exercise therapy is cost-effective and can be widely practiced at the societal level. Studies have demonstrated that exercise improves cognitive performance and outperforms medication as treatment and it has a high positive effect on various neurological disorders. Therefore, researchers and medical practitioners should actively promote exercise therapy to patients with movement disabilities and the need for multidisciplinary collaboration (Nagamatsu et al., 2014).

In an analysis of references, the review of "Idiopathic REM sleep behavior disorder and neurodegeneration-an update" shows the importance of using polysomnography in diagnosing sleep disorders. As explained in other studies (Amara et al., 2020), the improvement of sleep disorders in patients with Parkinson's disease by exercise can be properly diagnosed by polysomnography. Exercise is potential for the prevention and rehabilitation of various diseases, however, it is currently not fully implemented as treatment in the clinical practice. In the future, exercise should be combined with medicine to be applied as therapy to patients on an equal footing with other medical interventions (Vuori et al., 2013). In recent years, from the keywords that have received great attention, it can be seen that the Parkinson's disease, movement disorders, deep brain stimulation, efficacy, progression, and *in vivo* have been the hot spots of research on movement disorders by exercise. So far, the main modalities for exercise-based non-pharmacological treatment of movement disorders include tai chi, balance, resistance, and interval training. These modalities have produced different efficacy for different movement disorders through different forms of exercises (Li et al., 2012; Pompeu et al., 2012; Corcos et al., 2013; Amara et al., 2020). The 2018 Physical Activity Guidelines for Americans recommend that people of all ages should maintain varying levels of exercise by maintaining physical activity for health benefits and disease prevention, including special populations with Parkinson's disease, Alzheimer's disease, stroke, and cerebral palsy (Piercy et al., 2018). However, taking medications as a treatment for some movement disorders such as tremor, dystonia, and Parkinson's disease can also be a cause of further movement disorders (Burkhard, 2014; Mehta et al., 2015). It is necessary to explore and investigate the non-pharmacological and non-invasive interventions in the treatment of current movement disorders (Ventura et al., 2015).

Analysis of hot keywords for Parkinson's disease and movement disorders

Parkinson's disease: Parkinson's disease is mainly suffered by the elderly, and the prevalence increases with age (Pringsheim et al., 2014), the motor symptoms of Parkinson's disease can be relieved by medication, but inevitably there are certain side effects (van der Kolk et al., 2018). Many studies have now confirmed that the motor symptoms of Parkinson's can be effectively improved by aerobic exercise, Tai Chi, and resistance training (Li et al., 2012; Pompeu et al., 2012; Corcos et al., 2013; van der Kolk et al., 2018; Marusiak et al., 2019), and even in older adults with other chronic diseases, the risk of chronic disease can be similarly reduced by physical activity (Piercy et al., 2018). In studies of patients with Parkinson's disease, 74–98% of patients were affected by sleep disorders (Amara et al., 2020), and good sleep is essential for mental and physical health (Buysse, 2014). Sleep disorders can have health consequences if not treated, such as obstructive sleep apnea, insomnia, chronic sleep insufficiency, etc. (Cho and Duffy, 2019). But few medications can effectively improve Parkinson's sleep disorder, and the existing medication may bring certain side effects, there are studies have proved that resistance training and interval training can improve the sleep disorder of Parkinson's disease patients, and improve the quality of sleep. In the future, non-pharmacological treatments such as exercise will be an alternative treatment for Parkinson's sleep disorders (Amara et al., 2020).

Movement disorders: In previous research concepts, dyskinesia was usually considered as an impairment in the ability to control movement triggered mainly by basal ganglia dysfunction, but nowadays, as relevant research continues to develop, the sensory system plays an important role in dyskinesia, especially peripheral sensory feedback. The regulation of proprioception is defective in Parkinson's disease patients (Patel et al., 2014), and motor deficits caused by gait and balance abilities have a greater impact on Parkinson's disease patients (Coelho et al., 2010), mostly due to the integration of deficits in multiple feedback systems of visual, auditory, and proprioceptive, leading to motor deficits (Wright et al., 2010; Martens and Almeida, 2012; Sacrey and Whishaw, 2012).

Motor training with response stimuli, movement techniques, and other targeted to the relevant systems can overcome movement disorders such as gait (Van Gerpen et al., 2012). Studies in patients with Akathisia and restless legs syndrome have also shown that symptoms can be effectively relieved by continuous exercise. In future studies, research on the effects of the integrated effects of multiple feedback systems on movement disorders should be strengthened (Patel et al., 2014). There is evidence that a simple 12-week low to moderate intensity walking training program in patients with functional movement disorders significantly improves symptoms of movement disorders (Dallocchio et al., 2010). A growing body of research demonstrates that the nervous system can be protected, adapted, regenerated, and neurologically improved through training programs (Ang and Gomez-Pinilla, 2007), suggesting that cognitive-behavioral therapy combining physical movement and cognitive interventions can provide an easy, effective, and feasible means of treating symptoms (Sharpe et al., 2011). In intervention studies of exercise on cognitive performance, attention, and social behavior in movement disorders, regular participation in regular exercise in children with attention deficit hyperactivity disorder was effective in improving cognitive function, attention, and social behavior, and in improving motor performance, thereby reducing motor symptoms (Medina et al., 2010; Den Heijer et al., 2017; Christiansen et al., 2019) and there is also evidence that multidisciplinary crossover approaches such as physical combined with psychotherapy can be positive for some patients (Schrag et al., 2004), and compared to pharmacotherapy is more economical, efficient and practicable compared to medication. In a controlled trial, just 5 days of intensive physical therapy improved more than 60% of patients (Czarnecki et al., 2012). And many cognitive-behavioral treatment programs can be easily combined with exercise forms (Otto et al., 2007). Patients with movement disorders should be targeted in their training programs in the same way as medication programs, which may produce very different symptoms and have a different impact on life even when suffering from the same degree of disorder (Czarnecki et al., 2012). In future research, multidisciplinary cooperation on movement disorder-related disorders, such as neurology, geriatrics, psychology and physical therapy such as exercise should be extensively strengthened to conduct collaborative research and explore more scientific and effective treatment options in the field of movement disorders.

Strengths and limitations

This study is the first bibliometric analysis based on the WOS Core Collection database summarizing the trends and frontiers of exercise-based non-pharmacological treatments for movement disorders research in the world from 2010 to 2021. A total of 2,626 articles were counted from 96 countries and 886 academic journals. The data of the analyzed articles were more comprehensive, counting the number of publications, countries, institutions, journals, authors, literature types, references, research directions, and keywords.

This study also has limitations in the search strategy because it was only for the WOS Core Collection database, non-English published articles were not included, and only referred to articles and reviews which may have biased the analysis results based on these factors. The results of articles with higher citation frequencies are already known, meanwhile, articles with newer publication years, high influence, and high quality may not have higher citation frequencies.

Conclusion

The CiteSpace software was mainly used in this study to show the trends in the field of exercise based non-pharmacological treatment for movement disorders research from 2010 to 2021. It also shows the collaborative network among countries, institutions, journals, and authors, and the in-depth analysis of article types, development directions, references, and hot keywords. The present bibliometric analysis provides a new research perspective on the research progress in this field. The research on exercise for movement disorders is receiving a lot of attention, and many research teams are conducting high quality randomized controlled trials to promote the rapid development of the field. Although there are some limitations of the study, it provides a more comprehensive analysis of the research trends and frontier hotspots in the field of non-pharmacological treatment of movement disorders research. The results of the analysis are conducive to more and future promising research in the field of movement therapy for movement disorders.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

J-WC wrote the article and data analysis. YG, Y-LZ, and KZ contributed to the conception of the study and helped further revise the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.977100/full#supplementary-material

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Research trends and hotspots of exercise for Alzheimer's disease: A bibliometric analysis

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Objective: Alzheimer's disease (AD) is a socially significant neurodegenerative disorder among the elderly worldwide. An increasing number of studies have revealed that as a non-pharmacological intervention, exercise can prevent and treat AD. However, information regarding the research status of this field remains minimal. Therefore, this study aimed to analyze trends and topics in exercise and AD research by using a bibliometric method.

Methods: We systematically searched the Web of Science Core Collection for published papers on exercise and AD. The retrieved data regarding institutions, journals, countries, authors, journal distribution, and keywords were analyzed using CiteSpace software. Meanwhile, the co-occurrence of keywords was constructed.

Results: A total of 1,104 papers were ultimately included in accordance with our specified inclusion criteria. The data showed that the number of published papers on exercise and AD is increasing each year, with papers published in 64 countries/regions and 396 academic journals. The Journal of Alzheimer's Disease published the most papers (73 publications). Journals are concentrated in the fields of neuroscience and geriatrics gerontology. The University of Kansas and the United States are the major institution and country, respectively. The cited keywords show that oxidative stress, amyloid beta, and physical exercise are the research hotspots in recent years. After analysis, the neuroprotective effect of exercise was identified as the development trend in this field.

Conclusions: Based on a bibliometric analysis, the number of publications on exercise and AD has been increasing rapidly, especially in the past 10 years. "Amyloid beta," "oxidative stress," and "exercise program" trigger the most interest among researchers in this field. The study of exercise program and mechanism of exercise in AD is still the focus of future research.

KEYWORDS

exercise, CiteSpace, Alzheimer's disease, visualized analysis, bibliometrics

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder caused by damage to brain neurons (Alzheimer's Association, 2022). Hallmark pathological changes include neuritic extracellular amyloid plaque and neurofibrillary tangles (Barthelemy et al., 2020). AD is characterized by cognitive decline and behavioral changes with memory, language, and thinking problems as the initial symptoms (Dubois et al., 2016, 2018). Progressive symptoms will continue to affect activities of daily living. The rate in which AD progresses varies from person to person. An estimated 55 million people living with dementia worldwide were reported by Alzheimer's Disease International in 2021, and patients with AD are expected to increase to 78 million by 2030 (Alzheimer's Disease International, 2021). AD accounts for the largest proportion of patients with dementia, and the proportion of those over 60 years old is about 65% (Jia et al., 2020). AD is a fatal illness, and the average survival time of AD is reported to vary from 4 to 8 years for patients aged 65 years and older (Larson et al., 2004). Globally, given the large population of patients with AD and the harmfulness of this disease, AD has become a considerable health and economic burden, calling for more effective measures to control this disease.

To date, AD is treatable but not curable. Current interventions are mostly aimed at slowing down the progression of AD, reducing its symptoms, and improving quality of life. Exercise is considered an important lifestyle modification that can help delay the beginning of cognitive deterioration and improve the quality of life of patients with AD (Lautenschlager et al., 2008; Petersen et al., 2018). Numerous studies have found that aerobic exercise, resistance exercise, and cognitive–physical exercise can help patients with AD in many aspects, such as improving cardiovascular fitness, attenuating neuroinflammation, and supporting the brain clearance of Aß peptides (Karssemeijer et al., 2017; Morris et al., 2017; Sun et al., 2018; Ribaric, 2022). Given the increase in the number of publications about the use of exercise in treating AD, identifying research trends and hotspots is highly significant. However, a quantitative analysis of this research theme has not yet been conducted.

Bibliometric analysis is a scientific method for constructing a co-occurrence network of research themes by using quantitative statistics (Hicks et al., 2015). The software tool, CiteSpace, is used to show a visual map of bibliometric results, such as journals, authors, institutes, keywords, citations, popular topics, and frontiers. Some reviews on the use of exercise to treat AD with different emphases have been published; however, a comprehensive and visualized analysis remains lacking (Karssemeijer et al., 2017; Ribaric, 2022). Therefore, we conduct a bibliometric analysis of exercise and AD research to reveal the dynamic development in this field. This study helps provide a comprehensive understanding of this topic and guide future research direction.

Methods

Search strategy

The data used in this study were collected from the Science Citation Index Expanded (SCI-E) of the Web of Science Core Collection database. The search strategy was as follows: TS = (exercise OR sport OR "physical activity" OR training OR running OR swimming OR dance OR walking OR yoga OR "tai chi" OR pilates OR qigong OR liuzijue OR wuqinxi OR yijinjing OR baduanjin) AND TS = Alzheimer*. The search strategy identified papers with these words mentioned in their title, abstract, author keywords, or keywords plus. Only articles and reviews were included as document types. The time span was from inception to June 30, 2022. All papers from the search were preliminarily included, and we screened all the papers by reading the title, abstract and author keywords, and excluded irrelevant literature (e.g., "computer running," "speech training," and "common training library"). Discrepancies were observed via discussion. **Figure 1** shows the flow diagram of the publications screening process.

Analytical tool

CiteSpace (Chaomei, 2006) is a visual analysis application developed by Dr. Chen Chaomei of Drexel University. It is based on theory of citation analysis, which has been applied by many scholars worldwide. CiteSpace is well recognized for transforming quantitative literature data into visual maps and networks to provide key information, including research trends, popular topics, and distribution of countries. Cluster and time-zone views are included in CiteSpace's visualization. Visual networks have been confirmed significant in research trends and key points. We can see different nodes and links in various CiteSpace visualization knowledge maps. Nodes represent different key points, countries, institutions, and journals. The larger the nodes, the greater number of occurrences or citations in this field. Different colors represent various years. A relatively early time is represented by cold-hued nodes, while a relatively late time is represented by warm-hued nodes. The centrality of a node indicates the importance of a node's status in a network. In CiteSpace, a node with a purple ring is considered a pivotal point with high centrality (Chen, 2017). Microsoft Excel (2019)

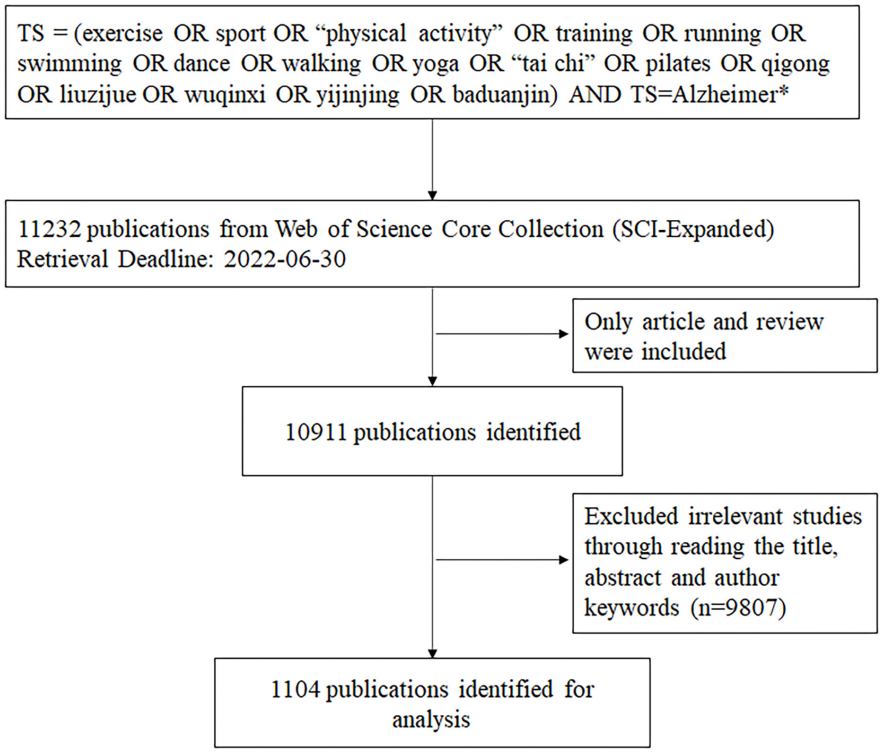


FIGURE 1
Flow diagram of the publications screening process.

was used to generate a graph of the trends in annual publications and citations.

Results

Publication trends

A total of 1,104 publications met our inclusion criteria. Researchers are paying more and more attention to AD each year. Consistent with this, despite some minor fluctuations but with an overall upward trend for the number of studies on exercise intervention in AD (Figure 2). The volume of published literature can be broadly divided into three periods: 1987–2000, 2000–2006, and 2006–2021. The number of publications in the first period was low, while the number of publications in the second and third periods increased significantly. The maximum number of relevant publications (n = 135) was reached in 2021. A considerable increase occurred in the second period, while the largest increase was recorded in the third period, with a number of 122 additional pieces of literature from 2006 to 2020. The citations of literature have largely increased every year, with the most significant increase occurring from 2016 to 2021. The large numbers of publications and literature citations in recent years have indicated the attention given by scholars to this area.

Analysis of countries/regions and institutions

The literature came from 64 countries/regions. In accordance with Table 1, among all the countries/regions where literature was published, the top 3 in terms of number of publications are as follows: the United States (424 publications), China (137 publications), and Brazil (86 publications). Among these countries/regions, the top three in terms of citations to literature are the United States, Australia, and Canada. Meanwhile, the countries with the highest average citations per item are Australia, Germany, and the United States in that order. The top three countries in terms of the h-index are the United States, Australia, and Germany. The United States dominates the field, with the highest number of publications, citations, centrality, and h-index. Although China and Brazil have more publications, they have fewer citations and their academic influence is more limited.

Table 2 lists the 10 institutions with the highest number of publications. The most productive institution is the University of Kansas (31 publications), and the University of Melbourne (28 publications) has the second highest number of publications, followed by the University of Minnesota (27 publications). Figure 3 illustrates the collaborative relationships among different institutions.

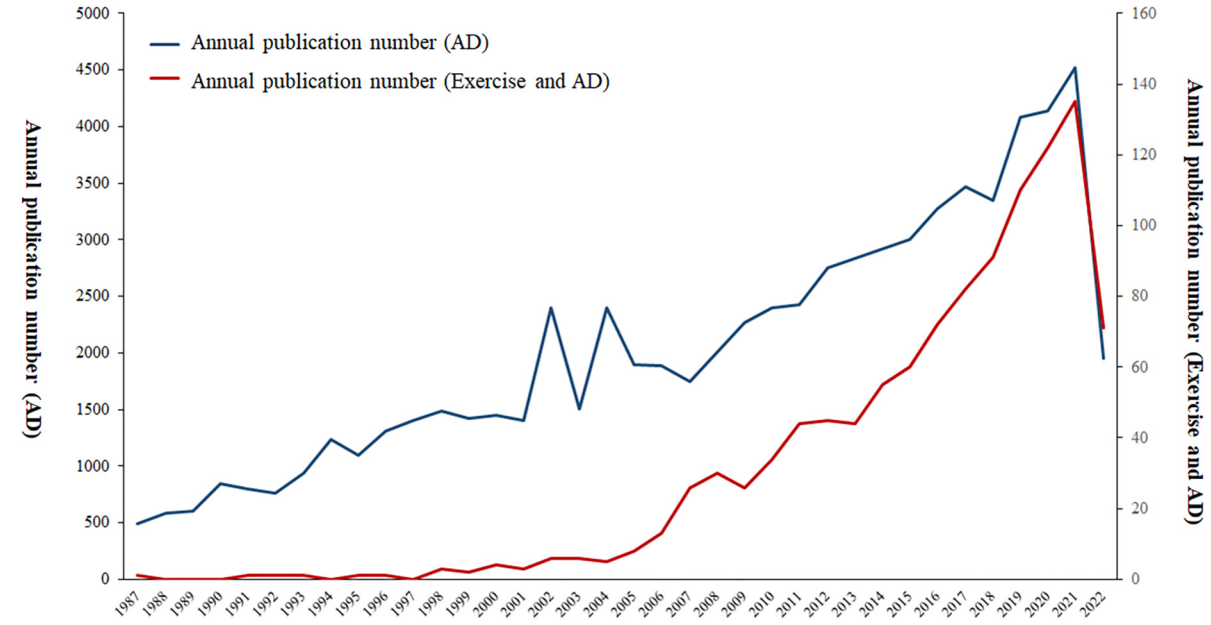


FIGURE 2
Annual number of publications on AD, exercise and AD from 1987 to 2022.

TABLE 1 Top 10 most productive countries/regions.

Country/Region	Publications	Citations	Average citations per item	Centrality	H-index
United States	424	25318	59.71	0.61	80
China	137	2561	18.69	0.08	27
Brazil	86	2280	26.51	0.01	26
Australia	77	4780	62.08	0.11	32
Canada	76	4061	53.43	0.04	25
United Kingdom	65	3055	47.00	0.08	30
Spain	63	1891	30.02	0.08	25
Germany	60	3680	61.33	0.04	30
Italy	49	1802	36.78	0.04	23
Japan	47	2509	53.38	0.06	23

TABLE 2 Top 10 most productive institutions.

Rank	Institution	Publications	Rank	Institution	Centrality
1	University of Kansas	31	1	University of Pittsburgh	0.14
2	University of Melbourne	28	2	University of Western Ontario	0.14
3	University of Minnesota	27	3	University of California San Francisco	0.12
4	University of Washington	22	4	Harvard University	0.11
5	University of Western Australia	21	5	University of Washington	0.1
6	University of Pittsburgh	18	6	Autonomous University of Barcelona	0.08
7	Harvard University	18	7	University of Melbourne	0.06
8	University of Copenhagen	17	8	Karolinska Institutet	0.06
9	Rush University	16	9	Edith Cowan University	0.06
10	Karolinska Institutet	16	10	University of Eastern Finland	0.06

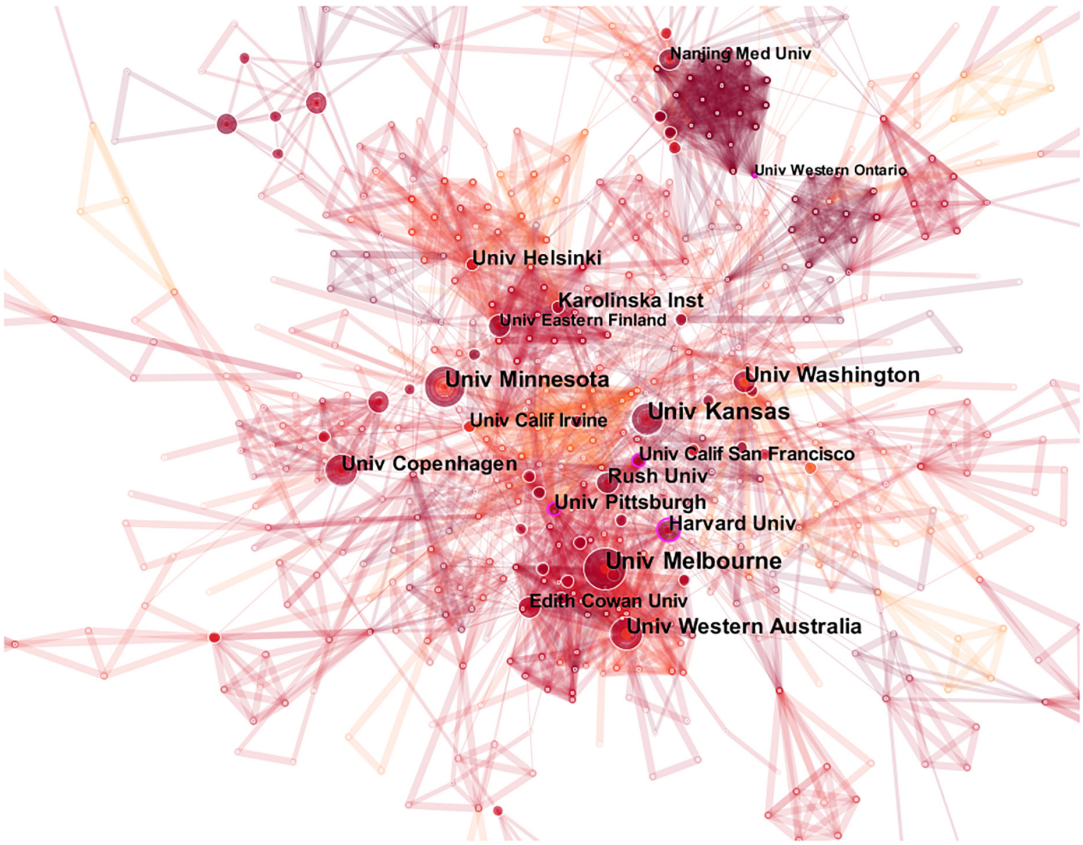


FIGURE 3
The map of co-institutions. The nodes in the map represent co-institutions, and lines between the nodes represent co-citation relationships. The purple ring represents centrality.

Links between the University of Melbourne, Harvard University, University of Pittsburgh, University of California San Francisco and other institutions indicate close collaboration. The centrality of the University of Pittsburgh, the University of Western Ontario, the University of California San Francisco and Harvard University is greater than 0.1, demonstrating a wide range of academic influence.

Analysis of authors

The papers were contributed by 5,267 authors. The top 10 authors in terms of number of publications are presented in Table 3. The top three most frequently cited authors were Cotman CW (2,387 citations), Lautenschlager NT (1,488 citations), and Cox KL (1,322 citations). Cotman CW had a significantly higher number of citations than the other authors. He also had the highest number of citations per item and the highest *h*-index, endowing him with greater academic influence. As shown in Figure 4, the field has formed a relatively large number of research teams, with many highly productive authors among them. The major research teams are those of Yu F, Cotman CW, Burns JM, Zhang L, and Hasselbalch SG.

Analysis of journals and categories

All the retrieved publications were published in 396 different journals. Table 4 lists the top 10 journals that are publishing in this area. The top five journals in terms of number of publications were as follows: Journal of Alzheimer's sisease (73 publications), Frontiers in Aging Neuroscience (34 publications), Behavioral Brain Research (26 publications), Current Alzheimer Research (21 publications), and International Journal of Molecular Sciences (21 publications). Among the top 10 journals, the Journal of Alzheimer's Disease was the most cited (2,435 citations), while the Journal of the Neurology had the highest average number of citations per term (128.56). Publications from the top 10 journals were primarily published in Neurosciences (409 publications) and Geriatrics and Gerontology (268 publications). The top ten web of science categories in this field also include: Clinical

TABLE 3 Top 10 most productive authors.

Author	Publications	Citations	Average citations per item	H-index
Yu, Fang	24	321	13.38	11
Burns, Jeffrey M.	22	797	36.23	13
Vidoni, Eric D.	18	281	15.61	9
Lautenschlager, Nicola T.	14	1488	106.29	11
Hasselbalch, Steen Gregers	14	462	33	12
Cotman, Carl W.	13	2387	183.62	12
Stella, Florindo	12	397	33.08	10
Strandberg, Timo	12	460	38.33	9
Cox, Kay L.	12	1322	110.17	9
Rolland, Yves	12	1048	87.33	9

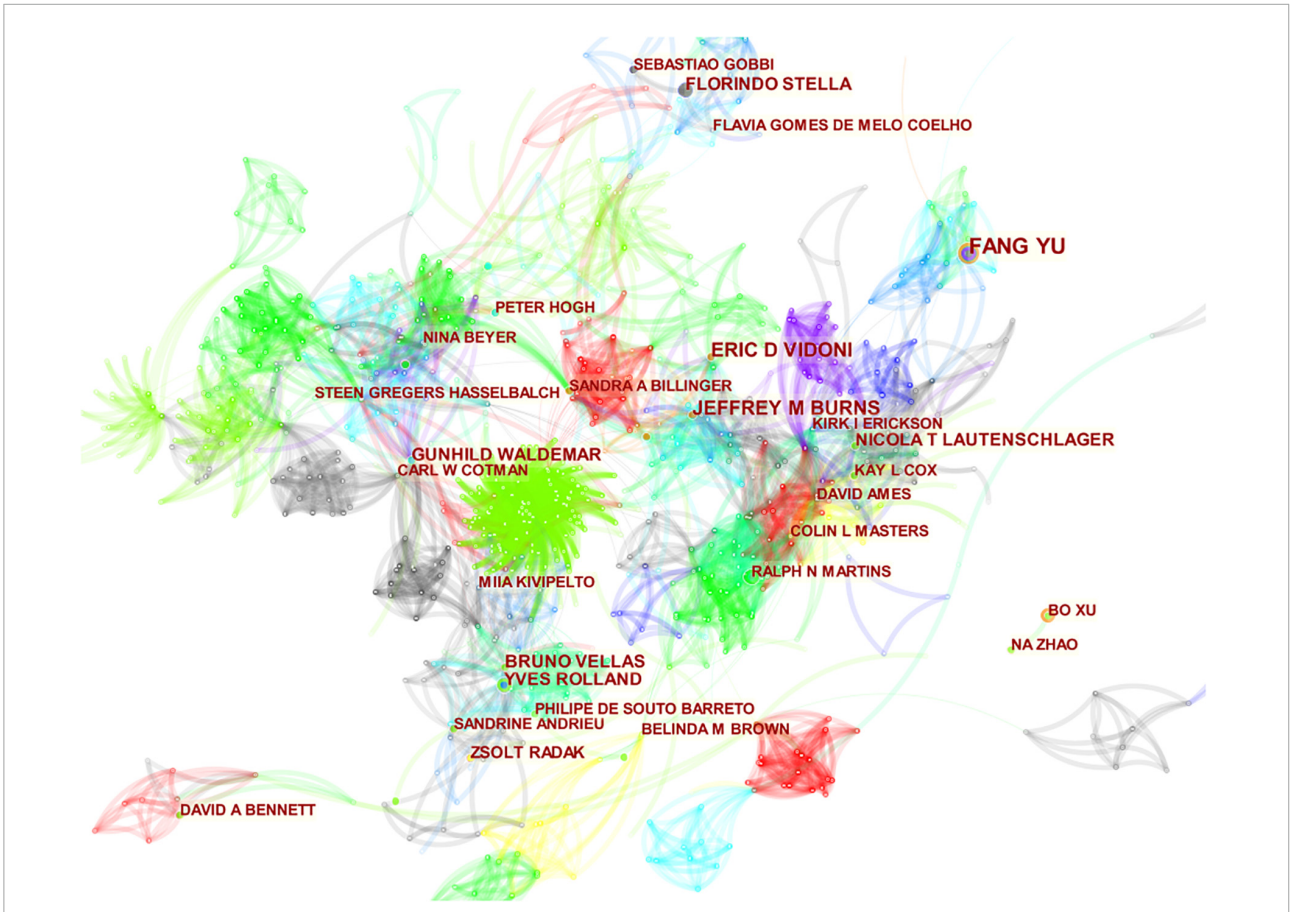


FIGURE 4
The map of co-authors. The nodes in the map represent co-authors, and lines between the nodes represent co-citation relationships. The purple ring represents centrality.

Neurology (177 publications), Gerontology (93 publications), Psychiatry (76 publications), Sport Sciences (76 publications), Biochemistry Molecular Biology (62 publications), Medicine General Internal (54 publications), Behavioral Sciences (50 publications), and Medicine Research Experimental (44 publications).

Analysis of the top 10 most cited papers

Table 5 lists the top 10 papers based on the number of total citations and average per year on exercise and AD research, which focused on the research themes of cognitive function,

TABLE 4 Top 10 most productive journals.

Journals	Publications	Citations	Average per item citations	2021 IF
Journal of Alzheimer's disease	73	2435	33.34	4.160
Frontiers in Aging Neuroscience	34	659	19.38	5.702
Behavioral Brain Research	26	962	36.92	3.352
Current Alzheimer Research	21	425	20.24	3.040
International Journal of Molecular Sciences	21	189	9.00	6.208
American Journal of Alzheimer's Disease and Other Dementias	18	380	21.11	2.632
Journal of the American Geriatrics Society	16	1260	78.75	7.538
Neurology	16	2058	128.56	11.800
Neurobiology of Aging	15	823	54.87	5.133
Alzheimer and Dementia	14	673	48.07	16.655

exercise plus behavioral management, cognitive training, and brain plasticity. The most cited papers was "An active and socially integrated lifestyle in late life might protect against dementia" by Fratiglioni L and published in the Lancet Neurology in 2004. The top-ranked papers were those published earlier, indicating that they have been consistently cited and have high reference value. Based on average per year of citations on exercise and Alzheimer's research, "Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models" by Lourenco MV in 2019 (68.5 citations per year), "Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model" by Choi SH in 2018 (59 citations per year), and "Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines" by Erickson KI in 2019 (56.5 citations per year) were relatively new in the field, focusing on the study of exercise for brain plasticity.

Analysis of keywords

Figure 5 shows the co-occurrence of keywords, which are highly closely linked to one another. Figure 6 presents the cluster diagram for the keywords. The clusters include oxidative stress, cerebral blood flow, skeletal muscle, mice, doubly labeled water, education, apolipoprotein e, nervous system autonomic, vitamin c, leisure activity, behavioral training. Figure 7 shows the top 25 keywords with the strongest citation bursts since 1987. These keywords are also the research frontiers in the field. The red bars indicate the emergence and duration of research hotspots. The top 25 keywords with the strongest citation bursts began in 2001. These words are mainly concentrated in two categories: program of exercise intervention in AD (e.g., physical exercise, aerobic exercise, treadmill exercise, voluntary exercise, and leisure activity), mechanism of exercise intervention in AD (e.g., amyloid beta, cerebral blood flow, amyloid precursor protein, and long term potentiation). The keywords with the strongest citation bursts are amyloid beta. Combined with the above data and analysis, the major research frontiers in recent years are exercise program, amyloid beta, and oxidative stress.

Discussion

Global research trends of exercise on Alzheimer's disease

This study described the landscape of exercise-based rehabilitation and prevention of AD by analyzing subject categories and the contribution of countries, journals, and authors. A total of 1,104 papers were obtained through the retrieval strategy.

Our study found that research on the relationship between exercise and AD started in 1987, and the number of published papers exhibited an increasing trend every year. The number of published papers in 2021 is 3.97 times that in 2010 and 33.75 times that in 2000. Among all the studies, eight highly cited publications were published in the last 10 years (2013–2021), which might be a period of high-quality development in the field of sports and AD research. The aforementioned findings suggest that exercise and AD are eliciting extensive attention among researchers and have become popular research issues in recent years. This phenomenon may be related to the increase in AD incidence rate with the magnification of the aging society and the rapid development of sports science and rehabilitation medicine (Garcia-Morales et al., 2021; Zong et al., 2022).

By analyzing the journals about exercise and AD, we determined that researchers concentrated in the fields of neuroscience and geriatrics. Among them, the Journal of Alzheimer's disease (73 publications), Frontiers in Aging Neuroscience (34 publications), Behavioral Brain Research (26 publications), Current Alzheimer Research (21 publications), and International Journal of Molecular Sciences (21 publications) have given the most attention to this field, demonstrating that the research field has focused on

TABLE 5 The top 10 papers based on the number of citations on exercise and AD research.

Title	Journal	Year	Citations
Total			
An active and socially integrated lifestyle in late life might protect against dementia	Lancet Neurology	2004	1217
Leisure activities and the risk of dementia in the elderly	New England Journal of Medicine	2003	1110
Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial	Journal of the American Medical Association	2008	1032
Physical activity and risk of cognitive impairment and dementia in elderly persons	*Archives of Neurology*	2001	952
Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older	Annals of Internal Medicine	2006	873
Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging	American Journal of Epidemiology	2002	862
The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis	Archives of Physical Medicine and Rehabilitation	2004	799
Effects of aerobic exercise on mild cognitive impairment: a controlled trial	*Archives of Neurology*	2010	718
Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease	Lancet Neurology	2005	667
Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama study	Neurology	2013	643
Average per year			
Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial	Journal of the American Medical Association	2008	68.8
Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models	Nature Medicine	2019	68.5
Long-term health benefits of physical activity: a systematic review of longitudinal studies	BMC Public Health	2013	64.3
An active and socially integrated lifestyle in late life might protect against dementia	Lancet Neurology	2004	64.05
Diagnosis and management of dementia: review	Journal of the American Medical Association	2019	61.75
Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model	Science	2018	59
Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines	Medicine and Science in Sports and Exercise	2019	56.5
Leisure activities and the risk of dementia in the elderly	New England Journal of Medicine	2003	55.5
Effects of aerobic exercise on mild cognitive impairment: a controlled trial	*Archives of Neurology*	2010	55.23
Bridging animal and human models of exercise-induced brain plasticity	Trends in Cognitive Sciences	2013	52.2

neuroscience and gerontology. The top three Web of Science categories are neuroscience, geriatrics gerontology, and clinical neurology. In addition, the top 15 categories include sport science, psychology, behavioral science, biochemistry molecular biology, and rehabilitation. This finding suggests that the exercise-based rehabilitation and prevention of AD are typically multidisciplinary collaborative effort. The etiology of AD is closely related to neuroscience and aging (Atri, 2019; Ribaric, 2022). Meanwhile exercise intervention and prevention belong to the category of sports science and rehabilitation, and their mechanism research involves behavior, cognition, physiology, and biochemistry. Therefore, establishing a multidisciplinary team to conduct exercise intervention and prevention of AD is beneficial.

The quantitative and visual analyses of countries/regions distribution show that the United States is the leading country in the field of exercise-based rehabilitation and prevention of AD, with the highest number of studies (424 publications), citations, centrality, and *h*-index. This result may be due to the internal drive caused by its aging society and the large amount of scientific research capital investment (the United States Department of Health Human Services, National Institutes of Health, and National Institute on Aging are the top three funders for this field, and all of which are United States

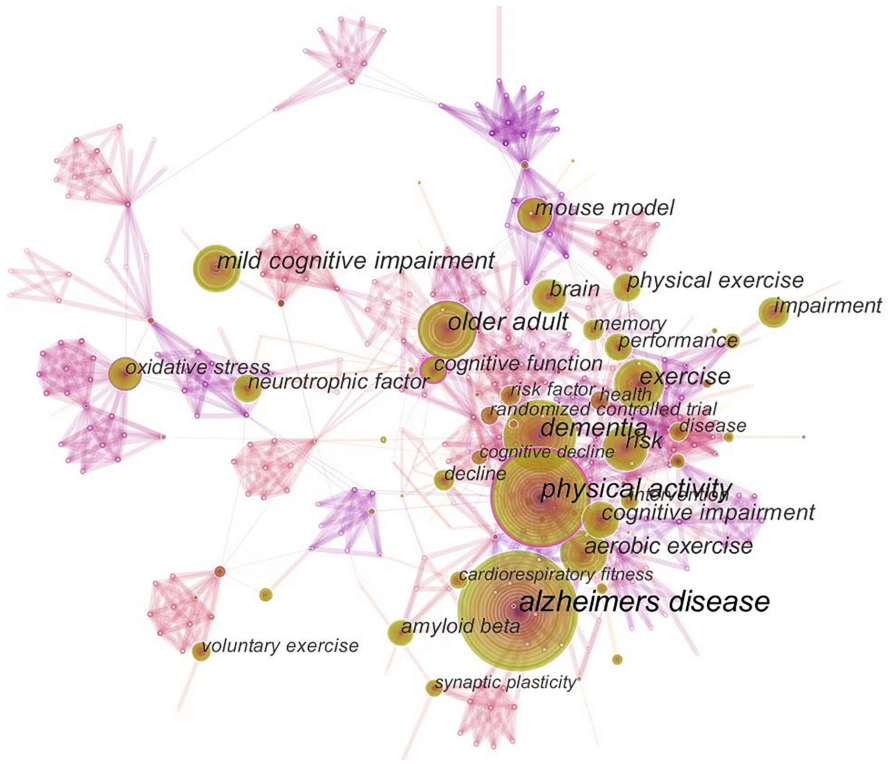


FIGURE 5
The map of keywords. The circle size and the link illustrated the frequency and relevance of keywords, respectively.

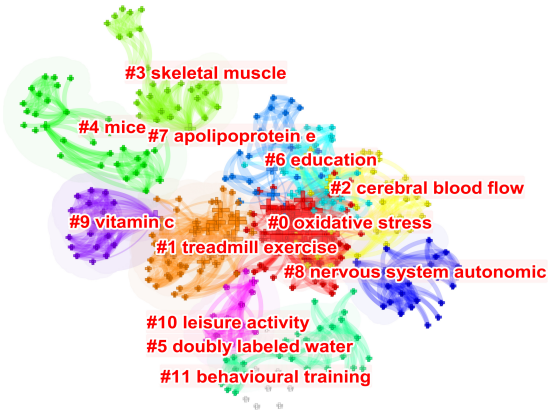


FIGURE 6
The cluster diagram for the keywords.

institutions). Some Asian countries, such as China and Japan, have participated in research on this field and made several achievements. Among them, China has performed well in the number of published papers (137 publications) and the support of funds (National Natural Science Foundation of China, ranked 4th among funding institutions). However, China exhibits no advantages in average per item, citations, and *h*-index, indicating that the quality of research should be further improved. The analysis of the reasons may be as follows: the density and breadth of international cooperation in this field is insufficient for China, and iconic research institutions are lacking. Therefore, high-quality research output is also lacking. This situation may limit the development of research on exercising and AD, because China, the world's most populous country, is also a country with rapidly increasing aging population, and thus, it urgently needs to make breakthroughs in this field. Therefore, we suggest that European and American research institutions should strengthen cooperation and exchanges with China and institutions to promote the progress of research on the exercise rehabilitation and prevention of AD worldwide.

From the perspectives of author contribution and co-citation, the author's co-occurrence chart (**Figure 4**) shows numerous nodes, and the connection between clusters was relatively close, indicating a high number of international researchers in this field. However, the research direction was relatively scattered. As shown in **Table 3**, Yu F (24 publications, 321 citations, and 11 *h*-indexes), an American researcher from the University of Minnesota, published the largest number of literatures. He began studying the effects of exercise on AD in 2006. This author believes that physical activity and exercise can prevent or relieve the cognitive and functional impairments

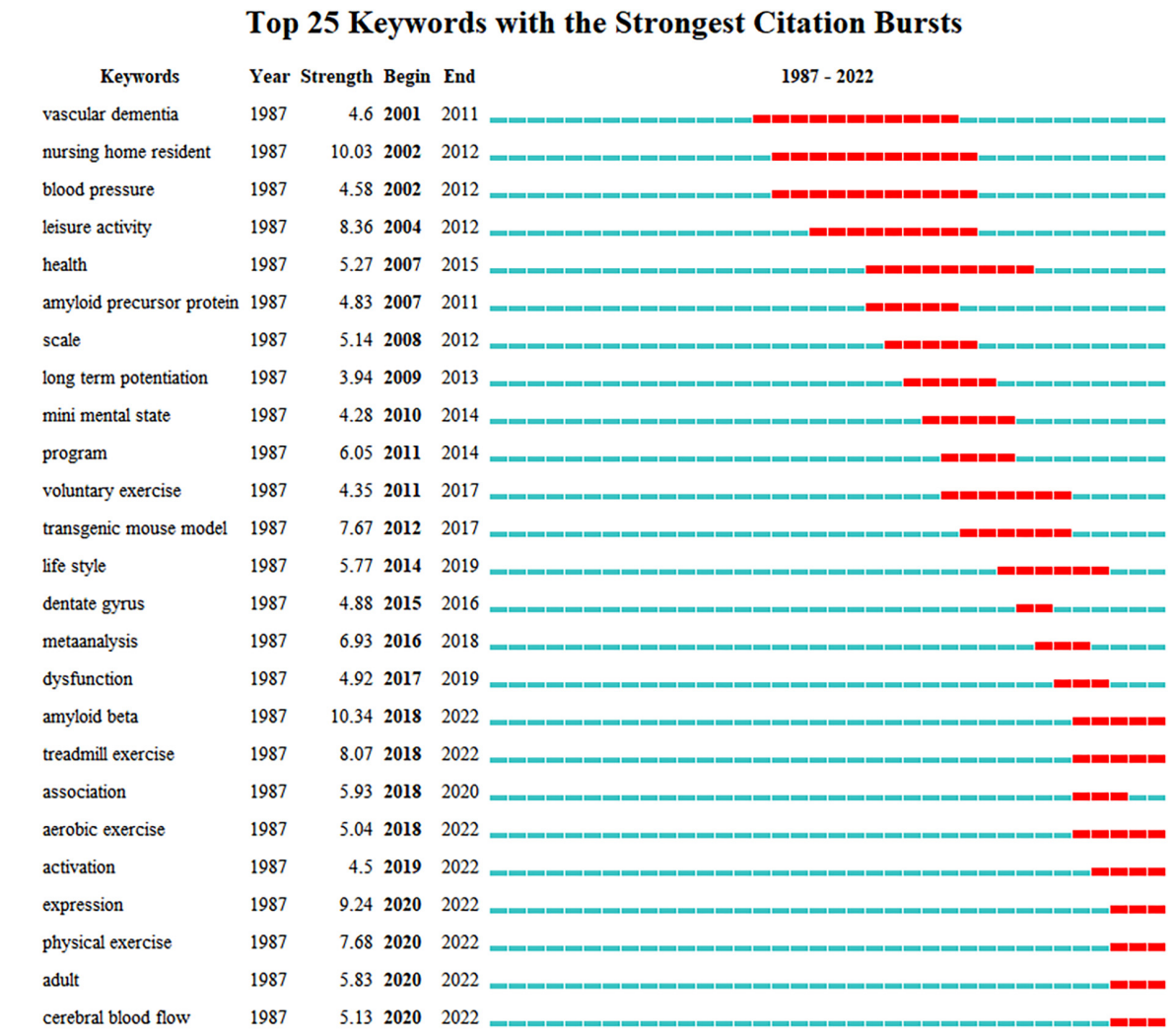


FIGURE 7
The keywords with the strongest citation bursts of publications. Each blue or red short line represents a year, and a red line stands for a burst detected year.

brought by AD because exercise may improve the pathogenesis of AD and stimulate the brain plasticity of patients (Yu et al., 2006; Gronek et al., 2019; Zong et al., 2022). Another key author named Cotman CW (13 publications, 2,383 citations, and 12 *h*-indexes) had the highest citation on the basis of a high number of papers, showing a good academic influence. He has been conducting research in this area since 1999, focusing on the mechanism of exercise intervention in AD. The author believes that the main way for exercise to improve cognitive function in AD patients is to reduce Aβ deposition (Adlard et al., 2005) and alleviate the neuroinflammation caused by oxidative stress (Parachikova et al., 2008; Ionescu-Tucker and Cotman, 2021). In addition, the authors observed that exercise can restore the hippocampal function in AD patients by enhancing the expression of brain-derived neurotrophic factor (BDNF) and other growth factors that promote neurogenesis, angiogenesis, and synaptic plasticity (Intlekofer and Cotman, 2013; Berchtold et al., 2019).

Literature review

In accordance with highly cited literature, keyword co-occurrence and explosion analysis cannot only reveal the core contents and research topics of publications in a certain field but also help us learn the current research focus and development trends in this field (Zhang et al., 2022).

The effect of exercise on Alzheimer's disease

According to the keyword burst chart (**Figure 7**), five burst keywords related to exercise were found: "leisure activity," "treadmill exercise," "physical exercise," "aerobic exercise," and

"voluntary exercise." Burst keywords "treadmill exercise" and "aerobic exercise," which appeared in 2018, have continued to appear in 2022. These burst keywords indicated that exercise program is the current research hotspot of the field. The effect of exercise on AD may vary based on the pattern, intensity, and lasting duration of exercise. A meta-analysis has been conducted to compare the effects of different exercise modalities (aerobic exercise, muscle strength training, and combined training) on the function of patients with AD (Lopez-Ortiz et al., 2021). The results of the meta-analysis showed that aerobic exercise can improve the cognitive and physical functions of AD patients, whereas muscle strength training and combined training had no significant effect. The forms of aerobic exercise included in this meta-analysis were cycling, walking, treadmill, and arm ergometry. As for exercise intensity, a medium to high intensity, which was measured by maximum heart rate or heart rate reserve, was usually used. A certain evidence indicates that high-intensity interval training is more beneficial than moderate-continuous exercise training for slowing down the progression of AD. The former can produce higher lactate levels, which elicit larger increases in BDNF, which participates in the neurotrophic signaling pathways of learning and memory function improvement (Boyne et al., 2019; Antunes et al., 2020). However, the study of Jahangiri et al. (2019) supports moderate and regular exercise, and they considered that high-intensive exercise will lead to excessive stress response, which may cause the symptoms of cognitive impairment. In addition, we summarized this meta-analysis and observed that the training time ranged from 30 to 90 min, and training lasted for 2–3 times a week. The total time of intervention ranged from 9 weeks to 9 months. In animal studies, we observed that most of the literature related to physical activity for AD used treadmill exercise (da Costa Daniele et al., 2020). Although numerous works have been conducted on the mechanism research of exercise benefits on AD, no study compared the different effects of various intensities, frequencies, and durations on the mechanism. Further studies evaluating differences in exercise programs are necessary.

Potential mechanism of exercise for Alzheimer's disease

First, we ranked the top 10 references in terms of the number of citations to identify references that may be important in exploring the frontier knowledge base of research. As indicated in **Table 3**, the paper titled, "Effect of physical activity on cognitive function in older adults at risk for Alzheimer's disease: a randomized trial," published by Lautenschlager et al. (2008) in the Journal of the American Medical Association (IF = 56.274) in 2008 was cited 1,033 times. This paper reports the first randomized controlled trial to determine whether physical activity reduces the incidence of cognitive decline among high-risk elderly population. The final results suggested that 6 months of physical activity improved the cognitive performance of AD subjects during the follow-up period of 18 months. This study laid the foundation for subsequent related research. Among the top ten papers cited average per year, "Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model," was published in Science (IF = 47.728) in 2018 (Choi et al., 2018) and "Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models," was published in Nature Medicine (IF = 53.44) in 2019 (Lourenco et al., 2019). Both papers focused on and explained the neuroprotective effects of exercise on AD from the perspectives of irisin, neurogenesis, and BDNF. In summary, we determined that the research trend of exercise and AD in recent years has shifted from discussing the influence of exercise on cognitive function to exploring the mechanism of exercise that improves cognitive function in AD patients. The current trend focuses on the neuroprotective effect of exercise.

From the keyword burst chart (**Figure 7**), the keywords with the highest burst value was "amyloid beta" (bursts strength value 10.03), and the burst has continued since 2018. This finding suggests that exercise clearance "amyloid beta" may be the research front of the mechanism research of exercise intervention in AD. The presence of neurotoxic amyloid plaques, which Aβ forms as a result of a pathological cascade reaction, is considered the gold standard for AD neuropathological diagnosis (Liang et al., 2022). The abnormal accumulation of extracellular Aβ causes evident neurotoxicity, which can induce brain inflammation, mitochondrial dysfunction, oxidative stress induced microglia activation, and other toxic side effects. This condition will exacerbate neuronal loss and promote the development of AD (Kinney et al., 2018). Therefore, removing the excessive accumulation of Aβ is an important train of thought in the treatment of AD. Exercise is considered an effective way to prevent and treat AD; such effectiveness may be related to the capability of exercise to participate in the clearance of the excessive accumulation of Aβ in the brain (Radak et al., 2010; Aczel et al., 2022). Adlard et al. (2005) published the study titled, "voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease," in the Journal of Neuroscience, and it was possibly the earliest study on the clearance of Aβ by exercise. The authors used TgCRND8 mice as animal models to observe the interaction between 5 months of voluntary exercise and AD cascade. Exercise caused extracellular hippocampus Aβ plaque reduction, and this result was related to the reduction of cortex Aβ 1–40 and Aβ 1–42. The authors believed that this mechanism is mediated by changes in the amyloid precursor protein processing after a short-term exercise. Recent systematic reviews have summarized the effects of involuntary chronic physical exercise on beta-amyloid protein in experimental models of AD. The results

from 36 included studies showed that regular physical exercise resulted in positive changes in amyloid precursor protein processing through different signal pathways, thus proving the anti-amyloid effect of exercise (Vasconcelos-Filho et al., 2021). In addition, different studies attempted to clarify the mechanism by which exercise reduces Aβ deposition to protect AD from different perspectives, such as Aβ generation, Aβ transporters crossing the blood–brain barrier, autophagy, degrading enzymes, etc. However, the mechanism by which exercise reduces Aβ deposition has remained unclear until now, therefore becoming the focus of attention of researchers.

Aβ deposition plays a key role in the progression of AD, and other pathological events (including mitochondrial dysfunction, oxidative stress, or neuroinflammation) contribute significantly to its development (Tan et al., 2021). According to the keyword centrality and cluster analysis results (**Figures 5**, **6**), studies related to "oxidative stress" have attracted wide attention. Oxidative stress causes mitochondrial dysfunction, which is associated with the development of AD-related pathology (Yu et al., 2018). In addition, oxidative stress promotes Aβ deposition during the development of AD. The excessive accumulation of Aβ induces oxidative stress of microglia, resulting in chronic neuroinflammation and further aggravating the oxidative stress-induced nerve damage (Liang et al., 2021). Exercise is closely related to the improved antioxidant capacity of the brain and reduced oxidative stress-induced injury (Liang et al., 2021). TgF344-AD rats were used as models to observe the effect of 8 months of exercise pre-training on AD. The results showed that exercise pre-training reduced Aβ deposition and tau hyperphosphorylation, inhibited mitochondrial dynamic imbalance, and significantly inhibited oxidative stress and neuroinflammation in AD rats (Yang et al., 2022). Another study (Gholipour et al., 2022) reported the effect of high-intensity interval training on AD. The results showed that high-intensity interval training can reduce hippocampal oxidative stress and Aβ deposition, reduce neuronal damage, and improve AD symptoms. Based on the above information, exercise training can be used as a potentially effective strategy to improve the activity of antioxidant enzymes in neurons, reduce the release of mitochondrial reactive oxygen species and levels of oxidative stress and neuronal apoptosis, and ultimately delay the progression of AD.

Strength and limitations

Our study has several strengths. To our best knowledge, this study is the first bibliometrics analysis to evaluate hotspots and frontier in the field of exercise and AD research. Publications were searched from the SCI-E of Web of Science. A total of 396 scholarly journals with 1,104 publications on exercise and AD research were used in our study. This research included the analysis of the number of publications, citations, h-index, subject categories of Web of Science, collaboration analysis among countries/institutions, co-citation analysis of references/authors, and analysis of keywords.

This study still has some limitations. First, we only searched the literature in the SCI-E of the Web of Science Core Collection database, since different databases have different properties, such as citation counting and export formats. Second, English papers accounted for 98% of the included papers in our study, because Web of Science database mainly indexed papers written in English. This may lead us to ignore relevant research published in other languages. Third, some recent publications of high quality may not received enough attention because of low citation frequency, whilst older articles have accumulated more citations. This may undermine the significance of more recently-published articles. Therefore, readers should be aware that all these may lead to bias for our results.

Conclusion

This study collected relevant literature on exercise and AD, analyzed information of major countries/regions, institutions, and core journals in this field, and summarized research hotspots and frontiers. The number of publications on exercise and AD has been increasing rapidly, especially in the past 10 years. Most of these publications are associated with neurosciences, geriatrics, and gerontology, but they also involve sports science, psychology, behavioral science, and rehabilitation. From this perspective, enhanced inter-agency and interdisciplinary cooperation is essential for the progress and development of this scientific field. The countries in America and Europe, especially the United States, dominate in terms of publication and research collaboration on exercise rehabilitation of AD. Asian countries need to actively seek international cooperation to enhance their global influence for the further development of this field. "Amyloid beta," "oxidative stress," and "exercise program" are considered the current research hotspots and frontiers in this field. Although the included studies contribute to the understanding of the underlying pathways of exercise on AD, the mechanism remains unclear. In addition, no study compared the different effects of various intensities, frequencies, and durations on the related mechanism. Further studies evaluating differences in exercise programs are necessary.

Author contributions

JG and BC contributed to conception and design of the study and revised the manuscript. YF, BC, and WZ collected and analyses the data. BC, JG, YF, and GS wrote the manuscript. All authors read and approved the final version of manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect and safety of Tai Chi on bone health in postmenopausal women: A meta-analysis and trial sequential analysis

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Background: Tai Chi may be a promising exercise to prevent and control bone loss in postmenopausal women. This meta-analysis and trial sequential analysis aimed to evaluate the effect and safety of Tai Chi on bone health in postmenopausal women.

Method: Seven databases were searched from their inceptions to 11 May 2022 to collect randomized controlled trials (RCTs) investigating the effect and safety of Tai Chi on bone health in postmenopausal women. Two independent reviewers identified the eligible studies, extracted data, and assessed the risk of bias of included studies using the revised Cochrane risk-of-bias tool for randomized trials. The primary outcome was the bone mineral density (BMD), and secondary outcomes included bone turnover markers and calcaneus quantitative ultrasound. Subgroup analyses were conducted based on the duration of Tai Chi. Sensitivity analyses and publication bias assessment were performed. RevMan software (version 5.4.1) and R software (version 3.6.1) were used for data synthesis. The certainty of evidence was rated with the Grading of recommendations assessment, development, and evaluation (GRADE) system. We also performed the trial sequential analysis to evaluate the reliability of the evidence.

Results: A total of 25 reports involving 24 studies were included. Four studies were considered as high overall risk of bias, and the rest were some concerns. Among included studies, there were three comparisons including Tai Chi vs. non-intervention, Tai Chi vs. other exercises, and Tai Chi plus nutraceutical vs. nutraceutical. Compared with non-intervention, Tai Chi was more effective to improve BMD of lumbar spine (MD = 0.04, 95% CI 0.02 to 0.07, I^2 = 0%, low certainty), femoral neck (MD = 0.04, 95% CI 0.02 to 0.06, I^2 = 0%, low certainty), and trochanter (MD = 0.02, 95% CI 0.00 to 0.03, I^2 = 0%, very low certainty), but there was no significant difference in increasing the BMD of Ward's triangle (MD = 0.02, 95% CI −0.01 to 0.04, I^2 = 0%, very low certainty). Trial sequential analysis showed

that the effect of Tai Chi vs. non-intervention on the BMD of lumbar spine and femoral neck was reliable, but the effect on the BMD of trochanter and Ward's triangle needed further verification. The subgroup analyses suggested that Tai Chi training for over 6 months had greater improvement in BMD of the lumbar spine, femoral neck, and trochanter than non-intervention. No significant differences were observed in the above outcomes of Tai Chi vs. other exercises, and Tai Chi plus nutraceutical vs. nutraceutical. There was insufficient evidence to support the effect of Tai Chi on bone turnover markers and calcaneus quantitative ultrasound. Few Tai Chi relevant adverse events occurred.

Conclusion: Tai Chi may be an optional and safe exercise for improving BMD loss in postmenopausal women, and practicing Tai Chi for more than 6 months may yield greater benefits. However, more rigorously designed RCTs are required to verify the benefits and to explore the optimal protocol of Tai Chi exercise for bone health.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=309148, identifier: CRD42022309148.

KEYWORDS

Tai Chi, post-menopause, BMD, meta-analysis, trial sequential analysis

Introduction

Post-menopause is a period of women's life following the permanent cessation of the menstrual cycles, during which time the women's bone health is threatened due to the decrease and cessation of ovarian estrogen secretion (Cauley, 2015). Bone mineral density (BMD) decreases rapidly during the menopause transition and continues to decline in post-menopause. According to a cohort study involving 1,038 women (Shieh et al., 2022), each additional year after the final menstrual period was associated with 0.006 and 0.004 g/cm^2 lower BMD of lumbar spine and femoral neck, respectively. The 10-year cumulative loss of BMD was 10.6% at the lumbar spine and 9.1% at the femoral neck (Cauley, 2015). Low BMD was one of the most important determinants of fracture risk (Barron et al., 2020). Approximately 30–40% of postmenopausal women were reported to have osteoporosis or low bone mass (Wright et al., 2014; Thulkar et al., 2016), and more than 30% experienced at least one fracture (Lippuner et al., 2009; Si et al., 2015; Jiang and Ni, 2016). Almost every fracture was associated with an increased risk of premature mortality (Center, 2017). Researchers found mortality increased over 2.43- and 1.82-fold following hip fractures and vertebral fractures in community-dwelling older women, respectively (Bliuc et al., 2009). Therefore, effective intervention to prevent and attenuate bone loss in postmenopausal women is necessary.

Bone is a dynamic tissue, with a capacity to remodel its material and structural properties to adapt mechanical loading (Feng and McDonald, 2011). Increased loading stimuli and vigorous muscular activity can augment bone mass and promote bone health (Wang et al., 2020). Therefore, exercise is recommended to maintain bone mass or slow bone loss for postmenopausal women (Daly et al., 2019; Kanis et al., 2019; Society, 2021). High impact and high weight-bearing exercises were found to be beneficial for postmenopausal women to increase BMD (Martyn-St James and Carroll, 2006; Kelley et al., 2012; Zhao et al., 2015; Kitsuda et al., 2021). However, due to safety and operability concerns, it's difficult to implement such exercise patterns for post-menopause women.

Tai Chi, a traditional Chinese exercise, is becoming popular around the world. According to the theory of traditional Chinese medicine, Tai Chi can promote the circulation of Qi and blood. Tai Chi is characterized by coordinated body posture and movements, deep rhythmic breathing, and meditation (Yeung et al., 2018). During Tai Chi practice, practitioners perform a series of slow and rhythmic circular motions and a lot of half-squats, and gravity-shift movements, which may introduce dynamic loading on bone. Evidence showed Tai Chi can prevent falls, enhance flexibility and improve balance function with good security (Del-Pino-Casado et al., 2016; Zhong et al., 2020). In addition, it is an easily acceptable exercise that can be practiced anywhere and anytime without special equipment. Therefore, Tai Chi may be a promising exercise to prevent and reduce bone loss in postmenopausal women.

Recently, Zhang et al. (2021) conducted a network meta-analysis and found mind-body exercise (e.g. Tai Chi, yoga, dance, Wuqinxi) might be an optimal exercise type to increase

the BMD of the lumbar spine and femoral neck among patients with osteoporosis and osteopenia. Previous two systematic reviews (SRs) of Tai Chi for BMD in postmenopausal women had been published in 2016 (Sun et al., 2016) and 2017 (Liu and Wang, 2017) respectively, but their conclusions were contradictory. As more relevant trials have been conducted in recent years, we performed this meta-analysis of randomized controlled trials (RCTs) to update the evidence about the effect and safety of Tai Chi on bone health in postmenopausal women and used the trial sequential analysis (TSA) to assess the reliability of the evidence.

Materials and methods

Study registration

The protocol of this meta-analysis and TSA has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=309148) (Registration No: CRD42022309148). We conducted this meta-analysis and TSA according to A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) and reported in the light of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement (Appendix 1).

Search strategy

Reviewers (YXL and DLZ) searched PubMed, Embase, The Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), Chinese Biomedical Literature Database (CBM), and Wanfang Database from their inceptions to 11 May 2022. According to the retrieval rules of each database, the search strategies were developed by combining Medical Subject Headings (MeSH) and free text words of Tai Chi and bone density. To identify more potential studies, we manually searched gray literature, reference lists of identified studies, and relevant registration websites (ClinicalTrials.gov and www.chictr.org.cn), and consulted experts in this field. The full search strategies for all databases are shown in Appendix 2.

Inclusion criteria

Type of studies

We included RCTs published in Chinese and English which studied the effect or/and safety of Tai Chi on bone health in postmenopausal women.

Type of participants

Postmenopausal women (author reported) or women (≥ 50 years old) (Wang et al., 2021) were included. There was no restriction on race or nation.

Type of interventions

We included RCTs that used Tai Chi (e.g. Tai Chi Quan, Tai Chi push hands, Tai Chi sword, etc.), or Tai Chi combined anti-osteoporosis medications (e.g. bisphosphonates, denosumab, calcitonin, etc.) or nutraceutical (e.g. calcium and vitamin D, etc.) as the experimental group. There were no restrictions on the duration and frequency of Tai Chi.

Type of comparators

Participants in the control group received non-intervention, anti-osteoporosis drug, nutraceutical, or other exercises (e.g. walking, running, resistance training, etc.).

Outcome measurements

The primary outcome included BMD using dual-energy x-ray absorptiometry (lumbar spine, femoral neck, trochanter, Ward's triangle, and total hip). Secondary outcomes were indicators related to bone health, including: 1) Calcaneus quantitative ultrasound: BMD of the calcaneus, bone quality index, broadband ultrasound attenuation, speed of sound; 2) Bone turnover markers: serum bone formation markers: procollagen type I N-terminal propeptide (PINP), alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BAP), osteocalcin (OSC), etc.; serum bone resorption markers: C-terminal telopeptide of type I collagen (CTX), tartrate-resistant acid phosphatase (TRAP), etc.; 3) Tai Chi-related adverse events.

Exclusion criteria

Studies were excluded if they met any of the following conditions: 1) Cross-sectional studies, reviews, case-control studies, N of one RCTs (Li et al., 2022); 2) Full text or the data cannot be obtained through various approaches; 3) Repeated publications.

Study selection

All the retrieved records were imported into Endnote software (X9), and duplicates were removed. Two independent reviewers (LXZ and TL) screened the rest records by reading titles and abstracts. Then, full texts of all potential studies were obtained and scrutinized. After that, the two reviewers cross-checked the included studies. In case of disagreements,

a third reviewer (JL) was involved. If there were multiple publications from the same study, we included the publication with more complete data or included multiple publications with complementary data.

Data extraction

Two reviewers (CZJ and RF) independently extracted the following data: 1) Study characteristics: first author, publication year, country, sample size; 2) Participants' characteristics at study level: age, menopausal duration; 3) Interventions: frequency, duration, and style of Tai Chi; 4) Comparators: type, dosage, frequency and duration of medication or nutraceutical; frequency, duration, type of other exercises; 5) Outcomes: primary outcome, secondary outcomes, and adverse events; 6) Information related to the risk of bias. Then two reviewers cross-checked the extracted data to ensure no mistakes. We resolved discrepancies through group discussion or with the participation of a third reviewer (JL). For multi-arm RCTs, we included the eligible comparisons or extracted the comparison with inferior effect size to obtain more conservative results.

We contacted the original authors *via* email for more information if the necessary data was missing or incomplete. If there was no reply, we analyzed the available data.

Risk of bias assessment

Two independent reviewers (XBL and TYL) used the revised Cochrane risk-of-bias tool for randomized trials (ROB 2) to assess the risk of bias of included studies from five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was judged as "low risk," "some concerns," or "high risk" according to corresponding algorithms. After learning the Cochrane risk-of-bias tool and pre-assessed, two independent reviewers assessed the risk of bias and then cross-checked. Two reviewers discussed the disagreements or consulted with a third reviewer (RJJ).

Data analysis

Among the included studies, three comparisons were involved, including Tai Chi vs. non-intervention, Tai Chi vs. other exercises, and Tai Chi plus nutraceutical vs. nutraceutical. For continuous variable, we used the post-intervention data. Since included outcomes for meta-analysis used the same units, we calculated the mean difference (MD). We conducted descriptive analysis for the data which couldn't be quantitatively analyzed. Heterogeneity was measured by the chi-squared test and I^2 statistic. When $P < 0.1$ or I^2 values $> 50\%$, the random-effect model was used to pool data. Otherwise, the fixed-effect model was performed. Forest plots and tables were utilized to present the pooled results. RevMan software (version 5.4.1) and R software (version 3.6.1) were used for data synthesis.

Subgroup analysis

Subgroup analyses of Tai Chi vs. non-intervention were conducted according to the duration of Tai Chi ($\leq$ 6 or $>$ 6 months).

Sensitivity analysis

We performed sensitivity analysis by eliminating studies one by one to verify the robustness of the results.

Publication bias

We used a funnel plot and *Egger's* test to detect publication bias when $\geq$10 studies with the same outcome were included in the analysis.

TSA

We conducted TSA for primary outcome using the TSA software (version 0.9.5.10-Beta). Fixed effects model with a maximum type I error of 5%, and a maximum type II error of 20% (80% power) were applied. Two-sided significance testing boundaries, required information size, trial sequential monitoring boundaries, futility boundaries, and cumulative z-score were presented in the TSA graph. The situation that included sample size over required information size, or the cumulative Z curve crossed the trial sequential monitoring boundaries or futility boundaries indicated that the results were reliable.

Certainty of evidence

We applied the Grading of recommendations assessment, development, and evaluation (GRADE) system to assess the certainty of evidence. Each outcome was evaluated from the following five aspects: limitations, inconsistency, indirectness, imprecision, and publication bias. Then the certainty of evidence was accordingly graded as "high," "moderate," "low," or "very low" (Balshem et al., 2011). GRADEpro (version 3.6) software was used to present the summary of findings.

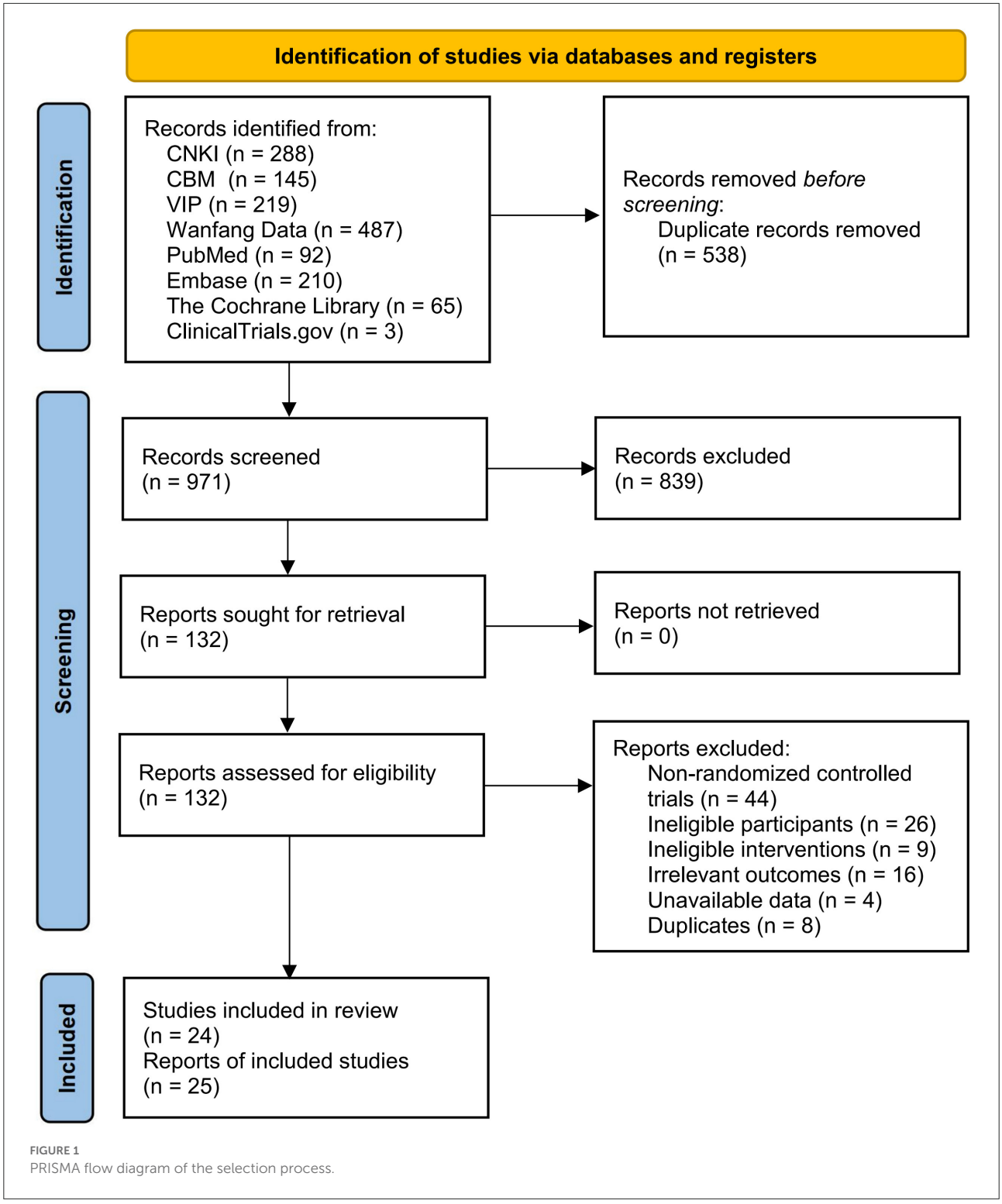


FIGURE 1
PRISMA flow diagram of the selection process.

Results

Study inclusion and characteristics

A total of 1,506 records were searched from databases and three records from websites. After removing 538 duplicated records, we further excluded irrelevant 839 records. Finally, we included 25 reports (Qin et al., 2000; Zhou, 2003, 2004; Chan et al., 2004; Zhou et al., 2005; Gao, 2006; Woo et al., 2007; Mao, 2009; Liu, 2010; Shen et al., 2010, 2012; Song et al., 2010, 2018; Zhu, 2011; Wayne et al., 2012; Kuo et al., 2014; Yu et al., 2014; Lu and Song, 2015; Wang et al., 2015; Xue, 2015; Ye et al., 2016; Xu, 2017; Cheng and Ba, 2020; Zhang, 2020; Zou, 2020), involving 24 studies through full-text reading (Figure 1). The list of excluded records with reasons is provided in Appendix 3. Shen et al. (2010, 2012) pertained to the same study. Among included studies, two studies was undertaken in America (Shen et al., 2010, 2012; Wayne et al., 2012), one from South Korea (Song et al., 2010), and the others were in China. Eight reports were published in English journals (Chan et al., 2004; Woo et al., 2007; Shen et al., 2010, 2012; Song et al., 2010; Wayne et al., 2012; Wang et al., 2015; Cheng and Ba, 2020), 9 were in Chinese journals (Zhou, 2003, 2004; Zhou et al., 2005; Mao, 2009; Yu et al., 2014; Lu and Song, 2015; Ye et al., 2016; Xu, 2017; Song et al., 2018), six were master's theses (Gao, 2006; Liu, 2010; Zhu, 2011; Xue, 2015; Zhang, 2020; Zou, 2020), and two were conference abstracts (Qin et al., 2000; Kuo et al., 2014). The duration of Tai Chi practice ranged from 2 to 24 months, and sample size varied from 16 to 344. Sixteen studies evaluated the BMD by dual-energy x-ray absorptiometry (Qin et al., 2000; Zhou, 2003, 2004; Chan et al., 2004; Zhou et al., 2005; Woo et al., 2007; Mao, 2009; Song et al., 2010, 2018; Wayne et al., 2012; Kuo et al., 2014; Yu et al., 2014; Wang et al., 2015; Ye et al., 2016; Xu, 2017; Cheng and Ba, 2020), six used calcaneus quantitative ultrasound (Gao, 2006; Liu, 2010; Zhu, 2011; Lu and Song, 2015; Zhang, 2020; Zou, 2020), and four observed the change of bone turnover markers (Liu, 2010; Shen et al., 2010, 2012; Wayne et al., 2012; Xue, 2015). Table 1 provides the characteristics of included studies.

Risk of bias

Seven studies (Woo et al., 2007; Song et al., 2010, 2018; Wayne et al., 2012; Lu and Song, 2015; Ye et al., 2016; Xu, 2017) specified the methods of randomization, and all studies did not provide information about allocation concealment. Seventeen studies (Qin et al., 2000; Zhou, 2003; Chan et al., 2004; Woo et al., 2007; Liu, 2010; Shen et al., 2010, 2012; Song et al., 2010, 2018; Wayne et al., 2012; Kuo et al., 2014; Yu et al., 2014; Lu and Song, 2015; Wang et al., 2015; Xue, 2015; Ye et al., 2016; Cheng and Ba, 2020; Zhang, 2020) reported the number of drop-outs or lost to follow-up. Two (Shen et al., 2010; Wayne et al., 2012) studies performed the intent-to-treat analysis and the remaining studies used per-protocol analysis. The primary and secondary outcomes were objective indicators. Two studies (Shen et al., 2010, 2012; Wayne et al., 2012) provided the registration numbers. In summary, four studies (Qin et al., 2000; Liu, 2010; Yu et al., 2014; Ye et al., 2016) were considered as high overall risk of bias, and the rest of the studies were rated as some concerns. The results of the ROB assessment are shown in Figure 2.

Meta-analysis

BMD

Tai Chi vs. non-intervention

Compared with non-intervention group, participants in Tai Chi group had higher BMD of lumbar spine (MD = 0.04, 95% CI 0.02 to 0.07, $P < 0.0001$, $I^2 = 0\%$), femoral neck (MD = 0.04, 95% CI 0.02 to 0.06, $P < 0.0001$, $I^2 = 0\%$), and trochanter (MD = 0.02, 95% CI 0.00 to 0.03, $P = 0.04$, $I^2 = 0\%$). Notwithstanding, there was no difference between Tai Chi and non-intervention group in the BMD of Ward's triangle (MD = 0.02, 95% CI −0.01 to 0.04, $P = 0.18$, $I^2 = 0\%$) (Figure 3).

Results of BMD in the lumbar spine, femoral neck, and Ward's triangle were stable after excluding studies one by one. But the pooled result of trochanter altered to insignificant after excluding Chan et al. (2004) (MD = 0.02, 95% CI −0.00 to 0.04, $P = 0.10$, $I^2 = 0\%$) or Xu (2017) (MD = 0.02, 95% CI −0.00 to 0.03, $P = 0.11$, $I^2 = 0\%$). The plots of sensitivity analysis results are shown in Figure S1 in Appendix 4.

Three studies (Qin et al., 2000; Woo et al., 2007; Yu et al., 2014) evaluated the percentage change of BMD. No differences between Tai Chi and non-intervention group were found in the percentage change of BMD in lumbar spine (MD = 0.83, 95% CI −0.12 to 1.77, $P = 0.09$, $I^2 = 28\%$), Ward's triangle (MD = 1.81, 95% CI −0.28 to 3.90, $P = 0.09$, $I^2 = 31\%$) and trochanter (MD = −0.07, 95% CI −1.35 to 1.22, $P = 0.92$, $I^2 = 0\%$) (Figure S2 in Appendix 4). Two studies reported that the percentage change of BMD of femoral neck (Qin et al., 2000) and total spine (Woo et al., 2007) in the Tai Chi group did not differ from the non-intervention group. However, Woo et al. (2007) found that Tai Chi could attenuate greater BMD loss of total hip than non-intervention.

One study (Song et al., 2010) showed that the improvement of BMD T score of femoral neck, Ward's triangle, and trochanter was significantly higher in the Tai Chi group than that in the education program group.

Tai Chi vs. other exercises

There were no differences between Tai Chi and other exercises in increasing BMD of lumbar spine (MD = 0.01, 95% CI −0.04 to 0.07, $P = 0.63$, $I^2 = 0\%$) (Figure 4). The result did not change during sensitivity analysis (Figure S3 in Appendix 4).

TABLE 1 Characteristics of included studies.

Study	Site	Total sample size (Randomized/analyzed)	Sample size of each group (Randomized/analyzed)	Age	Intervention		Comparator		Duration	Outcome
					Type	Frequency	Type	Frequency		
Chan et al. (2004)	China (Hong Kong)	132/103	E: 67/54 C: 65/49	E: 54.4 ± 3.3 C: 53.6 ± 3.2	Yang-style Tai Chi (Quan)	50 min/time, 5 times/week	Non-intervention	NA	12 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Trochanter)
Cheng and Ba (2020)	China	44/34	E: 22/17 C: 22/17	E: 61.3 ± 2.4 C: 61.9 ± 2.5	24-style Tai Chi (Quan)	40 min/time, 5 times/week	Non-intervention	NA	12 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Ward's triangle) BMD (Trochanter)
Gao (2006)	China	48/48	E: 16/16 C1: 16/16 C2: 16/16	E: 63.8 ± 3.5 C1: 64.2 ± 3.9 C2: 64.1 ± 3.7	36-style Tai Chi (Fan)	60 min/time, 7 times/week	C1: Non-intervention C2: Dancing	C1: NA C2: 60 min/time, 7 times/week	10 weeks	BMD of calcaneus BQI BUA SOS
Kuo et al. (2014)	China (Tai Wan)	75/61	E: NI/21 C1: NI/20 C2: NI/20	NI	Tai Chi (Quan) + calcium and vitamin D supplements	NI	C1: Calcium and vitamin D supplements C2: Aerobic training + resistance training + stretching + calcium and vitamin D supplements	C1: NI C2: 60 min/time, 3 times/week	3 months	BMD (Lumbar spine) BMD (Femoral neck)
Liu (2010)	China	60/45	E: 20/16 C1: 20/14 C2: 20/15	E: 63.7 ± 3.1 C1: 62.4 ± 2.3 C2: 63.2 ± 2.8	24-style Tai Chi (Quan)	55-60 min/time, ≥ 5 times/week	C1: Non-intervention C2: Brisk walking	C1: NA C2: 100-140 steps/min, 55-60 min/time	4 months	BQI BUA SOS ALP
Lu and Song (2015)	China	70/61	E: 35/31 C: 35/30	E: 62.1 ± 5.5 C: 62.9 ± 5.3	Chen-style Tai Chi (Quan)	40 min/time, 6 times/week	Brisk walking	40 min/time, 6 times/week	12 months	BQI

(Continued)

TABLE 1 (Continued)

Study	Site	Total sample size (Randomized/analyzed)	Sample size of each group (Randomized/analyzed)	Age	Intervention		Comparator		Duration	Outcome
					Type	Frequency	Type	Frequency		
Mao (2009)	China	80/80	E1: 20/20 E2: 20/20 C1: 20/20 C2: 20/20	56.8 ± 2.9	E1: Tai Chi (Quan) E2: Tai Chi (Quan) + calcium-vitamin D chewable tablet	45-50 min/time	C1: Non-intervention C2: Calcium-vitamin D chewable tablet	C1: NA C2: 2 tablets/time, 1 time/day	5 months	BMD (Lumbar spine)
Qin et al. (2000)	China (Hong Kong)	164/99	E: 93/45 C: 71/54	NI	85-style Tai Chi (Quan)	45 min/time, 5 times/week	Non-intervention	NA	12 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Ward's triangle) BMD (Trochanter)
Shen et al. (2012)	America	171/150	E1: 42/37 E2: 38/37 C1: 44/37 C2: 47/39	E1: 58.3 ± 7.7 E2: 57.6 ± 6.7 C1: 57.6 ± 7.5 C2: 56.5 ± 5.5	E1: 24-style Tai Chi (Quan) + placebo + calcium and vitamin D supplements E2: 24-style Tai Chi (Quan)+ green tea polyphenols + calcium and vitamin D supplements	60 min/time, 3 times/week	C1: Placebo + calcium and vitamin D supplements C2: Green tea polyphenols + calcium and vitamin D supplements	C1: 1 capsule (medicinal starch)/time, 2 times/day + 500 mg elemental calcium and 200 IU vitamin D daily C2: 1 capsule (green tea polyphenols)/time, 2 times/day + 500 mg elemental calcium and 200 IU vitamin D daily	6 months	BAP TRAP

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TABLE 1 (Continued)

Study	Site	Total sample size (Randomized/analyzed)	Sample size of each group (Randomized/analyzed)	Age	Intervention		Comparator		Duration	Outcome
					Type	Frequency	Type	Frequency		
Shen et al. (2010)	America	171/171	E1: 42/42 E2: 38/38 C1: 44/44 C2: 47/47	E1: 58.3 ± 7.7 E2: 57.6 ± 6.7 C1: 57.6 ± 7.5 C2: 56.5 ± 5.5	E1: 24-style Tai Chi (Quan) + placebo + calcium and vitamin D supplements E2: 24-style Tai Chi (Quan)+ green tea polyphenols + calcium and vitamin D supplements	60 min/time, 3 times/week	C1: Placebo + calcium and vitamin D supplements C2: Green tea polyphenols + calcium and vitamin D supplements	C1: 1 capsule (medicinal starch)/time, 2 times/day + 500 mg elemental calcium and 200 IU vitamin D daily C2: 1 capsule (green tea polyphenols)/time, 2 times/day + 500 mg elemental calcium and 200 IU vitamin D daily	6 months	ALP
Song et al. (2018)	China	106/88	E: 35/28 C1: 36/31 C2: 35/29	E: 64.3 ± 3.2 C1: 64.7 ± 4.1 C2: 64.8 ± 2.9	24-style Tai Chi (Quan)	70 min/time, 5 times/week	C1: Non-intervention C2: Brisk walking	C1: NA C2: ≥ 90 steps/min, 70 min/time, 5 times/week	12 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Ward's triangle) BMD (Trochanter)

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TABLE 1 (Continued)

Study	Site	Total sample size (Randomized/analyzed)	Sample size of each group (Randomized/analyzed)	Age	Intervention		Comparator		Duration	Outcome
					Type	Frequency	Type	Frequency		
Song et al. (2010)	South Korea	82/65	E: 41/30 C: 41/35	E: 63.0 ± 7.3 C: 61.2 ± 8.0	31-style Tai Chi (Quan)	Stage 1 (1-3 weeks): 2 times/week Stage 2 (4-24 weeks): 55-65 min/time, 1 time/week at learning centre + ≥ 20 min at home daily	Self-help education program	2 hours/month	6 months	BMD (Femoral neck) BMD (Ward's triangle) BMD (Trochanter)
Wang et al. (2015)	China	79/69	E: 40/34 C: 39/35	E: 58.5 ± 3.4 C: 58.5 ± 3.4	Yang style Tai Chi (Quan)	60 min/time, 4 times/week	Non-intervention	NA	12 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Ward's triangle)
Wayne et al. (2012)	America	86/86	E: 43/43 C: 43/43	E: 58.8 ± 5.6 C: 60.4 ± 5.3	Wu/Yang style Tai Chi (Quan) + standard care	30-60 min/time, 4 times/week	Standard care (calcium and vitamin D supplements + regular exercise)	NI	9 months	BMD (Femoral neck) BMD (Total hip) BMD (Lumbar spine) CTX OSC
Woo et al. (2007)	China (Hong Kong)	90/88	E: 30/28 C1: 30/30 C2: 30/30	E: 69.7 ± 2.8 C1: 69.3 ± 3.0 C2: 69.6 ± 3.2	24-style Tai Chi (Quan)	3 times/week	C1: Non-intervention C2: Resistance exercise	C1: NA C2: 3 times/week	12 months	BMD (Total hip) BMD (Total spine)
Xu (2017)	China	86/86	E: 43/43 C: 43/43	E: 56.2 ± 5.6 C: 57.1 ± 6.0	24-style Tai Chi (Quan)	≥ 40 min/time, ≥ 6 times/week	Non-intervention	NA	12 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Ward's triangle) BMD (Trochanter)

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TABLE 1 (Continued)

Study	Site	Total sample size (Randomized/analyzed)	Sample size of each group (Randomized/analyzed)	Age	Intervention		Comparator		Duration	Outcome
					Type	Frequency	Type	Frequency		
Xue (2015)	China	344/283	E: 171/136 C: 173/147	E: 62.1 ± 7.0 C: 64.0 ± 7.3	Tai Chi (Quan) + education	30 min/time, 3-5 times/week	Education	NI	24 months	PINP CTX
Ye et al. (2016)	China	50/39	E: 25/17 C: 25/22	E: 55.4 ± 6.1 C: 57.0 ± 8.5	Tai Chi (Quan)	≥ 60 min/time, 3 times/week	Non-intervention	NA	6 months	BMD (Lumbar spine) BMD (Femoral neck) BMD (Ward's triangle)
Yu et al. (2014)	China	77/61	E: 38/30 C: 39/31	E: 59.2 ± 3.6 C: 58.5 ± 3.5	8/24/42-style Tai Chi (Quan)	60 min/time, 4 times/week	Non-intervention	NA	12 months	BMD (Lumbar spine) BMD (Trochanter) BMD (Ward's triangle)
Zhang (2020)	China	40/37	E: 20/17 C: 20/20	E: 56.3 ± 5.2 C: 55.1 ± 6.7	32-style Tai Chi (Sword)	60 min/time, 5 times/week	Non-intervention	NA	3 months	BQI BMD of calcaneus
Zhou (2003)	China	36/34	E: 12/12 C1: 12/10 C2: 12/12	E: 57.1 ± 2.7 C1: 56.0 ± 2.8 C2: 56.8 ± 2.6	Tai Chi (Push hands)	45-60 min/time, 5-7 times/week	C1: Non-intervention C2: Walking + running	C1: NA C2: 45-60 min/time, 5-7 times/week	10 months	BMD (Lumbar spine)
Zhou (2004)	China	36/36	E: 12/12 C1: 12/12 C2: 12/12	55.9 ± 2.8	24/42-style Tai Chi (Quan)	45-60 min/time, 5-7 times/week	C1: Non-intervention C2: Rope skipping	C1: NA C2: 45 min/time, 5-7 times/week	10 months	BMD (Lumbar spine)
Zhou et al. (2005)	China	64/64	E1: 16/16 E2: 16/16 C1: 16/16 C2: 16/16	57.2 ± 3.4	E1: Tai Chi (Push hands) E2: Tai Chi (Push hands) + calcium-vitamin D chewable tablet	45-60 min/time, 5-7 times/week	C1: Non-intervention C2: Calcium-vitamin D chewable tablet	C1: NA C2: 1 tablet/time, 2 times/day	6 months	BMD (Lumbar spine)

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TABLE 1 (Continued)

Study	Site	Total sample size (Randomized/analyzed)	Sample size of each group (Randomized/analyzed)	Age	Intervention		Comparator		Duration	Outcome
					Type	Frequency	Type	Frequency		
Zhu (2011)	China	16/16	E: 8/8 C1: 8/8 C2: 8/8	E: 50.5 ± 3.1 C1: 50.8 ± 2.8 C2: 51.9 ± 3.4	Tai Chi (Quan)	25 min/time, 3 times/week	C1: Non-intervention C2: Rope skipping	C1: NA C2: 0.5 min/set, 25 sets/time, 3 times/week	6 months	BUA SOS BQI
Zou (2020)	China	28/28	E: 10/10 C1: 8/8 C2: 10/10	E: 65.1 ± 4.4 C1: 65.6 ± 2.7 C2: 65.3 ± 5.2	Tai Chi (Quan)	60 min/time, 3 times/week	C1: Non-intervention C2: Resistance training	C1: NA C2: 60 min/time, 3 times/week	2 months	BMD of calcaneus

E, experimental group; C, control group; min, minutes; BMD, bone mineral density; BQI, bone quality index; BUA, broadband ultrasonic attenuation; SOS, speed of sound; PINP, Procollagen type I N-terminal propeptide; CTX, C-terminal telopeptide of type I collagen; ALP, alkaline phosphatase; TRAP, tartrate-resistant acid phosphatase; BAP, bone-specific alkaline phosphatase; OSC, osteocalcin; MD, mean difference; NA, not applicable; NI, no information.

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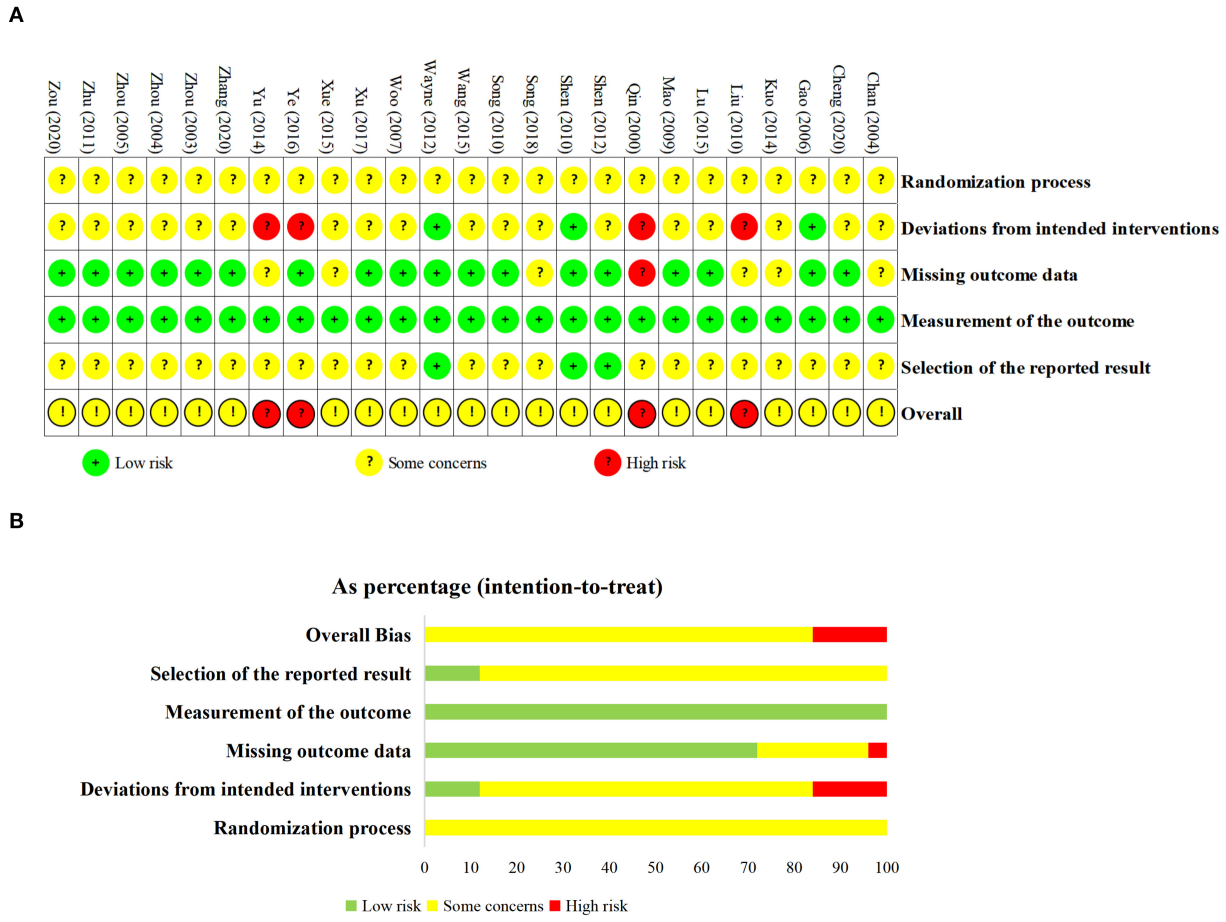


FIGURE 2
Results of risk of bias assessment. **(A)** the domain and overall judgments study-by-study; **(B)** proportions of studies at low risk, some concerns or high risk of bias for each domain.

Song et al. (2018) observed Tai Chi did not differ from brisk walking in improving the BMD of femoral neck, Ward's triangle and trochanter. Woo et al. (2007) found no difference existed in the percentage change of BMD of total hip between Tai Chi and resistance exercise group, and resistance exercise increased more BMD of total spine than Tai Chi. Kuo et al. (2014) reported that Tai Chi plus calcium and vitamin D supplements was not superior to circuit training program (aerobic training, resistance training, and stretching) plus calcium and vitamin D supplements in increasing BMD of femoral neck and lumbar spine.

Tai Chi plus nutraceutical vs. nutraceutical

No significant difference between Tai Chi plus nutraceutical and nutraceutical was found in BMD of lumbar spine (MD = 0.01, 95% CI −0.03 to 0.05, $P = 0.60$, $I^2 = 0\%$) (Figure 5). The results remained unchanged according to the sensitivity analysis (Figure S4 in Appendix 4).

Kuo et al. (2014) observed that the BMD of femoral neck did not differ significantly between Tai Chi plus nutraceutical group and nutraceutical group. Wayne et al. (2010) reported there was no difference in BMD of lumbar spine, femoral neck, and total hip between Tai Chi plus standard care and standard care group.

Calcaneus quantitative ultrasound

Tai Chi vs. non-intervention

Compared with the non-intervention group, the Tai Chi group had a significantly greater speed of sound, while had no difference in BMD of calcaneus, broadband ultrasonic attenuation, and bone quality index (Table 2). Based on sensitivity analysis, the results of speed of sound (MD = 17.09, 95% CI −1.09 to 35.28, P = 0.07, $I^2 = 0\%$) became non-significant after excluding Gao (2006) (Figure S5 in Appendix 4).

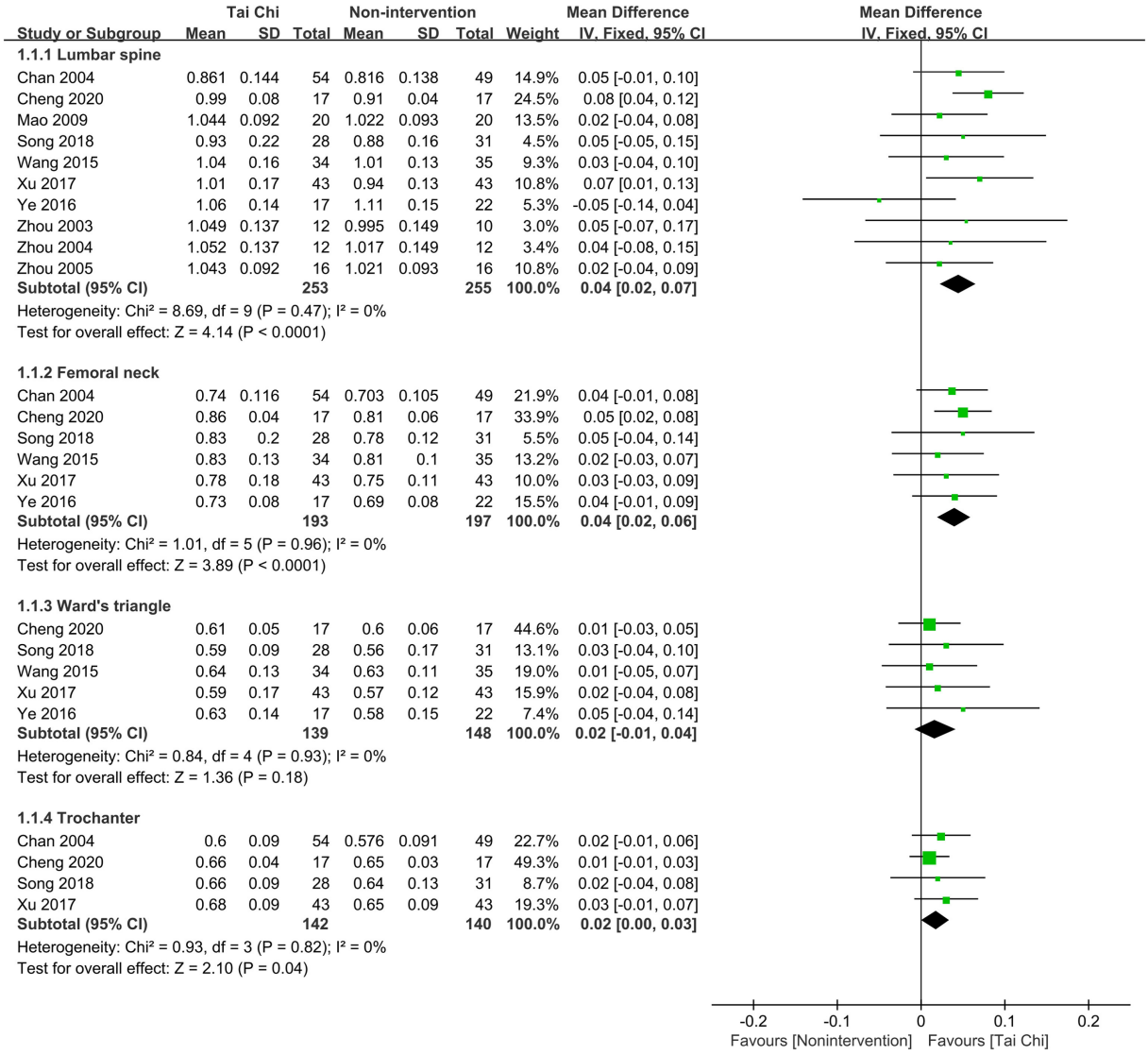


FIGURE 3
Forest plot of meta-analysis results for Tai Chi vs. non-intervention.

Tai Chi vs. other exercises

There were no significant differences in the BMD of calcaneus, speed of sound, broadband ultrasonic attenuation, and bone quality index between Tai Chi and other exercises (Table 2). And the above results did not alter after excluding studies one by one. The plots of sensitivity analysis are shown in Figure S6 in Appendix 4.

Bone turnover markers

Xue (2015) found that the Tai Chi plus education group had a higher level of serum PINP than the education group, but there was no difference in the level of serum CTX. Liu (2010) observed no difference of the comparisons of Tai Chi vs. non-intervention and Tai Chi vs. brisk walking in the level of serum ALP. Two articles reported Tai Chi plus nutraceutical group was not superior to the nutraceutical group in the level of serum ALP (Shen et al., 2010), BAP (Shen et al., 2012), TRAP (Shen et al., 2012). There were no differences between Tai Chi plus standard care and standard care in level of serum OSC (Wayne et al., 2012) and CTX (Wayne et al., 2012).

Subgroup analysis

Compared with non-intervention, practicing Tai Chi for more than 6 months showed greater BMD of the lumbar spine,

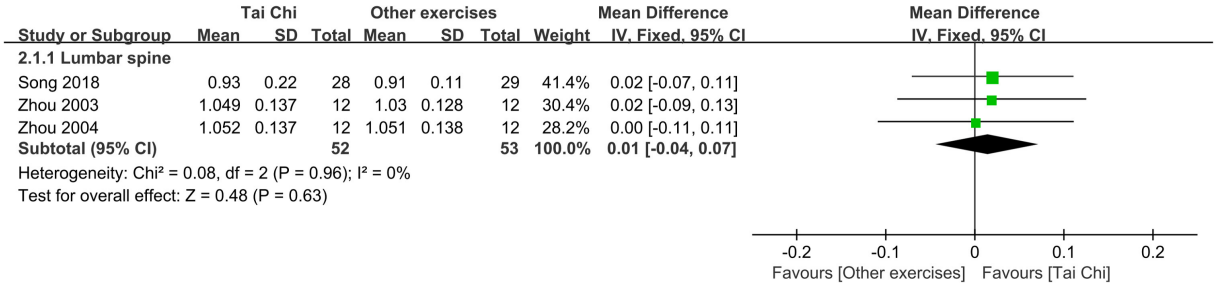


FIGURE 4
Forest plot of meta-analysis results for Tai Chi vs. other exercises.

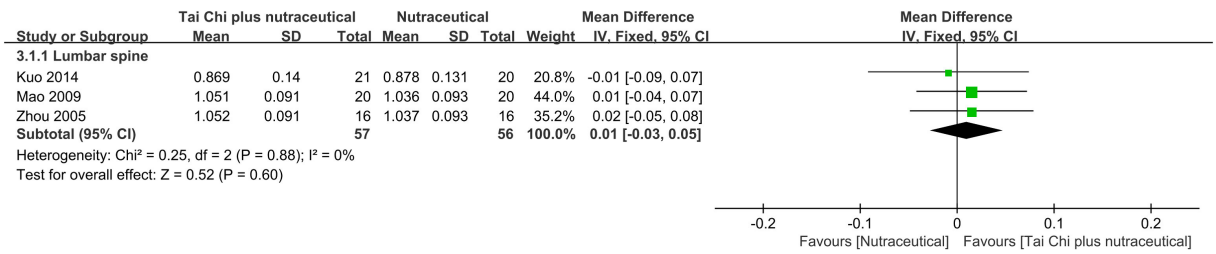


FIGURE 5
Forest plot of meta-analysis results for Tai Chi plus nutraceutical vs. nutraceutical.

femoral neck, and trochanter, while practicing it for less than or equal to 6 months was not superior to non-intervention in increasing BMD of the lumbar spine, femoral neck, and Ward's triangle (Table 3). The forest plots of subgroup analyses are shown in Figure S7 in Appendix 4.

Adverse events

Four studies (Shen et al., 2010, 2012; Wayne et al., 2012; Wang et al., 2015; Xue, 2015) stated no adverse events were attributed to Tai Chi practice. Chan et al. (2004) reported that one proximal fibular fracture occurred in the Tai Chi group due to a fall. Woo et al. (2007) observed no significant difference in the number of falls between Tai Chi, resistance exercise, and non-intervention groups during the study period. The remaining studies did not provide any information about adverse events.

TSA

According to TSA of Tai Chi vs. non-intervention, the included sample size reached the required information size in BMD of the lumbar spine (508 vs. 197) and femoral neck (390 vs. 197). Therefore, there was sufficient evidence favoring the effect of Tai Chi on BMD of the lumbar spine and femoral neck. However, the included sample size of BMD of Ward's triangle (287 vs. 785) and trochanter (282 vs. 785) did not achieve the required information size, and their cumulative Z curves did not cross the trial sequential monitoring boundaries or futility boundaries. Thus more studies are needed to verify the effect of Tai Chi on Ward's triangle and trochanter (Appendix 5).

Publication bias

Ten studies reported the BMD of lumbar spine of Tai Chi vs. non-intervention, thus we evaluated the publication bias. The funnel plot (Figure 6) and *Egger's* test ($P = 0.17$) suggested no evidence of publication bias existed.

Certainty of evidence

The results of certainty of evidence are shown in Appendix 6. The certainty of evidence for three outcomes (BMD of the lumbar spine and femoral neck of Tai Chi vs. non-intervention, and BMD of the lumbar spine of Tai Chi practicing for over 6 months vs. non-intervention) was graded as low. The evidence of the remaining outcomes was rated as very low certainty. The

TABLE 2 The meta-analysis results for outcomes of calcaneus quantitative ultrasound.

Outcome	Comparison	Number of studies	Analyzed subjects	Overall effect		Heterogeneity	
				MD (95% CI)	*P*	I^2	*P*
BMD of calcaneus	Tai Chi vs. non-intervention	3	87	0.22 (−0.22 to 0.66)	0.32	76%	0.02
	Tai Chi vs. other exercises	2	52	0.12 (−0.14 to 0.38)	0.35	0%	0.72
BQI	Tai Chi vs. non-intervention	4	115	4.19 (−3.65 to 12.03)	0.29	80%	0.002
	Tai Chi vs. other exercises	4	140	3.12 (−1.23 to 7.46)	0.16	0%	0.53
BUA	Tai Chi vs. non-intervention	3	78	6.79 (0.01 to 13.56)	0.05	57%	0.10
	Tai Chi vs. other exercises	3	79	1.30 (−5.01 to 7.62)	0.69	51%	0.13
SOS	Tai Chi vs. non-intervention	3	78	20.83 (10.44 to 31.22)	<0.0001	0%	0.65
	Tai Chi vs. other exercises	3	79	5.46 (−19.90 to 30.81)	0.67	74%	0.02

BMD, bone mineral density; BQI, bone quality index; BUA, broadband ultrasonic attenuation; SOS, speed of sound; MD, mean difference.

TABLE 3 Subgroup analysis according to the duration of Tai Chi compared with non-intervention.

Outcome	Duration of Tai Chi	Number of studies	Analyzed subjects	Overall effect		Heterogeneity	
				MD (95% CI)	*P*	I^2	*P*
BMD (Lumbar spine)	≤ 6 months	3	111	0.01 (−0.03 to 0.05)	0.65	0%	0.38
	> 6 months	7	397	0.06 (0.03 to 0.08)	<0.00001	0%	0.90
BMD (Femoral neck)	≤ 6 months	1	39	0.04 (−0.01 to 0.09)	0.12	-	-
	> 6 months	5	351	0.04 (0.02 to 0.06)	0.0004	0%	0.91
BMD (Ward's triangle)	≤ 6 months	1	39	0.05 (−0.04 to 0.14)	0.28	-	-
	> 6 months	4	248	0.01 (−0.01 to 0.04)	0.27	0%	0.96
BMD (Trochanter)	≤ 6 months	-	-	-	-	-	-
	> 6 months	4	282	0.02 (0.00 to 0.03)	0.04	0%	0.82

BMD, bone mineral density; MD, mean difference.

reasons for downgrading were mainly attributed to the risk of bias of included studies, imprecision and publication bias.

Discussion

Summary of findings

In this meta-analysis and TSA, we included 24 studies that investigated the effect and safety of Tai Chi on bone health in postmenopausal women. We found that Tai Chi training was superior to non-intervention in improving BMD of the lumbar spine and femoral neck, and the above evidence was reliable according to TSA. Tai Chi might improve the BMD of trochanter better than non-intervention, but sensitivity analysis and TSA indicated the result needed further verification. There were no significant differences in BMD of the lumbar spine, femoral neck, trochanter, and Ward's triangle when comparing Tai Chi with other exercises. Tai Chi plus nutraceuticals also did not differ from nutraceuticals in improving BMD of the lumbar spine and femoral neck. Insufficient data was obtained to support the effect of Tai Chi on bone turnover markers and calcaneus quantitative ultrasound. Subgroup analysis demonstrated that practicing Tai Chi for over 6 months improved more BMD of the lumbar spine, femoral neck, and trochanter than non-intervention. The certainty of evidence was low for three outcomes, including the BMD of the lumbar spine and femoral neck of Tai Chi vs. non-intervention and the BMD of the lumbar spine of Tai Chi practicing for over 6 months vs. non-intervention. The certainty of evidence of the rest outcomes was very low. Few Tai Chi-related adverse events occurred.

Comparison with other SRs

Previous relevant SRs hold contradictory conclusions. Liu and Wang (2017) included 350 participants from six studies

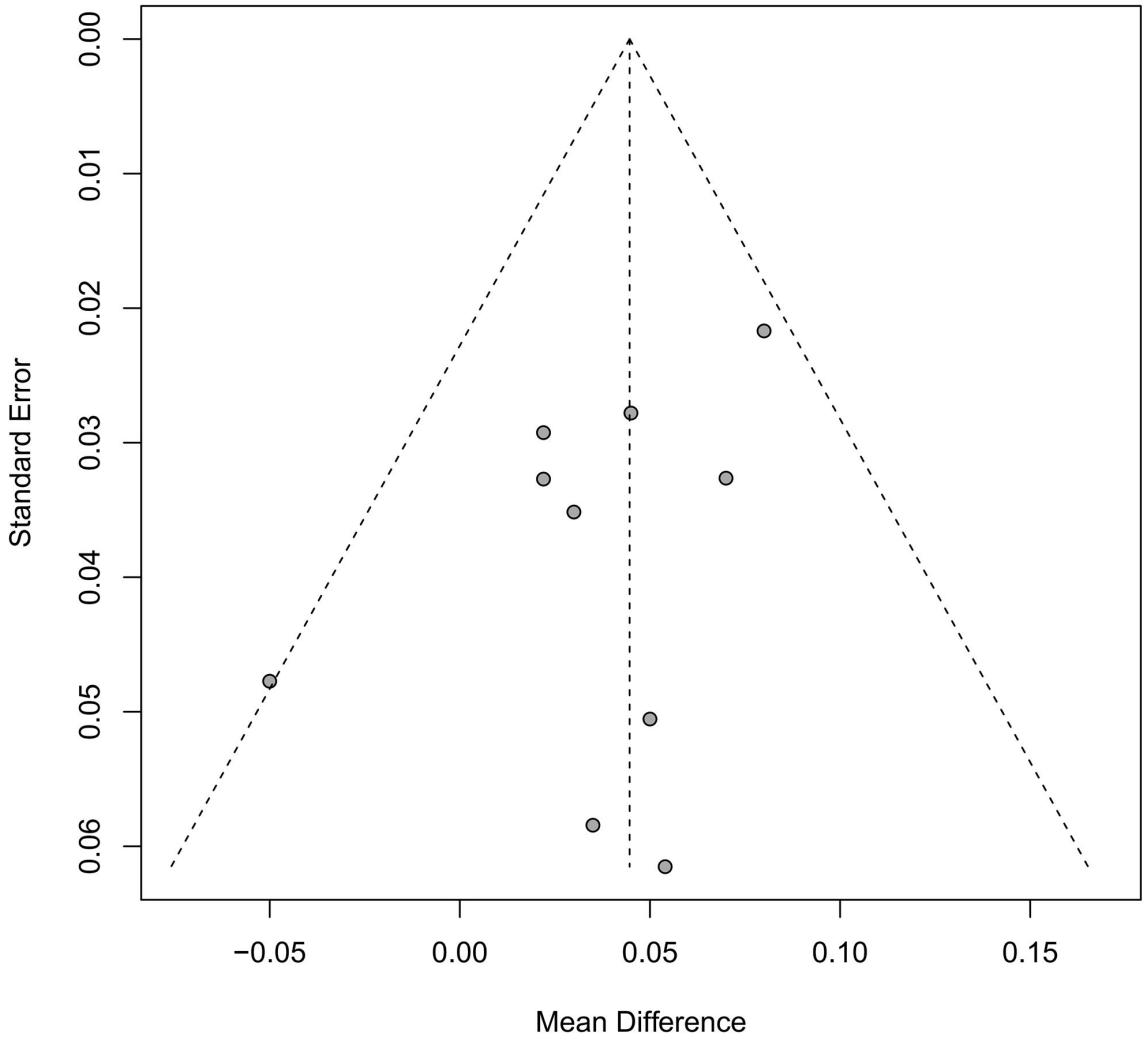


FIGURE 6
The funnel plot of BMD of lumbar spine of Tai Chi vs. non-intervention.

published up to 2016 and concluded that Tai Chi was not effective to attenuate BMD loss of the lumbar spine and femoral neck in postmenopausal women. Sun et al. (2016) pooled data from six studies before May 2015 and reported that Tai Chi had a significant effect on BMD of the lumbar spine when compared with no treatment, which was consistent with our results. While, Sun et al. (2016) included perimenopausal and postmenopausal women. Furthermore, Sun et al. (2016) double-counted the participants in the control group from a 3-arm study (Zhou, 2004), which might introduce a unit-of-analysis error (Rücker et al., 2017). Compared to Sun et al. (2016) and Liu and Wang (2017), we updated more RCTs, introduced more outcomes, validated results with TSA, and confirmed the effect of Tai Chi on BMD of lumbar spine and femoral neck in postmenopausal women.

Implications for clinical practice and future studies

During Tai Chi exercise, the practitioners hold a half-squat posture and switch between double-stance and single-stance weight-bearing, along with pivoting and twisting the trunk. Researchers found Tai Chi movements could produce vertical weight-bearing force and activate the lumbar erector spine muscle and lower extremity muscle (Chan et al., 2003; Wu and Hitt, 2005). Compared with a normal gait, the Tai Chi gait had a greater peak shear force and larger frontal-plane joint moment in the hip (Wu and Millon, 2008; Yang and Liu, 2020). Previous meta-analysis (Yang et al., 2021) demonstrated that Tai Chi could improve the thoracolumbar spine flexibility and enhance lower limb muscle strength. In our study, we found Tai Chi increased more BMD of the lumbar spine, femoral neck, and

trochanter. However, sensitivity analysis suggested the effect of Tai Chi for the BMD in trochanter was unstable. Additionally, Tai Chi was not superior to non-intervention in improving the BMD of Ward's triangle. We speculated that the reason might be related to the small sample size.

In our study, Tai Chi-induced BMD gain in the lumbar spine and femoral neck was 0.04 g/cm^2 when compared with non-intervention. Since the minimum clinically important difference (MCID) for BMD was not reported, we failed to determine the clinical significance. While Chen et al. (2006) found that an increase in lumbar spine BMD of 0.09 g/cm^2 reduced the risk of vertebral fracture in postmenopausal women with osteoporosis by 30–41%, Jacques et al. (2012) reported that among postmenopausal women with osteoporosis, patients with 3-year increase in BMD of 0–0.032 and 0.032 g/cm^2 were 0.48 and 0.27 times more likely to suffer from vertebral fracture than those with change of BMD < 0 g/cm^2, respectively. Future studies are needed to establish an MCID for BMD of different sites in postmenopausal women.

During bone remodeling, bone resorption lasts 4–6 weeks and subsequently bone formation maintains 4–5 months (Eastell and Szulc, 2017). Thus, in the previous SRs exploring the effect of exercise on BMD (Zhao et al., 2014, 2015; Kemmler et al., 2020; Mohammad Rahimi et al., 2020), they preferred to include trials in which exercise lasted for at least 6 months. Our results also found that practicing Tai Chi for less than or equal to 6 months had no effect on BMD while practicing Tai Chi over 6 months could improve more BMD than non-intervention. However, it must be acknowledged that our subgroup analysis of Tai Chi practicing for less than or equal to 6 months vs. non-intervention included few RCTs, which might decrease the statistical power.

Among included studies, the control exercises involved aerobic exercise combined with resistance training (Kuo et al., 2014), rope skipping (Zhou, 2004), running combined with walking (Zhou, 2003), and brisk walking (Song et al., 2018). These exercises were reported to improve BMD in premenopausal women (Pellikaan et al., 2018; Kemmler et al., 2020; Lan and Feng, 2022). Our results showed that Tai Chi was an effective exercise to increase BMD of lumbar spine and femoral neck, but no better than other exercises. Results of a network meta-analysis (Zhang et al., 2021) showed that mind-body exercise was the optimal exercise type to improve the BMD of the lumbar spine and femoral neck, while aerobic exercise and resistance exercise had a better effect on BMD of the total hip than mind-body exercise. It was inferred that different exercise patterns might have advantages in improving the BMD of different sites.

Previous studies demonstrated that nutraceuticals, such as calcium and vitamin D supplements might increase BMD of the lumbar spine and femoral neck among postmenopausal women with osteoporosis (Liu et al., 2020). However, nutraceuticals did not decrease the risk of fractures among community-dwelling older adults (Zhao et al., 2017). Propensity to fall was a significant risk factor for fracture. Tai Chi was reported to improve balance and reduce the incidence of falls in older people by 30% (Li et al., 2018; Zhong et al., 2020). Therefore, it's believed that a combination of Tai Chi and nutraceutical may have potential advantages to prevent falls and fractures.

Calcaneal quantitative ultrasound is an alternative approach to assess bone health, which was suggested for pre-screening and risk evaluation for osteoporosis (Gao et al., 2021; Yen et al., 2021). Notwithstanding, Frost et al. (2001) found that the precision of calcaneal quantitative ultrasound was not good enough to be used for monitoring response to treatment. Moreover, the Chinese Society of Osteoporosis and Bone Mineral Research did not recommend to use quantitative ultrasound for the evaluation of intervention efficacy (Xia et al., 2019). In our study, the results of calcaneal quantitative ultrasound seemed to be erratic, and high heterogeneity existed among studies. Therefore, researchers should combined calcaneal quantitative ultrasound with other more sensitive detection methods (e.g. dual-energy x-ray absorptiometry) to assess the response to intervention.

Due to limited included studies, we failed to confirm the effect of Tai Chi on bone turnover marks quantitatively. Xue (2015) observed that Tai Chi could improve the level of serum PINP. PINP is recommended as the preferred bone formation marker. That might indicate that Tai Chi can promote bone formation to improve the BMD. However, we found Tai Chi had no effect on other bone turnover markers. A recent SR (Kistler-Fischbacher et al., 2021) summarized that there was limited evidence to favor the effect of low-moderate-intensity exercise on bone turnover markers. Future studies can focus on this issue.

Strengths and limitations

This is the latest meta-analysis of Tai Chi for bone health in postmenopausal women and we performed TSA to explore whether the evidence in our meta-analysis was reliable. However, some limitations should be considered. Firstly, the BMD is a surrogate endpoint for fracture risk, and the MCIDs of BMD of different sites were unclear. Therefore, whether the improvement of BMD that we found would lead to eventual clinical benefits is unknown. Secondly, the optimal protocol of Tai Chi training was not yet been investigated. Thirdly, the majority of included participants were Chinese women, which might limit the general applicability of these results.

Conclusion

Tai Chi may be an optional and safe exercise for improving BMD loss in postmenopausal women, and practicing Tai Chi for more than 6 months may yield greater benefits. However, more

rigorously designed RCTs are required to verify the benefits and to explore the optimal protocol of Tai Chi exercise for bone health.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

RJ and JL conceptualized the study and provided methodological support. YL and DZ designed the search strategy. LZ and TaL selected the studies. CJ and RF extracted the data. XL and TiL assessed the risk of bias. XL, CJ, and RF wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.935326/full#supplementary-material

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Physical activities and risk of neurodegenerative diseases: A two-sample Mendelian randomization study

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Objectives: Physical activity (PA) is considered beneficial in slowing the progression and improving the neurodegenerative disease prognosis. However, the association between PA and neurodegenerative diseases remains unknown. In this study, we conducted a two-sample Mendelian randomization (MR) analysis to estimate the causal association between PA phenotypes and neurodegenerative diseases.

Materials and methods: Genetic variants robustly associated with PA phenotypes, used as instrumental variables, were extracted from public genome-wide association study (GWAS) summary statistics. Neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD), were considered outcomes. GWAS information was also obtained from the most recent large population study of individuals with European ancestry. Multiple MR methods, pleiotropy tests and sensitivity analyses were performed to obtain a robust and valid estimation.

Results: We found a positive association between moderate-to-vigorous physical activities and ALS based on the inverse variance weighted MR analysis method (OR: 2.507, 95% CI: 1.218–5.160, p = 0.013). The pleiotropy test and sensitivity analysis confirmed the robustness and validity of these MR results. No causal effects of PA phenotypes were found on PD and AD.

Conclusion: Our study indicates a causal effect of PA on the risk of neurodegenerative diseases. Genetically predicted increases in self-reported moderate-to-vigorous PA participation could increase the risk of ALS in individuals of European ancestry. Precise and individualized prescriptions of physical activity should be provided to the elderly population.

KEYWORDS

physical activity, neurodegenerative diseases, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, Mendelian randomization

Introduction

With the aging of the population, the incidence of neurodegenerative diseases is increasing. Neuronal deterioration and degeneration lead to a plethora of clinical neurological deficits, including motor dysfunction and cognitive decline (Kiernan et al., 2011; Knopman et al., 2021). The most common age-related neurodegenerative diseases include amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD), all of which exert a vast burden on individual families and society as a whole (Macpherson et al., 2017). To date, there are no curative therapies for neurodegenerative diseases. However, some modifiable factors, including physical activity (PA) and dietary habits, have been considered beneficial in slowing disease progression and improving disease prognosis (Grazioli et al., 2017; Mak et al., 2017; Gubert et al., 2020). Targeting these modifiable factors could also be effective in alleviating symptoms and relieving the abovementioned burdens.

Physical activity has recently attracted neurologists' attention due to the mounting evidence supporting its role in maintaining brain health (Stillman and Erickson, 2018; Di Liegro et al., 2019; Donofry et al., 2021). Moderate PA has been related to the regulation of neuroplasticity and cell death from molecular perspectives and cognitive and motor functions at the behavioral level (de Sousa Fernandes et al., 2020; Liang et al., 2021; Maugeri et al., 2021). PA can promote autophagy and modulate mitophagy (Almeida et al., 2018), which play an important role in the pathogenesis of neurodegenerative diseases. Therefore, PA is thought to be beneficial for individuals experiencing neurodegenerative diseases, and its protective and preventive effects have been repeatedly noticed (Karssemeijer et al., 2017; Jia et al., 2019; Fan et al., 2020; Mahalakshmi et al., 2020; Kouloutbani et al., 2022). Furthermore, it has been accepted that PA could affect the risk of developing neurodegenerative diseases (Hamer and Chida, 2009; Lian et al., 2019). However, most of the epidemiological findings were obtained from a single center or a small study population (Veldink et al., 2005; Feddermann-Demont et al., 2017). The findings are also not consistent, and thus the association between PA and neurodegenerative diseases remains controversial (Pupillo et al., 2014; Feddermann-Demont et al., 2017; Kivimaki et al., 2019). Hence, large-scale or multicenter investigations focusing on the relationship between PA and neurodegenerative diseases are still required to understand the therapeutic potential of PA.

Mendelian randomization (MR) is a burgeoning analytical approach for exploring the causal relationship between exposures and outcomes. Genetic variants robustly associated with the level of exposure are often used as instrumental variables (IVs) in MR to estimate these causative associations. Unlike traditional randomized controlled trials, MR can identify potential causative factors of diseases, provide more information on whether a particular factor is a cause or a result of a disease, and ascertain whether modifying a specific factor will provide benefits. MR has been widely used in neurological diseases and has discriminated many of their causative factors.

Therefore, we utilized the MR method to investigate and estimate the causal relationship between PA and neurodegenerative diseases in individuals with European ancestry and hypothesize that PA could reduce the risk of neurodegenerative diseases. In our study, a two-sample MR analysis was performed to detect the potential causal association between PA and the risk of neurodegenerative diseases (ALS, PD, and AD) by using genetic variants robustly associated with PA phenotypes, including self-reported and objective accelerometer-based PA levels obtained from published genome-wide association studies (GWASs).

Materials and methods

Genome-wide association study summary statistics for physical activities

Summary statistics for physical activities were obtained from a recently published GWAS of over 377,000 UK biobank participants (Klimentidis et al., 2018). This study identified significant genetic variants associated with PA engagement, which included self-reported and accelerometry-based levels of PA in daily and leisure-time exercise habits. For self-reported PAs, responses to a touchscreen questionnaire similar to the International Physical Activity Questionnaire (Craig et al., 2003) were collected and divided into two phenotypes, listed as self-reported moderate-to-vigorous physical activities (MVPA) and self-reported vigorous physical activities (VPA). For the accelerometry-based PAs, exercise data were recorded from a wrist-worn Axivity-AX3 accelerometer (Doherty et al., 2017). Two measurements derived from the portable device were examined, including the overall acceleration average (OAA) and fraction of accelerations > 425 milligravities (FAA); this cutoff value was determined in accordance with the metabolic equivalents of vigorous physical activities (Hildebrand et al., 2014; Klimentidis et al., 2018).

Abbreviations: ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; AD, Alzheimer's disease; PA, physical activity; MR, mendelian randomization; SNP, single nucleotide polymorphism; MVPA, self-reported moderate-to-vigorous physical activity; VPA, self-reported vigorous physical activity; OAA, overall acceleration average; FAA, fraction of accelerations > 425 milli-gravities; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

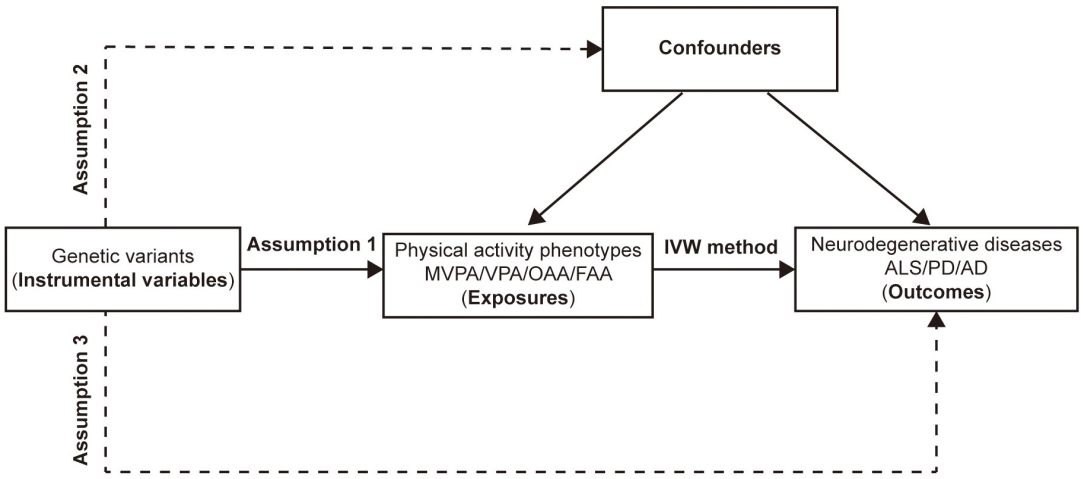


FIGURE 1
Assumptions and design of the two-sample mendelian randomization in this study. Genetic variants significantly associated with physical activity phenotypes are used as instrumental variables. MVPA, Self-reported moderate-to-vigorous physical activity; VPA, Self-reported vigorous physical activity; OAA, Overall acceleration average; FAA, Fraction of accelerations > 425 milli-gravities; IVW, Inverse variance weighted; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; AD, Alzheimer's disease.

Genome-wide association study summary statistics for neurodegenerative diseases

The genome-wide association data for ALS were obtained from publicly available GWAS summary statistics, including 20,806 ALS patients and 59,804 control individuals of European ancestry (mainly from the United States, Italian, French, and Belgian) (Nicolas et al., 2018). Both familial and sporadic ALS were included in the GWAS analysis. All patients were diagnosed according to the El Escorial criteria, and all had an onset age older than 18 years. The most recent and largest GWAS of PD involving 482,730 European participants, conducted by the International Parkinson's Disease Genomics Consortium, was used for the summary statistics for PD outcome. The study detected and reported more than 15 million SNPs in 33,674 PD patients and 449,056 controls (Nalls et al., 2019). We obtained GWAS summary data for AD from a GWAS meta-analysis in a total European population of 63,926 participants (21,982 AD patients and 41,944 cognitively normal controls) performed by the International Genomics of Alzheimer's Project (Kunkle et al., 2019).

Instrumental variable selection

To screen out significant single-nucleotide polymorphisms (SNPs) associated with PA as valid IVs, a cutoff p-value of 5×10^{-8} with genome-wide significance was chosen. In addition, the threshold of r^2 was set as 0.001 to minimize the confounding factors. Consequently, in the PA GWAS, nine genome-wide significant SNPs for MVPA (n = 377,234) and five significant SNPs for VPA (n = 261,055) were separately identified. Furthermore, we identified eight and two SNPs with genome-wide significance for OAA and FAA, respectively. Considering that there were only 2 genome-wide significant SNPs for FAA, a more relaxed cutoff the p-value of 5×10^{-7} was used, and eight SNPs were consequently selected (Choi et al., 2019; Zhuo et al., 2021). In addition, the threshold for minor allele frequency was set to 0.01. When no SNPs of the PA phenotypes were found in the outcome GWAS, they were replaced by their proxies, which were identified from LDlink.[1] Furthermore, we removed SNPs associated with confounders and outcomes based on the PhenoScanner V2 database.[2] As listed in **Supplementary Table 1**, SNPs that fulfilled the three core requirements were finally selected as IVs to assess the causal relationship between PA and neurodegenerative diseases.

Statistical analysis

Mendelian randomization has been widely used to explore the causal effect of exposure on outcome (Liao et al., 2022a). Genetic variants that could explain the actual level of exposure are often used as IVs. In MR analysis, as shown in **Figure 1**, three fundamental assumptions should be satisfied to ensure the validity of the IVs: (1) the chosen IVs should be significantly associated with exposure (PA); (2) the available

1 https://ldlink.nci.nih.gov/
2 http://www.phenoscanner.medschl.cam.ac.uk/

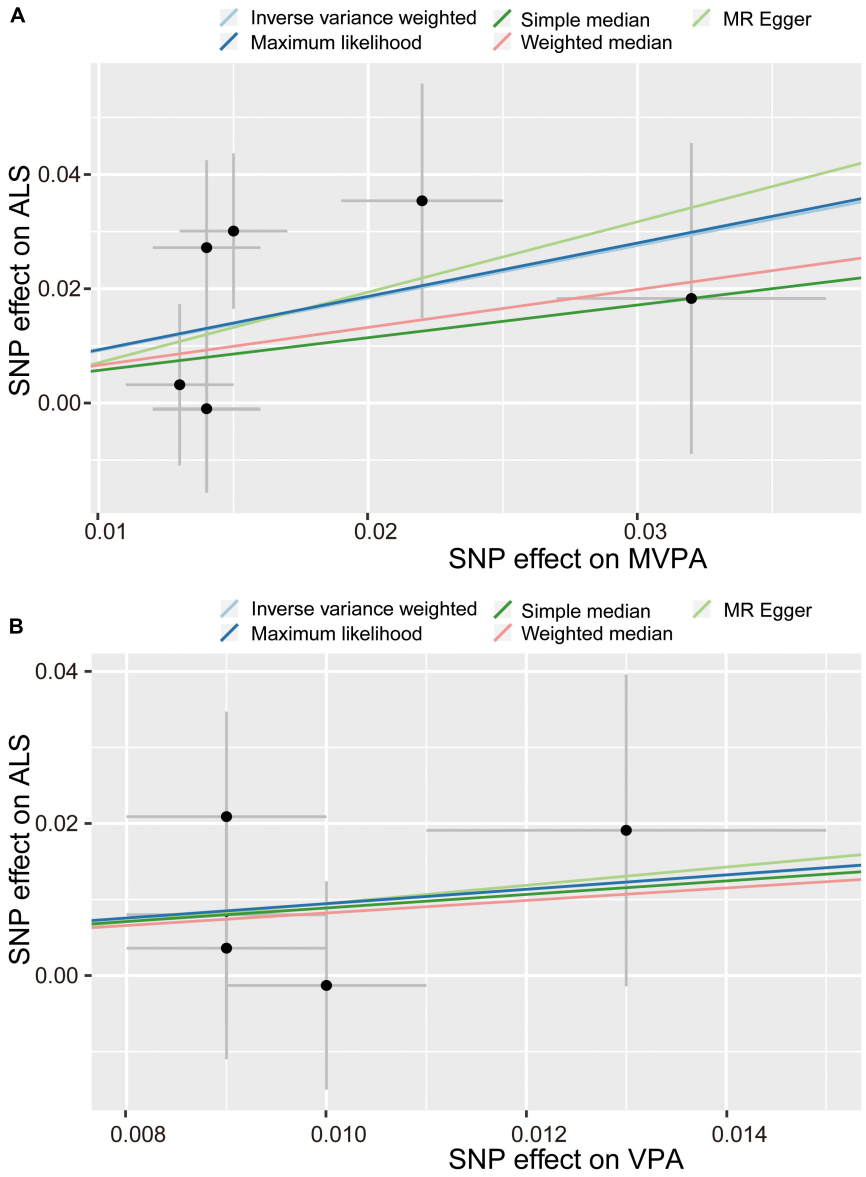


FIGURE 2
Scatter plot of causal effect of MVPA **(A)** and VPA **(B)** on ALS. MVPA, Self-reported moderate-to-vigorous physical activity; VPA, Self-reported vigorous physical activity; SNP, single nucleotide polymorphism; ALS, amyotrophic lateral sclerosis.

IVs should not be associated with any confounding factors of the exposure-outcome relationship; and (3) the chosen IVs should not affect the outcome, except possibly *via* the exposure-outcome relationship. In detail, genetic variants robustly associated with the PA phenotypes (namely, the exposure) were used as IVs, and neurodegenerative diseases, including ALS, PD, and AD, were regarded as outcomes. Thus, a two-sample MR was adopted as the main statistical approach to investigate the causal associations between each IV-exposure and IV-outcome (ALS, PD, AD) pairing.

The inverse variance weighted (IVW) method has been widely used in MR analysis, developed as a meta-analysis of the variant-specific causal estimates and used to obtain a pooled estimation of the causal effect. The IVW method has certain advantages over other similar methods, especially when the IVs enrolled in the analysis were robustly valid. When there were weak IVs, the MR–Egger method could also be applied to obtain a less biased causal estimation. In addition, to minimize the influential impact of abnormal SNPs, the median-based method was performed as a supplement to the IVW method. Finally, the maximum likelihood method was utilized when the populations overlapped.

After MR analysis, sensitivity analysis, including heterogeneity and pleiotropy, was performed. Cochran's *Q*

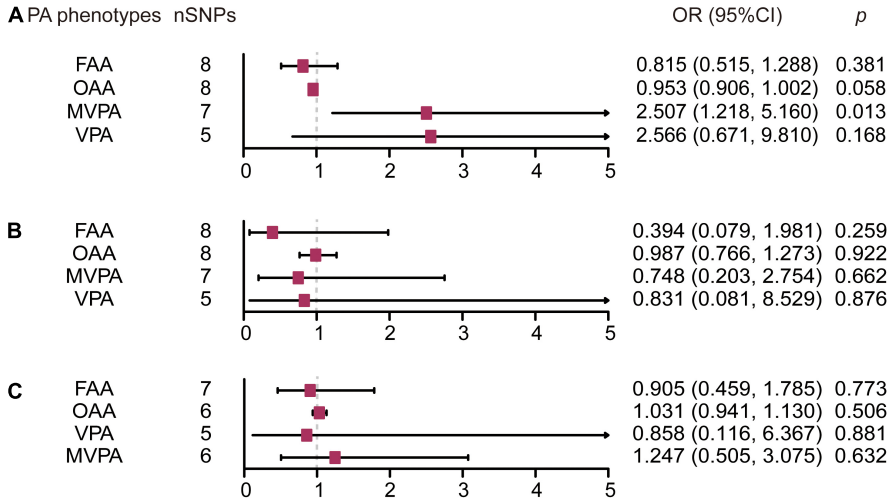


FIGURE 3
Forest plot of causal effect of physical activity phenotypes on amyotrophic lateral sclerosis **(A)**, Parkinson's disease **(B)**, and Alzheimer's disease **(C)** estimated by the inverse variance weighted method. PA, physical activity; SNP, single nucleotide polymorphism; MVPA, Self-reported moderate-to-vigorous physical activity; VPA, Self-reported vigorous physical activity; OAA, Overall acceleration average; FAA, Fraction of accelerations > 425 milli-gravities; OR, odds ratio; CI, confidence interval.

statistic was calculated to measure heterogeneity which is widely used (Huang et al., 2021; Liao et al., 2022b). A large Q statistic value indicates that the effect of individual PA phenotype-associated SNPs on outcomes enjoys a relatively large difference, which suggests the existence of heterogeneity and that the findings should be cautiously interpreted. Moreover, a random-effect IVW method was implemented to assess the causal association between the PA phenotypes and outcomes. To explore the directional pleiotropy of the PA phenotype-associated SNPs, the MR–Egger regression test was adopted by comparing the deviation of the MR–Egger intercept from zero, and an intercept p-value of less than 0.05 suggested the presence of horizontal pleiotropy. Furthermore, Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis was also performed to identify any possible horizontal pleiotropy (Verbanck et al., 2018). Additionally, leave-one-out analysis was used to determine the potential PA phenotype-associated SNPs that might influence the causal effect and identify potential outliers.

R software (version 4.1.1, for Windows) was used to conduct our two-sample MR. We adopted three main packages for statistical analysis, data output and visualization: (1) "TwoSampleMR,"[3] (2) "MRPRESSO,"[4] and (3) "forestplot."[5] A two-tailed p-value less than 0.05 was considered statistically significant.

3 https://github.com/MRCIEU/TwoSampleMR
4 https://github.com/rondolab/MR-PRESSO
5 https://cran.r-project.org/web/packages/forestplot/index.html

Results

The summarized statistics of all selected SNPs of different PA phenotypes are listed in **Supplementary Table 1**. Based on the PhenoScanner V2 database, one of the nine MVPA related SNPs was associated with AD, so we omitted this SNP from the MR analysis of the MVPA-AD association.

Physical activity with amyotrophic lateral sclerosis

For the MVPA phenotype, no evidence of heterogeneity was present according to Cochran's Q statistic ($Q = 5.270$, $p = 0.384$). As shown in **Figures 2A**, **3A**, we found evidence of a positive association between MVPA and ALS based on the IVW method (OR: 2.507, 95% CI: 1.218–5.160, $p = 0.013$), indicating that a genetically determined increased MVPA engagement could increase the risk of ALS. The maximum likelihood method yielded a similar positive effect (OR: 1.669, 95% CI: 1.220–5.309, $p = 0.013$). In addition, the other MR results shared similar patterns of effect (**Table 1**), although the statistical significance was absent (MR–Egger OR: 3.433, 95% CI: 0.218–54.024, $p = 0.421$; simple median OR: 1.772, 95% CI: 0.631–4.974, $p = 0.278$; weighted median OR: 1.939, 95% CI: 0.709–5.300, $p = 0.197$). No directional pleiotropy was suggested by the MR–Egger intercept with an intercept value of −0.005 and p-value of 0.826 (**Table 2**). MR-PRESSO analysis also indicated that there was no horizontal pleiotropy (**Table 2**), so there were no outliers for any IVs (global test: $p = 0.813$). The leave-one-out

TABLE 1 Estimated association between physical activity phenotypes and amyotrophic lateral sclerosis.

PA phenotypes	MR methods	Number of SNPs	*P*	OR (95% CI)
MVPA	IVW	7	0.013*	2.507 (1.218–5.160)
	MR Egger	7	0.421	3.433 (0.218–54.024)
	Maximum likelihood	7	0.013*	2.545 (1.220–5.309)
	Simple median	7	0.278	1.772 (0.631–4.974)
	Weighted median	7	0.197	1.939 (0.709–5.300)
VPA	IVW	5	0.168	2.566 (0.671–9.810)
	MR Egger	5	0.840	3.318 (0–145568.627)
	Maximum likelihood	5	0.168	2.575 (0.670–9.896)
	Simple median	5	0.310	2.432 (0.437–13.528)
	Weighted median	5	0.339	2.277 (0.421–12.317)
OAA	IVW	8	0.058	0.953 (0.906–1.002)
	MR Egger	8	0.656	1.057 (0.839–1.331)
	Maximum likelihood	8	0.036*	0.951 (0.907–0.997)
	Simple median	8	0.068	0.947 (0.894–1.004)
	Weighted median	8	0.069	0.944 (0.887–1.004)
FAA	IVW	8	0.381	0.815 (0.515–1.288)
	MR Egger	8	0.257	0.013 (0.000–11.571)
	Maximum likelihood	8	0.336	0.809 (0.526–1.245)
	Simple median	8	0.868	1.050 (0.590–1.867)
	Weighted median	8	0.830	1.066 (0.598–1.900)

*p-value less than 0.05 is considered statistically significant.
PA, physical activity; MR, mendelian randomization; SNP, single nucleotide polymorphism; MVPA, Self-reported moderate-to-vigorous physical activity; VPA, Self-reported vigorous physical activity; OAA, Overall acceleration average; FAA, Fraction of accelerations > 425 milli-gravities; IVW, Inverse variance weighted; OR, odds ratio; CI, confidence interval.

test showed that the causal estimation of genetically predicted MVPA on ALS risk was mostly not influenced by a single SNP, implying the robustness and validity of our results. For the VPA phenotype, our results suggested a consistent trend of the causal estimation that VPA engagement could promote the onset of ALS across different statistical methods, although the p-values were not significant (Figure 2B and Table 1). No evidence of heterogeneity or pleiotropy was shown (shown in Table 2). For OAA, according to the maximum likelihood method, an inverse association between OAA and ALS risk was revealed (OR: 0.951, 95% CI: 0.907–0.997, $p = 0.036$). However, other MR methods yielded different trends (Table 2). For FAA, our MR analysis indicated no causal association between FAA and ALS risk by either the IVW method or other methods (shown in Table 1 and Figure 3A).

Physical activity with Parkinson's disease

For the self-reported PA phenotype, including MVPA and VPA, shown in Supplementary Table 4, there was no evidence of heterogeneity as measured by the Q statistics (MVPA $Q = 8.211$, $p = 0.145$; VPA $Q = 6.558$, $p = 0.087$). Multiple MR methods, including the IVW method, showed that the trend of the effect of MVPA on PD risk was consistent that the risk of PD tended to decrease when the genetically determined MVPA engagement increased despite the association was non-significant (Supplementary Table 2 and Figure 3B). Similar findings were also observed in the causal effect estimation between VPA and PD. MR–Egger intercept and MR-PRESSO analyses found no evidence for any pleiotropy in the MVPA-PD and VPA-PD associations, indicating the stability of our analysis (Supplementary Table 4). For accelerometry-based PA, heterogeneity was detected in both the OAA and FAA phenotypes, as indicated by the large Q statistics (OAA $Q = 89.134$, $p = 0.000$; FAA $Q = 33.208$, $p < 0.001$). Thus, a random-effects model for the IVW method was utilized to investigate the causal relation between these two phenotypes and PD (Supplementary Table 2). Neither OAA nor FAA exerted a causal effect on the possibility of developing PD (OAA OR: 0.987, 95% CI 0.766–1.273, $p = 0.922$; FAA OR: 0.394, 95% CI: 0.079–1.981, $p = 0.259$).

Physical activity and Alzheimer's disease

There was no evidence of heterogeneity in the MVPA-AD relationship ($Q = 2.730$, $p = 0.604$); thus, the IVW, MR–Egger, median-based and maximum likelihood methods were all used to evaluate the causation of MVPA on AD (Supplementary Table 4). Demonstrated in Supplementary Table 3 and Figure 3C, it was implied that there was no significant causal association, and the effect pattern varied for the different methods (IVW: OR: 1.247, 95% CI: 0.505–3.075, $p = 0.632$; MR Egger OR: 19.620, 95% CI: 0.96–401.027, $p = 0.125$; weighted median OR: 1.288, 95% CI: 0.430–3.853, $p = 0.651$; simple median OR: 0.995, 95% CI: 0.337–2.932; $p = 0.992$). As heterogeneity was detected in the VPA-AD, OAA-AD, and FAA-AD relationships, the random-effects IVW method was used to estimate whether these were causal relationships (Supplementary Table 3 and Figure 3C). The analysis showed VPA and FAA were both inversely associated with AD risk, although the association was not significant (VPA

TABLE 2 Sensitivity test of the mendelian randomization analysis between physical activity phenotypes and amyotrophic lateral sclerosis.

PA phenotypes	MR methods	Heterogeneity test		Horizontal pleiotropy		MR-PRESSO	Steiger test
		Cochran's Q	*P*	Egger_intercept	*P*	*P* of global test	*P*
MVPA				−0.005	0.826	0.514	<0.001*
	IVW	5.327	0.503				
	MR-Egger	5.270	0.384				
VPA				−0.003	0.965	0.813	0*
	IVW	1.647	0.800				
	MR-Egger	1.645	0.649				
OAA				−0.028	0.400	0.312	0*
	IVW	8.436	0.296				
	MR-Egger	7.423	0.283				
FAA				0.103	0.277	0.354	0*
	IVW	8.188	0.316				
	MR-Egger	6.613	0.358				

*p-value less than 0.05 is considered statistically significant.
PA, physical activity; MR, mendelian randomization; MVPA, Self-reported moderate-to-vigorous physical activity; VPA, Self-reported vigorous physical activity; OAA, Overall acceleration average; FAA, Fraction of accelerations > 425 milli-gravities; IVW, Inverse variance weighted.

OR: 0.858, 95% CI: 0.116–6.367, $p = 0.881$; FAA OR: 0.905, 95% CI: 0.459–1.785, $p = 0.773$), while OAA was positively related to AD risk but also not significant (OAA OR: 1.031, 95% CI: 0.941–1.13, $p = 0.506$).

Discussion

In this study, we conducted two-sample MR to investigate the causal relationship between PA and neurodegenerative diseases. Although it has been previously reported that PA could reduce the risk of developing neurodegenerative diseases, our results demonstrated that different physical phenotypes exert different effect on neurodegenerative diseases and there was only a causal association between MVPA and ALS. It was revealed that genetically determined increased MVPA engagement could significantly increase the risk of ALS.

Amyotrophic lateral sclerosis is a rare and fatal neurodegenerative disease caused by degeneration of the motor neurons (Shi et al., 2022). The effect of PA on ALS continues to be controversial. Some studies have revealed that PA is not a risk factor for ALS and that increased PA does not increase susceptibility to ALS (Valenti et al., 2005; Pupillo et al., 2014; Feddermann-Demont et al., 2017). However, these studies included limited populations, the conclusions were not validated. Recently, some studies with a larger population size have shown opposite results. A multicenter case–control study suggested that a higher risk of ALS is associated with PA in leisure time and occupational activities after adjustment for confounders (Visser et al., 2018). Furthermore, a cross-sectional study also indicated that patients who reported at least moderate engagement in PA (three times a week) during early adulthood were more likely to be diagnosed with ALS than those who did not (Raymond et al., 2021). Our analysis also supports that more involvement in PA is associated with ALS risk.

Among the selected methods in our analysis, with the validity of the IVs and the absence of pleiotropy, the IVW method was the most efficient (Zhu, 2021). Specifically, in the analysis of MVPA, the causal relationship was significant in two different analytical approaches including the IVW and the maximum likelihood, and the direction of effect remained similar. However, in the analysis of OAA, the significant result was only yielded by the maximum likelihood methods and the tendency were not consistent by different methods which weakened the validity and robustness of the results. Thus, our results demonstrated that more MVPA engagement was casually related with ALS risk. It needs intensive investigation whether PA could alter the risk of ALS by interfering with some already known ALS etiologies. It has been reported that different intensities of PA could induce various glucose demands which leads to the alteration of the muscle metabolism and autophagy flux, and provide different effect in ALS mice (Desseille et al., 2017). Besides, different intensities of PA could also the alter the sizes of recruited motoneurons and modulate the neurotrophic signal in the neuromuscular junctions (Just-Borras et al., 2020). Anyway, the underlying molecular mechanisms between different PA phenotypes and ALS risk still require further exploration. Uncovering the relationship between PA and ALS will be beneficial in the development of more precise guidance for ALS patients.

In addition, we explored the effect of PA on PD. In contrast to the effect of PA on ALS, our results showed that PA was not causally associated with PD risk but genetically predicted increased engagement in MVPA and VPA were inclined to

protect against PD. Previous study has found that there is no obvious difference in PA levels between PD and healthy controls (Amara et al., 2019), which is inconsistent with our results. Besides, higher PA levels are associated with slower PD progression (Amara et al., 2019). Various studies have proposed that physical activity interventions could be effective in alleviating the motor and non-motor symptoms of PD, and in improving multiple outcomes in people with PD (Morberg et al., 2014; Okun, 2017; Cheng and Su, 2020; Hidalgo-Agudo et al., 2020). Our results did not invalidate these former studies despite no causality was found between PA and PD risk. Besides, a future investigation of the causal relationship between PA and PD progression are needed. On the other hand, it should be noted that PA could directly interfere with the PD-related pathophysiological process (Fan et al., 2020). In a PD rat model, early moderate treadmill running practice mitigates the accumulation of alpha-synuclein, which contributes to PD pathogenesis and motor dysfunction, and maintains levels of tyrosine hydroxylase in the substantia nigra, which plays an essential role in the metabolism of dopamine (Almeida et al., 2018). Additionally, it is suggested in PD mice model that PA could induce neuroprotection against cell death by promoting enhanced autophagy and neuronal regeneration (Jang et al., 2018), and by regulating both mitochondrial function and neuroinflammation (Tuon et al., 2015). Therefore, disclosing the role of PA in PD risk and progression would be of great benefit and could promote the prescription of PA as an efficient treatment method for PD.

It was previously reported that PA could improve cognitive function (Anderson-Hanley et al., 2012; Holthoff et al., 2015; Palta et al., 2019; Zhou et al., 2022), but the relationship between PA and AD risk remains unclear. Our analysis showed that there was no causal effect of either self-reported PA or accelerometry-based PA levels on AD onset, and the extent of engagement in PA was not a risk factor for AD. Our analysis is consistent with study results derived from meta-analysis of 19 prospective observational cohort studies. It contains more than 400,000 participants with a follow-up of at least 10 years demonstrated that less PA was not associated with a higher risk of dementia and AD (Kivimaki et al., 2019). Besides, existing evidence supporting that PA could reduce the risk of AD or dementia is insufficient (Brasure et al., 2018).

It is worth noting that the effect of PA on ALS, PD, and AD varies, which means that the roles of PA in neurodegenerative disease might differ from each other, and that there is no one-size-fits-all PA prescription for neurodegenerative diseases. It is necessary for clinicians to offer individualized and precise PA guidance for individuals with neurodegenerative disease.

There are some major strengths in our study. First, we explored for the first time the causal effect of different phenotypes of PA on neurodegenerative diseases by two-sample MR analysis. Second, we adopted multiple MR methods, including inverse variance weighted analysis, the MR–Egger method, the median-based method and the maximum likelihood method, to robustly estimate causal relationships, MR–Egger regression and MR-PRESSON to detect pleiotropy, and leave-one-out as the sensitivity test to examine the validity of the results. Third, the random-effect IVW method was implemented to assess the causal association if heterogeneity was present.

However, our MR analysis has some limitations. First, since the GWAS databases of PA and neurodegenerative diseases were all derived from individuals of European ancestry, the universality of our results is limited. Further studies are required to demonstrate whether our results are consistent for other ancestries. Second, although we ruled out SNPs associated with confounders in the MR analysis, some other unknown confounders are present that might influence the causal estimation. Third, PA engagement is determined not only by genetic factors but also by other factors; thus, it should be noted that our results could only explain the causal association of PA with neurodegenerative diseases. Fourth, the included SNPs significantly associated with PA are limited, which could decrease the statistical validity of our findings while minimizing the confounding influence and pleiotropy. Lastly, as the information of ALS, PD and AD phenotypes including genetic mutations are insufficient, the causality of PA on different phenotypes are unable to valuate. Therefore, further investigations to identify more genetic loci associated with PA engagement are needed.

Conclusion

To our knowledge, our MR analysis is the first to indicate a causal effect of PA on the risk of neurodegenerative diseases. Genetically predicted increases in MVPA participation could increase the risk of ALS in individuals of European ancestry. Precise and individualized prescriptions of physical activity should be provided to the elder population.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

KH conceived the project. QL and KH extracted data and performed the analysis. QL wrote the manuscript. All authors polished the manuscript and critically revised it for valuable intellectual content and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.991140/full#supplementary-material

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Synergistic multi-joint kinematic strategies to reduce tripping risks during obstacle-crossing in older long-term Tai-Chi Chuan practitioners

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Introduction: Losing balance or tripping over obstacles is considered one of the most common causes of falls in the elderly. Tai-Chi Chuan (TCC) has been shown to improve muscle strength, inter-joint coordination and balance control in the elderly. This study aimed to determine whether older long-term TCC practitioners would show multi-joint kinematic strategies that would reduce the risk of tripping during obstacle-crossing compared to peers without TCC experience.

Methods: Three-dimensional motions of the pelvis and lower extremities were measured using a motion capture system in fifteen older long-term TCC practitioners (TCC group) and 15 healthy controls without TCC experience during walking and crossing obstacles of three different heights. Crossing angles of the pelvis and lower limbs and toe-obstacle clearances were obtained and analyzed using two-way analyses of variance to study the between-subject (group) and within-subject (height) effects. A multi-link system approach was used to reveal the relationship between joint angular changes and toe-obstacle clearances.

Results: Compared to the controls, the TCC group showed increased leading and trailing toe-obstacle clearances ($p < 0.05$) with increased pelvic hiking and hip flexion but decreased hip adduction on the swing side and decreased knee flexion on the stance side during leading-limb crossing ($p < 0.05$), and increased pelvic hiking and anterior tilt but decreased hip adduction on the swing side, and decreased knee flexion on the stance side during trailing limb crossing ($p < 0.05$). All significant joint angular changes contributed to the increases in the toe-obstacle clearances.

Conclusion: The current study identified the kinematic changes of the pelvis and the lower limb joints and revealed a specific synergistic multi-joint kinematic strategy to reduce tripping risks during obstacle-crossing in older long-term TCC practitioners as compared to non-TCC controls. The observed multi-joint kinematic strategies and the associated increases in toe-obstacle clearances appeared to be related to the training characteristics of TCC movements. Long-term TCC practice may be helpful for older people in reducing the risk of tripping and the subsequent loss of balance.

KEYWORDS

Tai-Chi Chuan, kinematics strategies, balance control strategies, obstacle-crossing, fall risk

Introduction

More than one-third of people aged 65 and over fall at least once during a year (Tinetti and Kumar, 2010; Verma et al., 2016) and fall death rates are the highest among adults over the age of 60, according to the World Health Organization (World Health Organization [WHO], 2021). Factors affecting fall risks include intrinsic factors related to the ability of balance, such as vision, proprioception, vestibular system, musculoskeletal system, and sensorimotor functions (Sturnieks et al., 2008) and extrinsic factors such as environmental hazards (Van Dieen et al., 2005), including the presence of obstacles, slippery surfaces, curbs, and stairs (Tinetti et al., 1988; Tinetti and Kumar, 2010). An estimated 60–67% of falls in the elderly occur inside the home or in immediate surroundings (Stevens et al., 2014; Crenshaw et al., 2017) and often involve environmental hazards (Letts et al., 2010). Losing balance or tripping during obstacle-crossing is one of the most common causes of falls in the elderly (Chou et al., 2001; Menant et al., 2010). For successful obstacle-crossing, it is essential to maintain the body's stability while lifting the swing foot to clear the obstacle (Chen et al., 2008; Huang et al., 2008). Obstacle-crossing thus requires lower-limb strength (stance foot), precise end-point (swing foot) control and highly coordinated joint movements while maintaining body balance (Chen et al., 2004; Chen and Lu, 2006; Lu et al., 2006). Any inappropriate control of the locomotor system may affect the inter-joint and joint-to-endpoint kinematic coordination, leading to tripping over obstacles or body imbalance (Draganich and Kuo, 2004; McKenzie and Brown, 2004; Lu et al., 2006; Liu et al., 2010; Hsu et al., 2016). Since obstacles are an unavoidable part of our daily living, it is essential to improve the intrinsic fitness of older people to reduce fall risks while negotiating obstacles during daily activities (Bueno-Cavanillas et al., 2000; Prevention and Panel, 2001; Ikezoe et al., 2003).

Exercises such as walking, jogging, cycling, table tennis, resistance training, weight-bearing exercise, and Tai-Chi Chuan (TCC) are beneficial for older people to improve their general fitness and health (Martyn-St James and Carroll, 2008; Peterson et al., 2010; Oja et al., 2011; Kim et al., 2014; Ikenaga et al., 2017; Naderi et al., 2018; Pasqualini et al., 2019; Izquierdo et al., 2021). Among these exercises, TCC, a low-speed and low-impact ancient Chinese martial art, is becoming popular among the elderly for improving their general physical condition. TCC is an effective multi-factor exercise (Shubert et al., 2010; Bird et al., 2011), which has been shown to improve multiple intrinsic factors and the general mental and physical function in the elderly (Wu, 2002; Tsang et al., 2004; Mao et al., 2006; Ho et al., 2012; Okuyan Birimoğlu and Bilgili, 2017; Liu et al., 2019; Birimoglu Okuyan and Deveci, 2021). TCC consists of a series of slow, continuous, and gentle motions transitioning between single-limb support and double-limb, focusing on the dynamic stability of the stance limb and precise control of the swing limb and the weight shift between limbs. Through regular and prolonged TCC practice, one could increase muscle strength (Wu et al., 2002; Mao et al., 2006), flexibility (Lan et al., 2008; Huang and Liu, 2015), balance (Wu, 2002; Mak and Ng, 2003; Huang and Liu, 2015), inter-joint coordination (Wang et al., 2010a; Kuo et al., 2021b), and sensory organization in postural control (Tsang et al., 2004). Long-term TCC practice could also attenuate the age-related decline in general physical function and lead the practitioners to modify their gaits and movement patterns (Wolf et al., 1997; Lin et al., 2006; Mak et al., 2017). Furthermore, previous studies have shown that TCC training could have positive effects on posture, gait, and movement performance, such as improvement of standing balance (Ho et al., 2012) and walking performance (Hackney and Earhart, 2008; Li et al., 2012, 2014). Such benefits in TCC practice might reduce the risk in the elderly, which could happen during daily locomotion in diversified environments, e.g., obstacle negotiation.

During level walking, the locomotor system (i.e., the pelvis-leg apparatus) acts as a multi-link system with complex

yet coordinated movements (Saunders et al., 2005; Franz et al., 2009). These movements become more complex when individuals encounter obstacles or negotiate uneven terrains (Wang, 2003). Stepping over an obstacle changes the repetitive inter-joint movement patterns during level walking, placing greater challenges to the whole-body balance and end-point control with an increased risk of falling (Wang, 2003). With the pelvis-leg apparatus as a multi-link system, a change in the angle of a joint leads to angular changes at other joints, which together determine the end-point position of the swing limb. Such inter-joint and joint-to-end-point kinematic relationships can be synthesized from the kinematic changes at individual joints and the end-points to identify the kinematic strategies of obstacle-crossing in various populations (Hsu et al., 2016; Chien and Lu, 2017; Wu et al., 2019a). Recently, the whole-body balance control, lower-limb inter-joint coordination and the multi-objective optimal control of obstacle-crossing have been studied in older people with long-term TCC experience, showing better performance as compared to non-TCC peers (Kuo et al., 2021a,b, 2022). However, no study has reported the kinematic strategy of the pelvis-leg apparatus and its effects on the end-point position control in relation to the risk of tripping.

This study aimed to determine the kinematic strategies of the pelvis-leg apparatus during obstacle-crossing in older healthy people with long-term TCC experience as compared to the non-TCC healthy controls. It was hypothesized that older people who had practised TCC over a long time would have higher toe-obstacle clearance with a reduced risk of tripping *via* a specific kinematic strategy of the pelvis-leg apparatus compared to non-TCC peers.

Materials and methods

Study design

The current observational cross-sectional study, which included participants aged over 65 years, was conducted by trained therapists in a university hospital gait laboratory from June 2009 to June 2010. The research methods consisted of the application of a validated skin marker-based motion capture system and forceplates to appraise temporal-spatial and end-point parameters and pelvic orientations and lower limb joint angles when crossing obstacles of three different heights (**Figure 1**). All the experiments and procedures conformed to the Ethical Principles for Medical Research Involving Human Subjects (World Medical Association Declaration of Helsinki). All subjects gave informed written consent as approved by the Institutional Review Board (IRB No. DMR98-IRB-072).

Subjects

iFfteen healthy older adults with long-term TCC experience (TCC group) were recruited from a local TCC club to participate in the current study. Fifteen healthy controls without TCC experience but doing daily walking or jogging (Control group) were also recruited to match the TCC group for gender, age and BMI. The inclusion criteria for both groups: (1) aged 65 years and above, (2) active community-dwelling individuals, (3) physical independence in daily activities, (4)

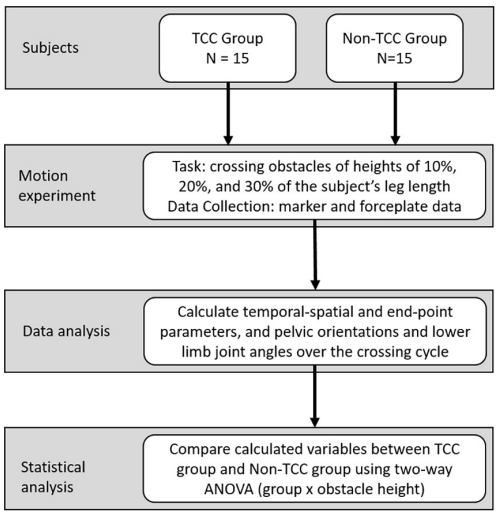


FIGURE 1
Fifteen long-term TCC practitioners and fifteen non-TCC practitioners were recruited for this study. All the practitioners were requested to cross the obstacles at three different heights during walking. At the same time, the three-dimensional motions of the pelvis and lower extremities were measured using a motion capture system. After data collection, joint angles of lower extremities and pelvic kinematics were calculated, and the data from the TCC group and Control group were compared.

TABLE 1 Means (standard deviations) of the demographic characteristic for the TCC (n = 15) and Control (n = 15) groups. P-values and t-values for between-group comparisons using independent t-tests are also given.

	TCC	Control	t-value	p-value
Age (years)	71.1 (5.4)	72.4 (6.1)	0.545	0.591
Body height (cm)	162.7 (6.7)	159.7 (5.6)	−1.199	0.243
Body mass (kg)	58.7 (6.5)	58.0 (10.4)	−0.188	0.852
Gender, number of females/males	4/11	4/11	–	–
TCC experience (years)	22.0 (10.5)	0	–	–

TCC, Tai-Chi Chuan.

with normal or corrected vision, and (5) free from any neuromusculoskeletal injuries, disease or dysfunction that might affect gait and obstacle-crossing, such as ligament deficiency, joint degeneration, muscle weakness, vestibular deficiency, and stroke. Additionally, the TCC group should have practised TCC at least 60 min a day and 5 days a week for ten or more years, and the Control group should do walking or jogging daily. The exclusion criteria for both groups were: (1) with any cognitive impairments, (2) prior surgeries on the neuromusculoskeletal system, such as total joint replacements, (3) with cardiovascular or pulmonary diseases, and (4) fall experiences within a year at the time of the experiment.

Experimental protocol

In a gait laboratory, each of the subjects walked at their preferred walking speed along a 10-meter walkway and crossed a tube-like obstacle placed horizontally across a height-adjustable frame located in the middle of the walkway (Chen and Lu, 2006). Two infrared-retroreflective markers placed on each end

TABLE 2 Means (standard deviations, SD) of the crossing speed, stride length, and end-point parameters in the TCC and Control groups when crossing obstacles of different heights.

Variables	Obstacle height (%LL)	TCC	Control	*F*-values	Main effects	Partial eta squared
Crossing speed (m/s)	10	0.70 (0.05)	0.80 (0.14)	$F_G = 4.050$ $F_H = 58.878$	$P_G = 0.115$ $P_H < 0.001\downarrow$	0.12 0.73
	20	0.65 (0.08)	0.71 (0.11)			
	30	0.60 (0.08)	0.64 (0.11)			
Leading stride length (% LL)	10	134.2 (8.0)	139.5 (11.7)	$F_G = 0.997$ $F_H = 8.336$	$P_G = 0.328$ $P_H < 0.001\downarrow$	0.04 0.26
	20	133.8 (8.4)	136.4 (11.1)			
	30	132.6 (8.3)	134.9 (12.1)			
Leading toe-obstacle distance (% LL)	10	87.63 (8.65)	88.43 (10.81)	$F_G = 0.001$ $F_H = 1.130$	$P_G = 0.977$ $P_H = 0.331$	0.01 0.04
	20	89.30 (8.07)	87.84 (10.14)			
	30	87.58 (8.05)	87.92 (10.74)			
Leading heel-obstacle distance (% LL)	10	16.69 (2.88)	18.94 (4.96)	$F_G = 0.809$ $F_H = 6.160$	$P_G = 0.377$ $P_H = 0.004\downarrow$	0.03 0.19
	20	15.77 (3.45)	16.61 (4.13)			
	30	14.94 (4.28)	15.40 (4.72)			
Leading toe-obstacle clearance (mm)	10	172.1 (34.1)	138.8 (39.7)	$F_G = 5.896$ $F_H = 5.837$	$P_G = 0.025^*$ $P_H = 0.006\uparrow$	0.23 0.23
	20	185.9 (28.3)	164.8 (23.3)			
	30	190.0 (28.3)	167.9 (34.4)			
Trailing stride length (% LL)	10	128.0 (7.7)	141.7 (11.8)	$F_G = 7.834$ $F_H = 1.165$	$P_G = 0.010^*$ $P_H = 0.311$	0.25 0.05
	20	128.6 (8.9)	139.1 (11.1)			
	30	129.2 (10.7)	137.3 (10.9)			
Trailing toe-obstacle distance (% LL)	10	25.35 (4.69)	24.65 (4.41)	$F_G = 0.295$ $F_H = 2.558$	$P_G = 0.592$ $P_H = 0.087$	0.01 0.09
	20	26.04 (4.59)	24.36 (4.40)			
	30	24.46 (4.58)	24.11 (4.94)			
Trailing heel-obstacle distance (%LL)	10	72.46 (6.33)	85.90 (8.90)	$F_G = 10.324$ $F_H = 0.621$	$P_G = 0.003^*$ $P_H = 0.541$	0.28 0.02
	20	75.66 (6.45)	83.69 (8.43)			
	30	75.31 (8.95)	81.15 (10.61)			
Trailing toe-obstacle clearance (mm)	10	164.5 (30.4)	131.0 (44.2)	$F_G = 5.857$ $F_H = 0.748$	$P_G = 0.025^*$ $P_H = 0.479$	0.22 0.03
	20	179.3 (43.1)	134.5 (49.8)			
	30	173.9 (36.5)	145.4 (54.9)			

LL, leg length; F_G, f-value for subject group; F_H, f-value for obstacle height; P_G, p-value for subject group; P_H, p-value for obstacle height; * indicates a significant group effect ($P_G < 0.05$); ↑ indicates a linearly increasing trend and ↓ indicates a linearly decreasing trend ($P_H < 0.05$).

of the tube were also used to define the position and height of the obstacle. Thirty-nine infrared-retroreflective markers placed on specific anatomical landmarks were used to track the motions of the body segments, namely ASISs, PSISs, greater trochanters, mid-thighs, medial and lateral epicondyles, heads of fibulae, tibial tuberosities, medial and lateral malleoli, navicular tuberosities, fifth metatarsal bases, big toes and heels, and mandibular condylar processes, acromion processes, C7, medial and lateral humeral epicondyles, and ulnar styloid (Hong et al., 2015). Three-dimensional trajectories of the markers were measured using a seven-camera motion capture system (Vicon 512, Oxford Metrics Group, UK) at 120 Hz, while two regularly calibrated forceplates (AMTI, USA) (Hsieh et al., 2011) placed on either side of the obstacle were used to measure the ground reaction forces at 1080 Hz. The forceplate data were used to determine the gait events, including bilateral heel-strikes and toe-offs. The test conditions were crossing obstacles of 10, 20, and 30% of the subject's leg length (i.e., the distance between the ASIS and medial malleolus) in a random order, with each lower limb leading (Chen and Lu, 2006). A 5-min break was allowed when changing obstacle-height conditions. A trial was defined as unsuccessful if the subject hit the obstacle during the crossing. In the current study, all the subjects could cross the obstacles successfully without hitting the obstacle. Data for three successful crossing trials for each lower limb leading were obtained for each obstacle height for each subject.

Kinematic data analysis

With the measured marker data, temporal-spatial and end-point parameters were calculated. The crossing speed was calculated as the distance traveled by the mid-point of the ASIS markers in the walking direction divided by the time spent from the leading toe-off immediately before crossing to the trailing heel-strike immediately after crossing. The crossing stride of the leading limb began at toe-off immediately before the obstacle and ended at the subsequent toe-off, while that for the trailing limb was defined as heel-strike immediately before the obstacle to the subsequent heel-strike (Liu et al., 2018). Toe-obstacle clearances for both the leading and trailing limbs were calculated as the vertical distance between the toe marker of the swing limb and the obstacle when the toe marker was directly above the obstacle. The toe-obstacle distances were defined as the horizontal distance between the obstacle and the toe marker during stance immediately before stepping over the obstacle, while the heel-obstacle distances were defined as the horizontal distance between the obstacle and the heel marker during stance immediately after stepping over the obstacle (Wu et al., 2019a).

For the calculation of the orientations of the pelvis and the angles of the lower limb joints, each body segment was embedded with an orthogonal coordinate system with the positive x-axis directed anteriorly, the positive y-axis superiorly and the positive z-axis to the right following ISB recommendations (Wu and Cavanagh, 1995). The orientations of the pelvis were described relative to the laboratory coordinate system, with the leading limb as the reference limb. Pelvic hiking (drop) indicated that the hip was higher (lower) than the contralateral hip, while ipsilateral rotation indicated that the ipsilateral hip was anterior to the contralateral hip (Wu et al., 2019b). A Cardanic rotation sequence of z-x-y was used to calculate the angles of each lower limb joint (Grood and Suntay, 1983). The calculated angles when the leading and trailing toes were above the obstacle, called crossing angles (Lu et al., 2006), were extracted for subsequent statistical analysis. Effects of soft tissue artifacts of the pelvis-leg apparatus were reduced using a global optimization method (Lu and O'connor, 1999).

TABLE 3 Means (standard deviations) of the crossing angles of the pelvis relative to the global in TCC practitioners (TCC) and non-TCC controls (Control) when the leading or trailing toe was above the obstacles of heights of 10, 20, and 30% of the subjects' leg length (LL).

Variables	Group	Obstacle height (%LL)			*F*-values	Main effects	Partial eta squared
		10%	20%	30%			
Leading toe above the obstacle							
Hiking	TCC	3.8 (0.9)	5.9 (2.0)	9.1 (1.3)	$F_G = 4.899$; $F_H = 40.99$	$P_G = 0.048$*; $P_H < 0.001$↑	0.19; 0.70
	Control	3.2 (1.3)	5.5 (1.1)	6.9 (3.0)			
Anterior tilt	TCC	−0.9 (3.1)	−1.9 (3.1)	−3.2 (2.7)	$F_G = 2.186$; $F_H = 40.89$	$P_G = 0.153$; $P_H < 0.001$↓	0.09; 0.65
	Control	−1.8 (2.4)	−3.6 (2.5)	−5.2 (2.7)			
Trailing toe above the obstacle							
Hiking	TCC	−0.2 (1.3)	1.6 (1.6)	3.5 (1.8)	$F_G = 8.548$; $F_H = 87.73$	$P_G = 0.008$*; $P_H < 0.001$↑	0.28; 0.80
	Control	−1.8 (1.4)	−0.1 (1.4)	1.9 (1.8)			
Anterior tilt	TCC	4.1 (2.3)	5.8 (1.9)	8.4 (3.0)	$F_G = 6.078$; $F_H = 90.13$	$P_G = 0.02$*; $P_H < 0.001$↑	0.22; 0.80
	Control	1.5 (3.1)	3.1 (3.5)	5.4 (3.1)			

F_G, f-value for subject group; F_H, f-value for obstacle height; P_G, p-value for subject group; P_H, p-value for obstacle height; * indicates a significant group effect ($P_G < 0.05$); ↑ indicates a linearly increasing trend and ↓ indicates a linearly decreasing trend ($P_H < 0.05$). Hiking indicates that the ipsilateral hip joint center is higher than the contralateral hip.

Statistical analysis

For statistical comparisons between TCC and Control, independent *t*-tests were used for the demographic data, while a two-way mixed-design analysis of variance (ANOVA) was used for the temporal-spatial and end-point parameters, and all the calculated kinematic variables with one between-subject factor (group) and one within-subject factor (obstacle height). For all the statistical analyses, data of each calculated variable from both sides were averaged before further averaged across trials for each subject. All the calculated variables were of normal distribution determined by a Shapiro–Wilk test, and Levene's test confirmed the homogeneity of variance across groups. In the absence of significant interactions, main effects were reported.

TABLE 4 Means (standard deviations) of the crossing angles of the hip, knee and ankle joints of the leading swing limb and trailing stance limb in TCC practitioners (TCC) and non-TCC controls (Control) when the leading toe was above the obstacle of heights of 10, 20, and 30% of subjects' leg length (LL).

Variables	Group	Obstacle height (%LL)			*F*-values	Main effects	Partial eta squared
		10%	20%	30%			
Leading swing limb							
Hip flexion	TCC	58.3 (6.0)	68.1 (5.0)	74.4 (5.7)	$F_G = 5.219$	$P_G = 0.033$*	0.21
					$F_H = 146.2$	$P_H < 0.001$↑	0.88
	Control	52.4 (5.2)	63.7 (5.6)	70.0 (6.8)			
Hip adduction	TCC	1.4 (3.2)	−0.7 (2.5)	−3.4 (3.9)	$F_G = 5.136$	$P_G = 0.032$*	0.17
					$F_H = 55.76$	$P_H < 0.001$↓	0.69
	Control	7.4 (7.4)	4.0 (7.6)	0.3 (7.6)			
Knee flexion	TCC	82.2 (7.5)	96.7 (9.2)	107.1 (5.5)	$F_G = 2.425$	$P_G = 0.134$	0.10
					$F_H = 180.9$	$P_H < 0.001$↑	0.89
	Control	85.0 (6.3)	101.2 (6.6)	110.7 (5.7)			
Knee adduction	TCC	−4.7 (3.7)	−4.1 (3.7)	−3.8 (4.8)	$F_G = 2.437$	$P_G = 0.132$	0.09
					$F_H = 10.89$	$P_H < 0.001$↑	0.32
	Control	−10.2 (6.2)	−7.8 (6.5)	−4.1 (7.2)			
Ankle dorsiflexion	TCC	10.6 (3.8)	12.1 (5.7)	8.7 (14.0)	$F_G = 0.186$	$P_G = 0.670$	0.01
					$F_H = 0.797$	$P_H = 0.456$	0.03
	Control	9.8 (5.1)	11.6 (5.7)	13.0 (6.1)			
Ankle adduction	TCC	0.1 (3.2)	−1.0 (3.1)	−0.9 (3.0)	$F_G = 0.065$	$P_G = 0.801$	0.01
					$F_H = 5.372$	$P_H = 0.008$↓	0.17
	Control	−0.3 (2.7)	−1.3 (2.8)	−1.1 (3.8)			
Trailing stance limb							
Hip flexion	TCC	4.1 (4.5)	3.8 (2.4)	2.9 (4.6)	$F_G = 1.361$	$P_G = 0.255$	0.05
					$F_H = 1.422$	$P_H = 0.251$	0.06
	Control	2.1 (3.6)	1.9 (4.2)	1.7 (3.8)			
Hip adduction	TCC	6.7 (2.2)	5.4 (2.2)	2.2 (2.8)	$F_G = 1.560$	$P_G = 0.225$	0.07
					$F_H = 43.27$	$P_H < 0.001$↓	0.66
	Control	5.5 (2.5)	3.7 (3.4)	1.3 (3.2)			
Knee flexion	TCC	4.9 (4.5)	5.0 (4.2)	4.8 (3.9)	$F_G = 5.338$	$P_G = 0.032$*	0.22
					$F_H = 0.112$	$P_H = 0.894$	0.89
	Control	8.6 (3.2)	8.5 (3.2)	8.3 (3.5)			
Knee adduction	TCC	0.1 (1.3)	−0.1 (1.3)	−0.5 (1.5)	$F_G = 3.390$	$P_G = 0.080$	0.14
					$F_H = 2.064$	$P_H = 0.140$	0.09
	Control	−1.5 (2.4)	−1.4 (2.3)	−1.7 (1.9)			
Ankle dorsiflexion	TCC	5.7 (3.8)	6.1 (3.4)	2.3 (9.1)	$F_G = 0.311$	$P_G = 0.582$	0.01
					$F_H = 4.893$	$P_H = 0.011$↓	0.16
	Control	6.7 (3.0)	5.1 (2.7)	4.5 (2.9)			
Ankle adduction	TCC	−6.5 (2.7)	−6.7 (2.8)	−5.7 (3.1)	$F_G = 0.732$	$P_G = 0.400$	0.03
					$F_H = 0.884$	$P_H = 0.419$	0.03
	Control	−5.5 (2.2)	−5.5 (2.3)	−5.4 (4.1)			

F_G, *f*-value for subject group; F_H, *f*-value for obstacle height; P_G, *p*-value for subject group; P_H, *p*-value for obstacle height; * indicates a significant group effect ($P_G < 0.05$); ↑ indicates a linearly increasing trend and ↓ indicates a linearly decreasing trend ($P_H < 0.05$).

Whenever an obstacle height main effect was found, a *post hoc* analysis was performed using a polynomial test to determine the linear trend. If significant interactions between the main factors were found, pair-wise between-group comparisons were performed using an independent *t*-test for each obstacle height, and a *post hoc* trend analysis was performed to determine the linear trend for each group. Results of the *P*-values, *T*-values, *F*-values and effect sizes in terms of partial η^2 were reported. A significance level of $\alpha = 0.05$ was set for all tests. The multi-link system approach (Hsu et al., 2016; Chien and Lu, 2017; Wu et al., 2019a) was used to synthesize the significant kinematic changes of individual joints and end-points to reveal the kinematic strategies of obstacle-crossing in the TCC group.

Sample size calculation

An *a priori* power analysis based on pilot data of the pelvic orientations and lower limb joint angles from four subjects for each group using G*POWER (Erdfelder et al., 1996) for two-way mixed-design analysis of variance (ANOVA) for the comparisons of the angles with one between-subject factor (group) and one within-subject factor (obstacle height) determined that a projected sample size of 14 subjects for each group would be needed with a power of 0.8 and a large effect size (Cohen's $d = 0.63$) at a significance level of 0.05. Thus, 15 subjects for each group were considered adequate for the main objectives of the current study.

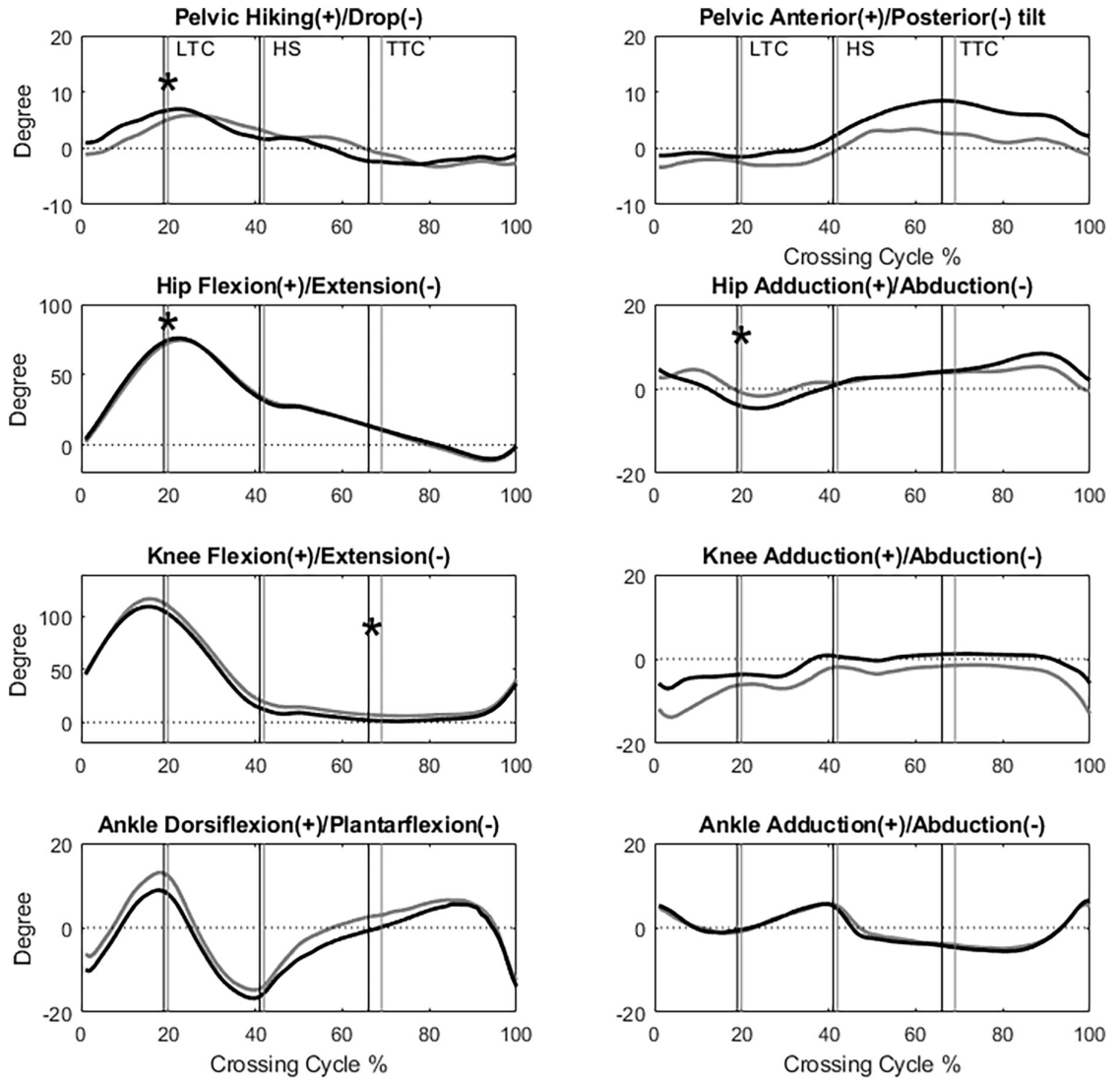


FIGURE 2
The angles of the pelvis, hip, knee and ankle joints of the leading limb in the sagittal and frontal plane of typical subjects of the TCC (black) and Control (gray) groups when crossing obstacles of 30% of leg length (LTC, leading toe above the obstacle; HS, heel-strike of the leading limb; TTC, trailing toe above the obstacle; *: Significant main group effect, $p < 0.05$).

Results

Subject demographics

Subject demographic data are given in Table 1. There were no significant between-group differences in age, sex, height, and mass.

Temporal-spatial and end-point parameters

All the temporal-spatial and end-point parameters had no interactions between the group and height factors. The TCC group showed significantly greater leading (p = 0.025, partial η^2 = 0.23) and trailing toe-obstacle clearances (p = 0.025,

TABLE 5 Means (standard deviations) of the crossing angles of the hip, knee and ankle joints of the trailing swing limb and leading stance limb in TCC practitioners (TCC) and non-TCC controls (Control) when the trailing toe was above the obstacle of heights of 10, 20, and 30% of subjects' leg length (LL).

Variables	Group	Obstacle height (%LL)			F-values	Main effects	Partial eta squared
		10%	20%	30%			
Trailing swing limb							
Hip flexion	TCC	27.3 (3.6)	32.2 (4.8)	36.5 (7.3)	F_G = 1.793	P_G = 0.192	0.07
					F_H = 54.65	P_H < 0.001↑	0.68
	Control	24.5 (6.0)	29.9 (5.7)	33.9 (6.0)			
Hip adduction	TCC	1.5 (2.7)	1.0 (3.8)	0.1 (4.6)	F_G = 6.118	P_G = 0.021*	0.20
					F_H = 0.669	P_H = 0.517	0.03
	Control	4.0 (3.1)	5.2 (5.1)	4.9 (6.2)			
Knee flexion	TCC	92.7 (3.2)	109.0 (8.6)	120.3 (8.0)	F_G = 2.581	P_G = 0.122	0.11
					F_H = 125.1	P_H < 0.001↑	0.85
	Control	96.8 (7.4)	112.0 (9.0)	124.4 (7.1)			
Knee adduction	TCC	−5.0 (4.0)	−5.7 (3.7)	−4.6 (3.8)	F_G = 34.885	P_G = 0.136	0.12
					F_H = 1.860	P_H = 0.170	0.09
	Control	−10.3 (7.0)	−8.3 (7.2)	−7.6 (6.7)			
Ankle dorsiflexion	TCC	2.9 (7.1)	8.0 (7.9)	8.4 (11.5)	F_G = 0.010	P_G = 0.920	0.01
					F_H = 19.89	P_H < 0.001↑	0.43
	Control	2.5 (7.5)	7.0 (9.0)	10.8 (7.8)			
Ankle adduction	TCC	0.1 (3.8)	−1.0 (4.8)	−1.5 (4.3)	F_G = 1.237	P_G = 0.276	0.05
					F_H = 3.223	P_H = 0.048↓	0.11
	Control	−2.0 (2.8)	−2.3 (3.6)	−2.5 (3.3)			
Leading stance limb							
Hip flexion	TCC	13.3 (5.2)	12.9 (5.2)	13.3 (7.6)	F_G = 1.559	P_G = 0.223	0.06
					F_H = 0.710	P_H = 0.496	0.03
	Control	11.4 (4.1)	10.4 (4.0)	10.9 (4.6)			
Hip adduction	TCC	8.7 (3.7)	7.9 (4.2)	4.2 (5.3)	F_G = 0.184	P_G = 0.671	0.01
					F_H = 51.125	P_H < 0.001↓	0.66
	Control	10.7 (4.0)	8.2 (4.2)	4.0 (5.3)			
Knee flexion	TCC	5.6 (6.6)	2.9 (7.4)	1.9 (9.0)	F_G = 6.608	P_G = 0.017*	0.22
					F_H = 20.47	P_H < 0.001↓	0.47
	Control	11.6 (4.6)	8.9 (3.4)	7.6 (3.1)			
Knee adduction	TCC	0.6 (1.1)	0.6 (1.5)	0.8 (2.2)	F_G = 4.138	P_G = 0.055	0.17
					F_H = 3.895	P_H = 0.028↑	0.16
	Control	−1.6 (2.5)	−1.0 (2.3)	−0.5 (2.5)			
Ankle dorsiflexion	TCC	3.1 (3.0)	3.6 (2.7)	−1.5 (11.3)	F_G = 1.545	P_G = 0.225	0.06
					F_H = 3.759	P_H = 0.030↓	0.13
	Control	4.0 (3.0)	3.8 (3.3)	2.9 (4.5)			
Ankle adduction	TCC	−4.4 (2.6)	−5.3 (3.2)	−4.2 (2.6)	F_G = 0.077	P_G = 0.784	0.01
					F_H = 1.065	P_H = 0.352	0.04
	Control	−4.5 (2.2)	−4.3 (3.0)	−4.3 (2.8)			

F_G, f-value for subject group; F_H, f-value for obstacle height; P_G, p-value for subject group; P_H, p-value for obstacle height; * indicates a significant group effect (P_G < 0.05); ↑ indicates a linearly increasing trend and ↓ indicates a linearly decreasing trend (P_H < 0.05).

partial η^2 = 0.22) but smaller trailing stride lengths (p = 0.01, partial η^2 = 0.25) and heel-obstacle distance (p = 0.003, partial η^2 = 0.28) when compared to the Control group (Table 2). No significant between-group differences were found in crossing speed, leading stride lengths, toe-obstacle distances and leading heel-obstacle distance (Table 2).

Group effects on crossing angles

All the kinematic variables had no interactions between the group and height factors. When the leading toe was above the obstacle, compared to the Control group, the TCC group showed significantly increased swing-side pelvic hiking (p = 0.048, partial η^2 = 0.19) and swing hip flexion (p = 0.033, partial η^2 = 0.21) but decreased swing hip adduction (p = 0.032, partial η^2 = 0.17) and stance knee flexion (p < 0.032, partial η^2 > 0.22) (Tables 3, 4 and Figure 2). When the trailing toe was above the obstacle, the TCC group showed significantly increased swing-side pelvic hiking (p = 0.008, partial η^2 = 0.28) and anterior tilt (p = 0.02, partial η^2 = 0.22) but decreased hip adduction (p = 0.021, partial η^2 = 0.20) in the swing limb and knee flexion in the stance limb (p < 0.017, partial η^2 > 0.22) (Tables 3, 5 and Figure 3). The observed significant angular changes of the pelvis and individual joints in the TCC group all contributed to the increased leading and trailing toe-obstacle clearances (Figures 4, 5).

Height effects on crossing angles

With increasing obstacle height, both TCC and Control groups linearly reduced the crossing speeds, leading stride length, leading toe-obstacle distance, leading heel-obstacle

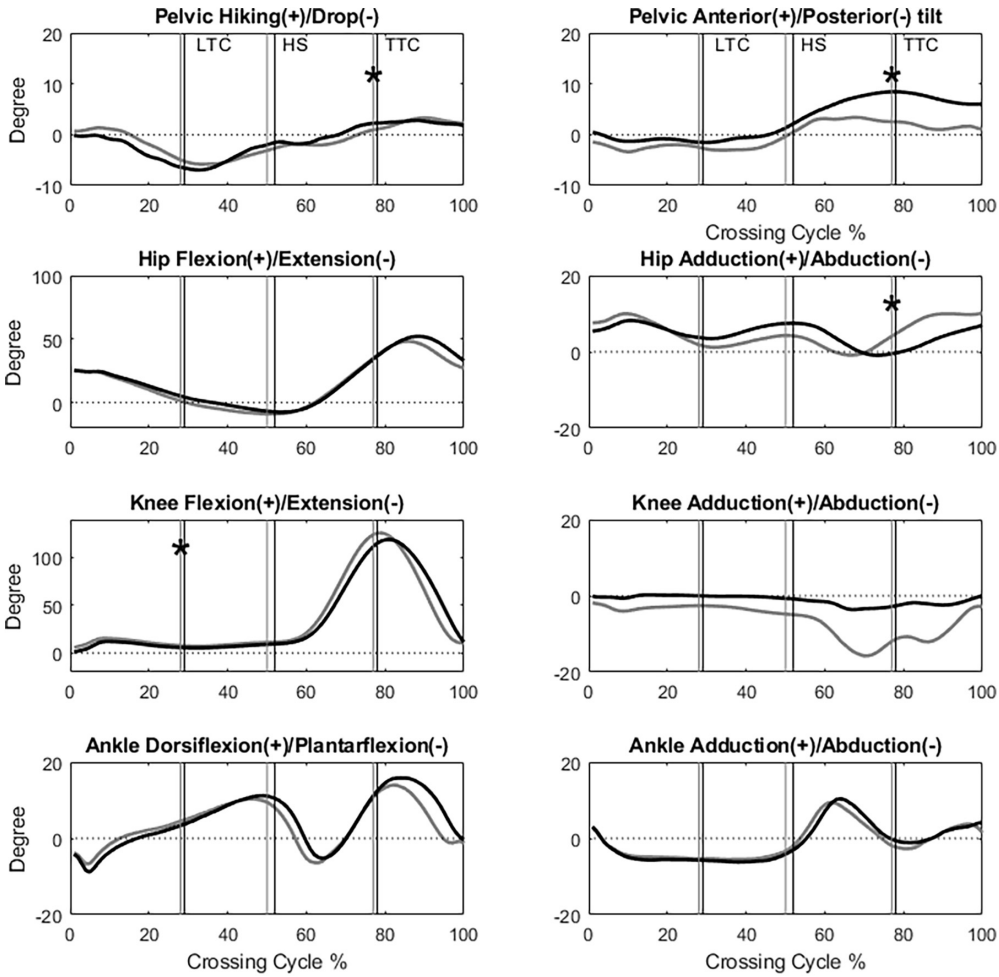


FIGURE 3
The angles of the pelvis, hip, knee and ankle joints of the trailing limb in the sagittal and frontal plane of typical subjects of the TCC (black) and Control (gray) groups when crossing obstacles of 30% of leg length (LTC, leading toe above the obstacle; HS, heel-strike of the leading limb; TTC, trailing toe above the obstacle; *: Significant main group effect, p < 0.05).

distance, and trailing heel-obstacle distance but linearly increased the leading toe-obstacle clearance ($p < 0.01$, partial $\eta^2 > 0.19$, Table 2). When the leading toe was above the obstacle, both groups linearly increased swing-side pelvic hiking and posterior tilt, hip flexion, knee flexion, and ankle abduction of the swing limb, but linearly decreased the hip adduction and knee abduction in the swing limb, as well as decreased the ankle dorsiflexion of the stance limb ($p < 0.02$, partial $\eta^2 > 0.16$, Tables 3, 4). On the other hand, when the trailing toe was above the obstacle, both groups linearly increased swing-side pelvic hiking and anterior tilt, hip flexion, knee flexion, ankle dorsiflexion and abduction of the swing limb, and knee adduction of the stance limb, as well as linearly decreased the hip adduction, knee flexion and ankle dorsiflexion of the stance limb ($p < 0.05$, partial $\eta^2 > 0.11$, Tables 3, 5).

Discussion

The current study aimed to identify the kinematic strategies of the pelvis-leg apparatus in older long-term TCC practitioners during obstacle crossing, an activity of daily living that exposes older people to a higher risk of falls (Tinetti and Speechley, 1989; McFadyen and Prince, 2002). Compared to the Control group, the TCC group showed increased leading and trailing toe-obstacle clearances *via* a specific multi-joint kinematic strategy involving the pelvis, the hip of the swing limb and the knee of the stance limb, which appeared to be related to the training characteristics of TCC movements. The current results suggest that with the specific kinematic strategy, the older individuals with TCC experience for thirteen or more years had reduced tripping risks compared to their non-TCC peers. Further study may be needed to determine the period

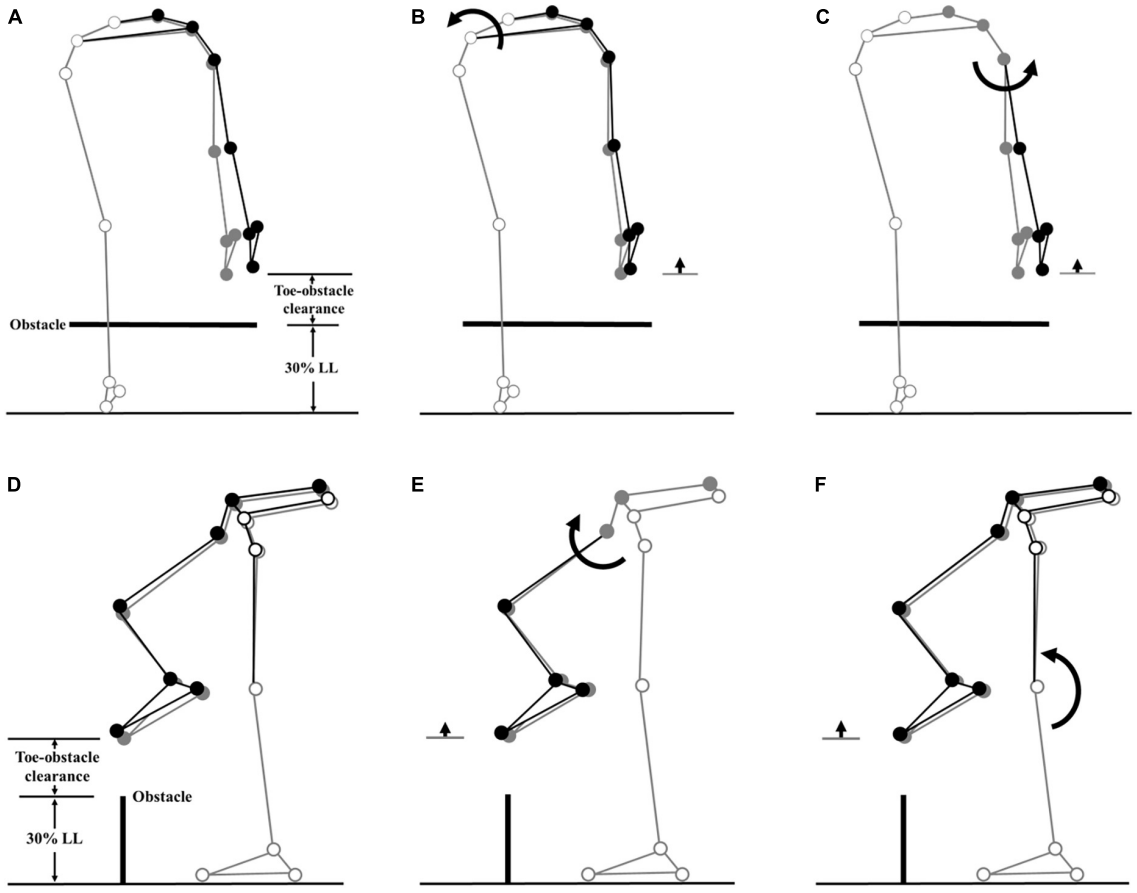


FIGURE 4
Effects of the observed significant angular changes at individual joints on the leading toe-obstacle clearance in the TCC group (black stick figure) compared with the Control group (gray stick figure) when the leading toe was above an obstacle of 30% LL in height. The stick model was drawn using each group's marker positions of a typical subject, the segments with solid gray circles being joints of the reference limb. With the stance foot fixed to the ground, only one joint was rotated at a time according to the mean angular change reported in Tables 3, 4, while keeping the angles of the other joints fixed, and the segments of the stance limb and the segments of the swing limb distal to the current joint stationary. In the frontal plane, the observed increase of toe-obstacle clearance in the TCC group **(A)** was associated with significantly increased pelvic hiking **(B)** and decreased swing hip adduction **(C)**, while in the sagittal plane, the observed increase of toe-obstacle clearance **(D)** was associated with the significantly increased swing hip flexion **(E)** and decreased stance knee flexion **(F)**.

of TCC practice required to have similar benefits in older people.

During leading-limb crossing, the TCC group increased the leading toe-obstacle clearance, an indication of reduced risk of tripping (Sparrow et al., 1996), with a kinematic strategy consisting of increased swing-side pelvic hiking and swing hip flexion and decreased swing hip adduction and stance knee flexion. The TCC group also increased the trailing toe-obstacle clearance by increasing the swing-side pelvic hiking and anterior tilt and decreasing the swing hip adduction and stance knee flexion. All the significant pelvic and joint kinematic changes contributed to the increase of the toe-obstacle clearances. This is in contrast to kinematic changes found in patient populations such as patients with type II diabetes mellitus (Hsu et al., 2016), isolated posterior cruciate ligament deficiency (Kuo et al., 2017), and severe idiopathic thoracic scoliosis (Wu et al., 2019a), in which some kinematic changes were tending to increase the toe-obstacle clearance while others showed the opposite effects. Such antagonistic kinematic changes may be interpreted as some kinematic changes with positive effects (potential upward deviations of the end-point) were needed to compensate for the negative (decreasing) effects on toe-obstacle clearance of some joint kinematic deviations. The TCC group appeared to have acquired a synergistic multi-joint kinematic strategy in which each kinematic change contributed positively to the observed increase of toe-obstacle clearance.

In the kinematic strategy adopted by the TCC group, the motion of the pelvis was the main contributor to the increased toe-obstacle clearance, especially the pelvic hiking that lifted the swing limb and the end-point directly. Considering the end-point as the tip of a pendulum rotating about a joint, being proximal to the hip and knee, the pelvic anterior tilt also had a greater effect on the position of the end-point and thus the toe-obstacle clearance (Chen et al., 2016; Wu et al., 2019a). On the other hand, the kinematic changes at the swing hip and stance knee appeared to provide refinement for precision control of the end-point. Overall, the observed synergistic multi-joint kinematic strategy in older long-term TCC practitioners was also accompanied by more in-phase but less variable inter-joint coordination patterns in the lower limbs during obstacle

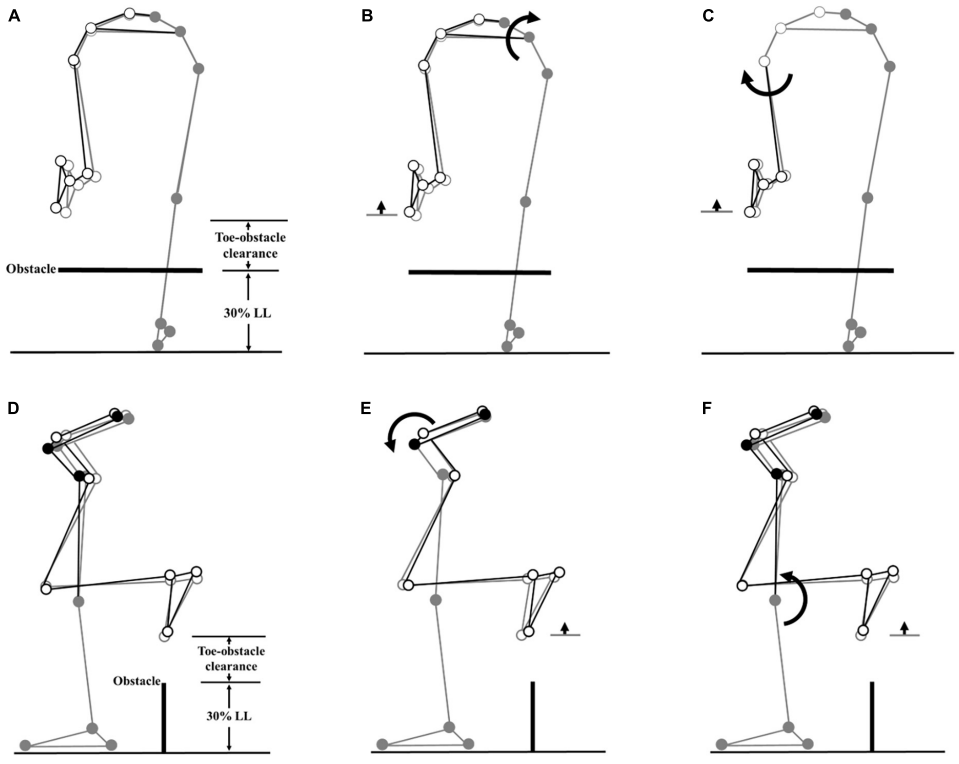


FIGURE 5
Effects of the observed significant angular changes at individual joints on the trailing toe-obstacle clearance in the TCC group (black stick figure) compared with the non-TCC controls (gray stick figure) when the trailing toe was above an obstacle of 30% LL in height. The stick model was drawn using each group's marker positions of a typical subject, the segments with solid gray circles being joints of the reference limb. With the stance foot fixed to the ground, only one joint was rotated at a time according to the mean angular change reported in **Tables 3**, **5**, while keeping the angles of the other joints fixed, and the segments of the stance limb and the segments of the swing limb distal to the current joint stationary. In the frontal plane, the observed increase of toe-obstacle clearance in the TCC group **(A)** was associated with significantly increased pelvic hiking **(B)** and decreased swing hip adduction **(C)**, while in the sagittal plane, the observed increase of toe-obstacle clearance **(D)** was associated with the significantly increased pelvic anterior tilt **(E)** and decreased stance knee flexion **(F)**.

crossing previously found, compared to older people without TCC training (Kuo et al., 2021b).

The altered motions of the pelvis involved in the synergistic multi-joint kinematic strategy in older long-term TCC practitioners did not seem to cause adverse effects on the balance control during obstacle-crossing as previously reported in older people without TCC experience (Hsu et al., 2016; Kuo et al., 2017; Wu et al., 2019a). While the increased swing-side hiking and an anterior tilt of the pelvis increased the toe-obstacle clearance, they would also potentially affect the motions of the trunk and thus the body's centre of mass (COM), leading to perturbations to whole-body posture and balance with increased risk of loss of balance, another major contributing factor to falls in older people (Overstall et al., 1977; Blake et al., 1988; Campbell et al., 1990). This is especially critical for leading-limb crossing as the neuromechanical challenges for balance control are greater than trailing-limb crossing when the body moves away from the trailing stance limb (Wu et al., 2020). Failure to recover balance would lead to falls once a trip or loss of balance occurs. For the TCC group, in contrast to older people without TCC experience, the body posture changes led to increased leading toe-obstacle clearance and reduced anterior COM-COP IA with better stability (Kuo et al., 2022). Moreover, the long-term TCC practitioners were found to show a well-controlled, more conservative COM-COP motion for a smoother and more stable bodyweight transfer (Hahn and Chou, 2004; Wang et al., 2010b) with relatively less mechanical energy expenditure than older peers (Kuo et al., 2021a) *via* a less variable lower-limb inter-joint coordination (Kuo et al., 2021b). A similar phenomenon was also found during trailing-limb crossing. The results of the current and previous studies suggest that long-term older TCC practitioners cross obstacles with a lesser risk of tripping and loss of balance than non-TCC practitioners *via* the specific kinematic strategy.

The kinematic strategy in the end-point and pelvis-leg motion control observed in the current long-term TCC practitioners during obstacle-crossing appeared to be related to the training characteristics of TCC movements, which were all helpful for increasing the lower limb muscle strength and body flexibility, improving whole-body balance, and reducing the variability of the inter-joint coordination of the lower limbs during obstacle-crossing (Jacobson et al., 1997; Lan et al., 1998; Wu, 2002; Mak and Ng, 2003; Kuo et al., 2021b). TCC practice is also helpful for improving attention, memory, executive functions and motor planning (Wong et al., 2009; Man et al., 2010; Lv et al., 2022). Long-term practice of TCC was found to help improve memory (Yue et al., 2020) and sensory organization in postural and balance control (Wong et al., 2001, 2009; Wu, 2002; Wu et al., 2002; Mak and Ng, 2003; Tsang et al., 2004). The positive effects of TCC practice are beneficial to the performance of obstacle-crossing, which requires not only physical strength but also the ability of motor planning (Clark et al., 2014) and an adequate allocation of cognitive resources, including memory (Patla and Vickers, 1997; Mohagheghi et al., 2004), attention and executive function (Clark et al., 2014; Clark, 2015). A recent study showed that obstacle-crossing kinematic features in TCC were found to be Central Nervous System (CNS) controlled *via* an obstacle-height independent best-compromise strategy between the conflicting objectives of minimizing mechanical energy expenditure and maximizing the foot-obstacle clearance (Kuo et al., 2021a). It appears that long-term older TCC practitioners benefited from the positive effects of long-term TCC practice both physically and neurologically, contributing to the formation of the observed specific synergistic multi-joint kinematic strategy for crossing obstacles with reduced risks of tripping and loss of balance.

The current study was the first to identify the kinematic strategies of the pelvis-leg apparatus during obstacle-crossing in long-term older TCC practitioners. Further study on the kinetics of the lower limb joints and the associated muscular activities *via* EMG analysis may be needed to provide more insight into the neuromechanical control involved in the observed kinematic strategy. The current study was also limited to a cross-sectional design as studies before and after TCC training cannot be used in TCC with thirteen years of experience. However, the current results provide important evidence to encourage further longitudinal studies on the multi-joint kinematic strategies before and after short-term TCC training, which will help identify the specific causal effects of TCC training on the postural adjustments during obstacle-crossing in the older population.

The current results have several possible clinical implications and applications. Older people may benefit from the positive effects of long-term TCC practice both physically and neurologically, which helps to form the observed synergistic multi-joint kinematic strategy for obstacle-crossing. Knowledge of the similarities or differences in the control strategies and the resulting joint mechanics between TCC and non-TCC groups would be helpful in developing improved fall prevention strategies and for making better use of TCC training in fitness programs for the elderly. It is suggested that TCC practice may be adjusted and integrated into the daily activities of inpatient and long-term care facilities, which may reduce the risk of tripping when negotiating obstacles and improve the general physical condition of the older population.

Conclusion

The current study identified the kinematic changes of the pelvis and the lower limb joints and, through a multi-link analysis, revealed a specific synergistic multi-joint kinematic strategy adopted to reduce tripping risks during obstacle-crossing in older long-term TCC practitioners as compared to non-TCC healthy controls. In such a strategy, each significant kinematic change contributed positively to the

observed increase of leading and trailing toe-obstacle clearances. The current results suggest that the older long-term TCC practitioners had the necessary physical and neurological abilities for the observed kinematic strategies and the associated toe-obstacle clearances. Long-term TCC practice appeared to be helpful for older people in reducing the risk of tripping and the subsequent loss of balance.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the China Medical University and Hospital Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

H-PH: conceptualization, data curation, resources, formal analysis, and writing–original draft. C-CK and S-HL: data curation, resources, and writing–original draft. S-CC: data curation, formal analysis, and writing–original draft. T-JH: data curation, resources, and writing–original draft. T-WL: conceptualization, supervision, writing–original draft, and writing–review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect and mechanism of traditional Chinese exercise for chronic low back pain in middle-aged and elderly patients: A systematic review

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Background: Increasing lines of evidence indicate that traditional Chinese exercise (TCE) has potential benefits in improving chronic low back pain (CLBP) symptoms. To assess the clinical efficacy of TCE in the treatment of CLBP, we performed a systematic review of existing randomized controlled trials (RCTs) of CLBP and summarized the neural mechanisms underlying TCE in the treatment of CLBP.

Methods: A systematic search was conducted in four electronic databases: PubMed, Embase, the Cochrane Library, and EBSCO from January 1991 to March 2022. The quality of all included RCTs was evaluated by the Physiotherapy Evidence Database Scale (PEDro). The primary outcomes included pain severity and pain-related disability.

Results: A total of 11 RCTs with 1,256 middle-aged and elderly patients with CLBP were included. The quality of all 11 included RCTs ranged from moderate to high according to PEDro. Results suggested that TCE could considerably reduce pain intensity in patients with CLBP. Overall, most studies did not find any difference in secondary outcomes (quality of life, depression, and sleep quality).

Conclusion: The neurophysiological mechanism of TCE for treating CLBP could be linked to meditation and breathing, posture control, strength and flexibility training, and regulation of pain-related brain networks. Our systematic review showed that TCE appears to be effective in alleviating pain in patients with CLBP.

KEYWORDS

chronic low back pain, traditional Chinese exercise, elderly people, Tai Chi, Qigong

Introduction

Incidence of low back pain (LBP) increases progressively with age (Neuhauser et al., 2005); it is estimated that 12% of adults over the age of 65 suffer from chronic LBP (CLBP) (Arnstein, 2010). When LBP in older population becomes chronic (lasting more than 12 weeks) (Deyo et al., 2014), it can lead to a variety of harmful consequences, including falls and fractures (Leveille et al., 2009), depression/anxiety (Meyer et al., 2007; Kroenke et al., 2013), social difficulties (Mackichan et al., 2013), and sleep disturbances (Weiner et al., 2006a). In addition, extraspinal conditions (i.e., osteoarthritis and fibromyalgia) are common in older adults with CLBP and may be linked to pain-related disability (Weiner et al., 2006b; Viniol et al., 2013; Rundell et al., 2017). Although clinicians have treated CLBP with conventional medication and surgery for a long time, many patients continue to experience pain without significant pain relief (Steffens et al., 2016; Maher et al., 2017). Therefore, over the past 30 years, many clinical guidelines have recommended that treatment of CLBP should focus on non-pharmacological treatments, such as exercise therapy and mind–body exercise (Bernstein et al., 2017; Qaseem et al., 2017; Wong et al., 2017; Stochkendahl et al., 2018; Zhang et al., 2019; Peng et al., 2022; Xiong et al., 2022). Exercise therapy, which includes a variety of interventions ranging from aerobic exercise to muscle strength training, has been shown to be useful in alleviating pain (Lawand et al., 2015; Wieland et al., 2017; Russo et al., 2018; Smith et al., 2022; Wu et al., 2022).

Under this condition, traditional Chinese exercise (TCE), as a therapeutic mind–body exercise, has been widely concerned by researchers (Koh, 1982; Chou et al., 2015; Guo et al., 2018). TCE [i.e., Tai Chi (Zou et al., 2017a) and Qigong (Zou et al., 2018a)] is becoming increasingly popular around the world and is being used to treat various diseases and prevent chronic disease progression (Zhu et al., 2016). TCE emphasizes mind–body integration; slow body movements should be synchronized with musculoskeletal relaxation, respiratory control, and mental focus in a meditative state (Luo et al., 2017; Zou et al., 2018c). In addition, TCE requires the stability of the trunk muscles to maintain the center of gravity, which embodies the principle of core stability training (Wang et al., 2013). In recent years, TCE has been successfully used worldwide for the treatment of CLBP and is recommended as a therapeutic activity according to the guidelines of the American College of Physicians (Qaseem et al., 2017). A meta-analysis also suggested that TCE might provide some pain relief in patients with LBP(Zhang et al., 2019). For instance, Blodt et al. (2015) suggested that Qigong training was no worse than exercise therapy for pain relief in patients with CLBP. Our previous work also supported that the patients with chronic non-specific LBP over the age of 50 engaging in Chen-style Tai Chi for 12 weeks had significantly reduced pain (Liu et al., 2019; Zou et al., 2019a). However, results from different randomized controlled trials (RCTs) are inconsistent, with some studies suggesting that yoga and Qigong had no effect on relieving CLBP possibly due to the small sample size or differences in pain sensitivity and processing in the elderly (Teut et al., 2016). The conclusions from current studies have remained controversial. In addition, there are no systematic reviews of TCE interventions for CLBP in the middle-aged and elderly. Therefore, further review and analysis of available data on TCE-related pain and disability in middle-aged and elderly patients with CLBP are necessary.

Materials and methods

Search strategy and inclusion criteria

This systematic review was registered with the Open Science Framework (10.17605/OSF.IO/NWGSF).[1] PRISMA guidelines were followed (Moher et al., 2009). PubMed, Embase, the Cochrane Library, and EBSCO were searched from January 1991 to March 2022 for relevant clinical trials (**Supplementary material 1**). The following combination of terms was used as search keywords in the title and abstract: T1 = Tai Chi OR "Tai Chi *" OR Qigong OR Liuzijue OR Wuqinxi OR Yijinjing OR Baduanjin OR "traditional exercise" OR traditional Chinese medicine OR "Chinese traditional exercise" OR "traditional Chinese exercise" OR "Chinese exercise," T2 = back pain OR low backache OR lower back pain OR lumbago OR lumbosacral pain OR sciatica. When screening clinical trials, the inclusion criteria are as follows:

(1) Types of studies. We included only published articles from RCTs that examined the effect of TCE on LBP. The article language was limited to English.
(2) Participants. All middle-aged and elderly patients (mean age > 35 years old) with a diagnosis of LBP were considered for this review.
(3) Interventions. The interventions included different types of TCE (i.e., Tai Chi, Baduanjin, Yijinjing, Qigong, Liuzijue, and Wuqinxi). Clinical trials comparing TCE with no intervention, placebo (waiting-list, unaltered lifestyle), or other treatments (such as exercise therapy, massage, and physical activity) were included.
(4) Types of outcome measures. Outcome measures should include at least one of two evaluations: pain and disability.

Study selection and data extraction

Two authors independently screened all titles, abstracts, and main text of the relevant papers according to the

1 https://osf.io/nwgsf

inclusion criteria. Papers that did not match the criteria for inclusion were omitted. Disagreements were settled by discussion or a third reviewer. The following information was extracted from the selected articles: (1) published data (author, year); (2) design of included studies (subject subgroup, sample size, randomization, follow-up, clinical outcome measures, and time points); (3) type of intervention (including dose regimen, duration); (4) characteristics of participants (including baseline demographic information and diagnostic/inclusion/exclusion criteria); and (5) adverse effects.

Quality assessment and data analysis

We used the Physiotherapy Evidence Database scale (PEDro) to assess the risk of bias for inclusion and the methodological quality of each study in this systematic review (**Supplementary Table 1**). Two authors independently evaluated the quality of the included RCTs, and all disagreements were settled by discussion or a third reviewer. The following information was evaluated: randomized allocation, concealed allocation, baseline comparability, blind subjects, blind therapists, blind assessors, adequate follow-up, intention-to-treat analysis, between-group comparisons, point estimates, and variability. Scores < 4 points were considered as poor quality; 4–5 points as modern quality; 6–8 points as high quality; 9–10 as excellent quality. The characteristics of the included RCTs were examined (**Table 1**). Then, The findings were then narratively presented in terms of the TCE's mechanisms in the treatment of LBP, which were detailed and discussed in the following sections.

Results

Search results

As shown in **Figure 1A**, 718 papers in related fields were retrieved from the four electronic databases. After removing 235 duplicates, 483 articles were screened for eligibility. Through reviewing the titles, abstracts, and full contents of the selected studies, we excluded another 472 articles (review = 62, protocol = 31, animal studies = 14, non-LBP = 93, non-TCE = 179, non-RCT = 80, no essential outcomes = 6, age of subjects less than 35 years old = 7). Finally, 11 RCTs were included in this review (Hall et al., 2011, 2016; Blodt et al., 2015; Teut et al., 2016; Qaseem et al., 2017; Liu et al., 2019; Phattharasupharerk et al., 2019; Zou et al., 2019a; Ma et al., 2020; Sherman et al., 2020; Yao et al., 2020).

Study characteristics

Table 1 shows the key characteristics of all included RCTs. Eleven RCTs involving 1,256 participants (810 females) ranging in age from 35 to 73 years were included. The sample size of each RCT ranged from 43 to 176. These RCTs were performed in China, Germany, Australia, England, Thailand, and the USA between 2013 and 2020 (**Figure 1B**). Three kinds of TCE programs were used to treat CLBP in all intervention groups (7 for Tai Chi, 3 for Qigong, and 1 for Wuqinxi). In the control group, active interventions (such as core training, exercise therapy, or yoga) or passive interventions (such as health education) were used. The treatment duration ranged from 6 weeks to 6 months, with each session lasting from 30 to 90 min, of which 12 weeks was the most common in six trials. The visual analogue scale (VAS) and the numerical rating scale (NRS) were used to evaluated the major outcomes for pain severity.

Quality assessment

Supplementary Table 1 summarizes the quality evaluation results for each RCT by using the PEDro scale. The quality of all 11 studies considered in this review ranged from moderate to high (**Figure 1C**). In most RCTs, participants, therapists, and assessors were not blinded.

Effect of traditional Chinese exercise on pain

All 11 included studies involving 1,256 patients with LBP examined the effect of different types of TCE on pain intensity. Ten studies suggested that TCE group outperformed the control group in terms of pain relief, but one of the studies found that the effectiveness of Qigong for pain relief decreased over time. Only one study found no significant difference in pain alleviation between the Qigong and the control groups (Teut et al., 2016).

Effect of traditional Chinese exercise on pain-related disability, quality of life, and sleep quality

Of the 11 included studies, five studies investigated the effects of TCE on back functional disability, three studies evaluated the effect on quality of life (QOL), and four studies determined the effect on sleep quality and satisfaction. Three studies suggested that Tai Chi had effectively improved back pain-related disability compared with the control group (Hall et al., 2011, 2016; Sherman et al., 2020).

TABLE 1 Summary of included studies.

References	Country	Participant characteristic, sample size	Disease	Drugs	Intervention	Time point	Duration of trial period	Primary Outcomes	Result
Hall et al., 2011	Australia	160 subjects *M* = 41, *F* = 119 Mean age (± SD): 44.4 ± 13.2	Persistent low back pain	NA	G1 (*n* = 80): Tai Chi G2 (*n* = 80): Control group(usual health care)	10 weeks	18 sessions over 10 weeks (2 times per week for 8 weeks followed by once per week for 2 weeks)	1. Pain intensity (NRS) 2. Disability (RMDQ)	Tai Chi produced greater reductions in pain symptoms and pain-related disability than the control intervention.
Weifen et al., 2013	China	320 subjects *M* = 192, *F* = 128 Mean age (± SD): 37.6 ± 5.4	Chronic non-specific low back pain	NA	G1 (*n* = 141): Tai Chi group G2 (*n* = 47): Backward walking group G3 (*n* = 47): Jogging group G4 (*n* = 38): Swimming group G5 (*n* = 47): No exercise group	6 months	G1: Five 45 min sessions per week for 6 months G2-5: Five 30 min sessions per week for 6 months	1. Pain intensity (NRS)	After three and six months, no statistically significant difference in the intensity of LBP was demonstrated between the tai chi and swimming groups; significant differences were demonstrated among the tai chi and backward walking, jogging, and no exercise groups.
Blodt et al., 2015	Germany	127 subjects *M* = 25, *F* = 102 Mean age (± SD): 46.7 ± 10.4	Chronic non-specific low back pain	No medication taken during the period of study	G1 (*n* = 64): Qigong group G2 (*n* = 63): Exercise therapy group	3 months	Weekly sessions of 90 min over a period of 3 months	1. Pain intensity (VAS)	Qigong was not proven to be non-inferior to exercise therapy in the treatment of chronic LBP.
Teut et al., 2016	Germany	176 subjects *M* = 20, *F* = 156 Mean age (± SD): 73 ± 5.6	Chronic non-specific low back pain	No medication taken during the period of study	G1 (*n* = 61): Yoga group G2 (*n* = 58): Qigong group G3 (*n* = 57): Control group (no additional intervention)	3 months	1. Yoga (24 classes, 45 min each, during 3 months) 2. Qigong (12 classes, 90 min each, during 3 months)	1. Pain intensity (VAS) 2. Pain (Functional Rating Index)	Participation in a 3-month yoga or qigong program did not improve chronic LBP, back function and quality of life.
Hall et al., 2016	England	102 subjects *M* = 25, *F* = 77 Mean age: 66.5	Chronic non-specific low back pain	NA	G1 (*n* = 51): Tai Chi group G2 (*n* = 51): Wait-list Control group (usual care)	10 weeks	Two 40 min sessions per week for the first 8 weeks, and one 40 min session class for the last 2 weeks	1. Pain intensity (NRS) 2. Pain related disability (RMDQ)	The total effects showed better outcome on measures for the tai chi group and were all significant at the 5% significance level.
Zou et al., 2019a	China	43 subjects *M* = 11, *F* = 32 Mean age: 58	Chronic non-specific low back pain	NA	G1 (*n* = 15): Tai Chi group G2 (*n* = 15): Core stability training group G3 (*n* = 13): Control group (normal daily activities)	12 weeks	Three sessions per week, with each session lasting 60 min for 12 weeks	1. Pain intensity (VAS) 2. Neuromuscular function assessment	Chen-style tai chi and Core stability training were found to have protective effects on neuromuscular function in aging individuals with non-specific LBP, while alleviating non-specific chronic pain.

(Continued)

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TABLE 1 (Continued)

References	Country	Participant characteristic, sample size	Disease	Drugs	Intervention	Time point	Duration of trial period	Primary Outcomes	Result
Phattharasupharerk et al., 2019	Thailand	72 subjects $M = 26$, $F = 46$ Mean age: 35.25	Chronic non-specific low back pain	No medication taken during the period of study	G1 ($n = 36$): Qigong group G2 ($n = 36$): waiting list (general advice)	6 weeks	60 min session per week for 6 weeks	1. Pain intensity (VAS) 2. Back functional disability (RMDQ)	The qigong group showed significant improvement in pain and functional disability both within the group and between groups.
Liu et al., 2019	China	43 subjects $M = 11$, $F = 32$ Mean age: 59	Chronic non-specific low back pain	NA	G1 ($n = 15$): Tai Chi group G2 ($n = 15$): Core stabilization training group G3 ($n = 13$): No intervention	12 weeks	Three 60-min sessions per week for 12 weeks	1. Pain intensity (VAS) 2. Knee and ankle joint position sense	Tai Chi and Core Stabilization training have significant effects on pain VAS but not on joint position sense.
Yao et al., 2020	China	72 subjects $M = 14$, $F = 58$ Mean age ($\pm$ SD): 53.5 ± 15	Chronic non-specific low back pain	No medication taken during the period of study	G1 ($n = 36$): Wuqinxi group G2 ($n = 36$): General exercise group	24 weeks	Four times a week with 1 h of each session for 24 weeks	1. Pain intensity (VAS) 2. Trunk Muscle Strength	Wuqinxi had better effects on chronic LBP for a long time compared with general exercise, including pain intensity and quality of life.
Ma et al., 2020	China	84 subjects $M = 59$, $F = 25$ Mean age: 36	Axial spondyloarthritis	NA	G1 ($n = 42$): Tai Chi group G2 ($n = 42$): Standard exercise therapy	12 weeks	Three 30–40 min sessions per week for 12 weeks	1. Pain intensity (VAS) 2. Spinal motor function	Compared with standard exercise therapy, "tai chi spinal exercise" has an ideal effect in patients with axial spondyloarthritis, which can more effectively relieve patient's LBP and improve spinal motor function, with shorter training time and better compliance.
Sherman et al., 2020	USA	57 subjects $M = 22$, $F = 35$ Mean age: 73	Chronic non-specific low back pain	NA	G1 ($n = 28$): Tai Chi group G2 ($n = 12$): Health education group G3 ($n = 17$): Usual care group	12 weeks	Two 60 min sessions per week for 12 weeks	1. 0–10-point pain intensity measure 2. Pain related disability (RMDQ)	Compared with health education, tai chi participants rated both the helpfulness of classes and their likelihood of recommending the classes to other significantly higher.

LBP, low back pain; VAS, visual analog scale; NRS, numerical rating scale; RMDQ, Roland-Morris Disability Questionnaire.

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Phattharasupharerk et al. and Blödt et al. reported that Qigong did not improve back functional disability effectively because the Roland–Morris Disability Questionnaire (RMDQ) scores did not meet the minimal clinically important difference level (Blodt et al., 2015; Phattharasupharerk et al., 2019). Additionally, Qigong and Wuqinxi had effectively improved QOL and depression compared with the baseline, but no statistical difference was found compared with the control group (Blodt et al., 2015; Teut et al., 2016; Yao et al., 2020). Overall, most studies did not find any difference in the secondary outcomes tested (disability, QOL, and sleep quality).

Adverse events

Only two studies reported adverse events. Amanda et al. found that four subjects reported a slight increase in back pain at the beginning of Tai Chi training, which was relieved by the third or fourth week of the training (Hall et al., 2011). Blödt et al. found that both the Qigong group (n = 10) and exercise group (n = 10) reported suspected adverse events (e.g., muscle soreness and tenseness, dizziness, mood fluctuation, and increased back pain) (Blodt et al., 2015).

Discussion

Effectiveness of traditional Chinese exercise on middle-aged and elderly patients with chronic low back pain

Pain management in elderly patients with CLBP is particularly challenging, and long-term opioid use was associated with an increased risk of comorbidities (Makris et al., 2014), psychological distress [e.g., depression (Maher et al., 2017)] and other health problems (e.g., falls, osteoporosis, and muscular atrophy) (Chou et al., 2015). A previous review suggested that people who experienced LBP had a higher risk of recurrence (Taylor et al., 2014). Therefore, current guidelines recommend that treatment should focus on reducing pain and its associated dysfunction, and exercise is an effective treatment option (Koes et al., 2010; Zhang et al., 2020). This systematic review included 11 RCTs involving 1,256 patients with CLBP aged over 35 years to assess the overall effect of TCE in middle-aged and elderly patients with CLBP. Our results indicated that TCE could be an effective therapy for reducing pain and improving function in the patients. All treatments (Tai Chi, Qigong, and Wuqinxi) showed positive effects compared with baseline measurements.

Pain intensity relates to the degree to which a person is harmed by CLBP and can be quantified to estimate the severity of pain (Ostelo and de Vet, 2005). The results from this systematic review suggest that TCE significantly reduce the VAS or NRS scores of patients with CLBP. Compared with the control and exercise therapy groups, TCE showed better effects in alleviating pain, which is consistent with prior reviews on other exercise therapies (Hayden et al., 2005; Macedo et al., 2013). Only one study showed that 3 months of yoga or Qigong training had no effect on back pain, back function, or QOL in older patients with CLBP (Teut et al., 2016). However, the number of studies was insufficient to conclude every type of TCE. Additionally, several RCTs showed that Tai Chi/Qigong significantly contributed to proprioception and neuromuscular function in the lower limbs (Zou et al., 2019a). An RCT involving 84 patients showed that Tai Chi was more effective in improving spinal movement function, with shorter training time and better compliance compared with standard exercise therapy. Another RCT showed that office workers with CLBP achieved better health behavior after 6 weeks of Qigong exercise as well as significantly improved mental state, back function, range of motion, and core muscle strength (Phattharasupharerk et al., 2019). Despite the negative findings of some studies, the fact that CLBP is difficult to manage suggests that TCE could be a possible option for managing pain in middle-aged and elderly patients with CLBP.

Underlying mechanisms of traditional Chinese exercise for improving chronic low back pain

TCE focuses on the integration of mental regulation, breathing, and movement control in addition to internal energy regulation (Zou et al., 2019b).

First, as a foundation of mind–body interaction, meditation and rhythmic breathing can effectively boost vitality and induce energy to flow through the body, which in turn drives body movement to alleviate pain (Zou et al., 2017b). Self-awareness combined with self-correction of posture and movement of the body, flow of breath, and mental stilling activates natural self-regulatory (self-healing) abilities and stimulates a balanced release of endogenous neurohormones and a variety of natural health recovery mechanisms (Jahnke et al., 2010; Linek et al., 2020). Multiple elements of health, including mood, pain, immunity, and peripheral autonomic nervous system function, can be regulated by concentration and mindful meditation (Wayne and Kaptchuk, 2008). Some TCE programs use meditation and imagination to guide and distract attention away from pain, which can help reduce pain and enhance psychosocial health. Evidence indicates that poor pain-related outcomes (e.g., pain levels and disability) have been linked to a higher level of pain catastrophizing (Peng, 2012). Pain-related catastrophizing is a negative cognitive response to pain. For example, Hall et al. found that Tai Chi could help with pain-related symptoms by changing cognitive appraisal results, such as lowing catastrophic outcomes (Hall et al., 2016). Additionally,

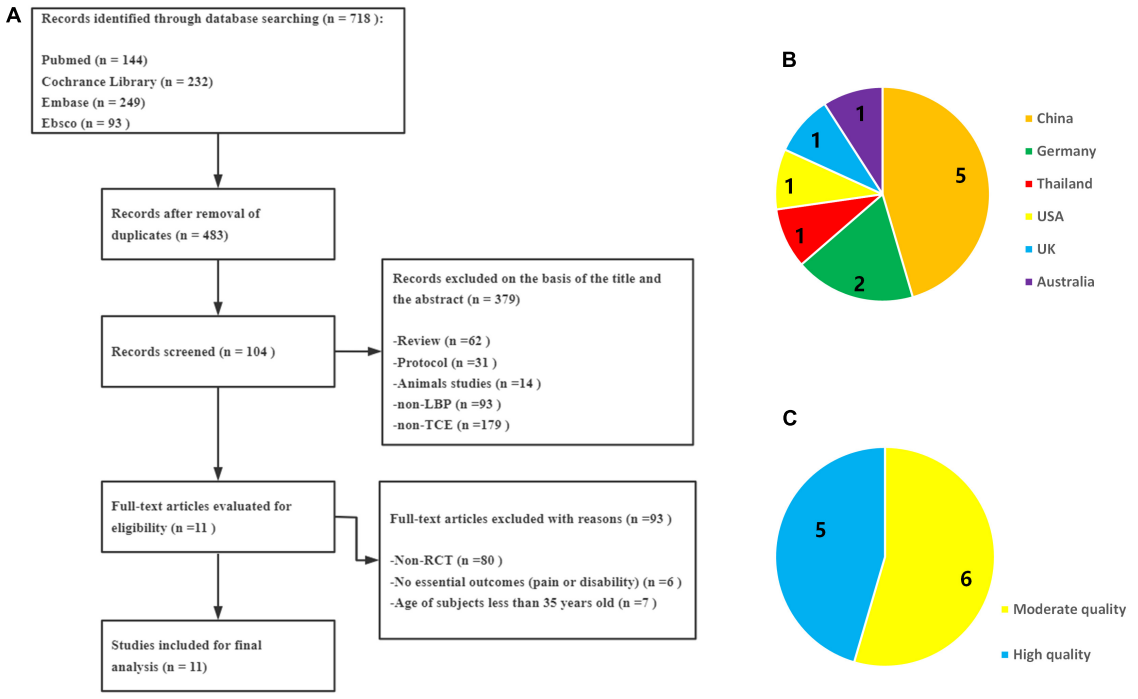


FIGURE 1
(A) A PRISMA flow diagram of the literature screening and selection processes. **(B)** Distribution of countries. **(C)** Quality assessment of PEDro.

a recent meta-analysis suggested that adults with chronic diseases obtained reduced muscle pain through mindfulness-based training (Zou et al., 2018b).

Second, TCE relieves pain by combining muscle strength, static balance, and dynamic balance, and these concepts are quite similar to other pain-relieving therapies, such as core stabilization training (Hall et al., 2011; Gordon and Bloxham, 2016). TCE can help relieve back pain by strengthening lumbar muscles and improving pelvic–lumbar neuromuscular function and proprioception. Qigong, Tai Chi, and Wuqinxi involve a series of slow, flowing, dance-like body movements. In particular, combining slow coordinated postures can transfer upper and lower body momentum and achieve balance depending on continuous squatting and weight shifting on both legs throughout the exercise (Zou et al., 2018b). Improvements in lower limb function and lumbar flexibility improved CLBP-related physical activities (i.e., sitting and standing, stair climbing, and walking) (Masharawi and Nadaf, 2013). Compared with taking anti-osteoporosis drugs, Wuqinxi can significantly reduce pain symptoms and increase the bone density of lumbar vertebrae, suggesting the positive effect of Wuqinxi on CLBP (Wei et al., 2015). Our previous work also suggested that Chen-style Wai Chi had protective effects on neuromuscular function in elderly patients with CLBP while relieving non-specific chronic pain (Zou et al., 2019a).

In addition to correcting postural control and enhancing muscle strength to relieve back pain, the pain-relieving effects of TCE may be linked to changes in TCE-induced brain activity. Long-term Tai Chi practice resulted in an increase in cortical thickness of the inferior segment of the circular sulcus of the insula as well as a decrease in the functional homogeneity of the left anterior cingulate cortex (ACC) (Wei et al., 2013, 2014). ACC plays a crucial role in the emotional aspects of pain (Fuchs et al., 2014; Barthas et al., 2015). Inhibiting ACC may help alleviate chronic pain (Gu et al., 2015). The improvement of ACC functional specificity after Tai Chi training may contribute to pain relief, thereby explaining its analgesic effect. An increase cortical thickness of insula observed in long-term Tai Chi practitioners may also contribute to pain relief through better processing of pain-related cognitive information. To uncover the neurological mechanism underlying TCE-mediated pain relief, further studies should be conducted into the direct relationship between pain perception and TCE-mediated alterations in these brain regions.

This systematic review has some limitations. First, it has location and language bias, with five studies from China, two studies from Germany, and only one study from Thailand, the USA, the UK, and Australia, which were all published in English. Second, the TCE intervention differed greatly in terms of exercise type (Tai Chi, Qigong, Wuqinxi), duration (6–24 weeks), frequency (2–5 times/week), and control group. In the future, a detailed categorization of different types of TCE programs and controls will be required. Third, most of the included RCTs did not adopt blind methods

(subject, therapist, and assessor blinding), which might lead to biased subjective expectations and exaggerate the research findings. Finally, most RCTs employed followed up for few months only, so the long-term efficacy of TCE in patients with CLBP remains unclear.

Conclusion

This systematic review shows that TCE is beneficial in relieving pain and improving pain-related dysfunction for middle-aged and elderly patients suffering from CLBP. As a convenient, cost-effective therapy with few adverse events, TCE could be recommended for elderly patients with CLBP. Nevertheless, the long-term efficacy of TCE in elderly patients with CLBP must be assessed, and theories on how TCE could treat and prevent CLBP require further investigation. In the future, more controlled studies with larger scale and stricter quality should be conducted to explore the long-term efficacy of TCE in elderly patients with CLBP.

Author contributions

X-QW and H-YX: software, formal analysis, data curation, writing – original draft preparation, visualization, and project administration. LH: conceptualization, methodology, validation, investigation, resources, supervision, and funding acquisition. S-HD and Q-HY: methodology, validation, and writing – review and editing. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.935925/full#supplementary-material

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Mechanisms of exercise for diabetic neuropathic pain

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Diabetic neuropathic pain (DNP) is a common disease that affects the daily lives of diabetic patients, and its incidence rate is very high worldwide. At present, drug and exercise therapies are common treatments for DNP. Drug therapy has various side effects. In recent years, exercise therapy has received frequent research and increasing attention by many researchers. Currently, the treatment of DNP is generally symptomatic. We can better select the appropriate exercise prescription for DNP only by clarifying the exercise mechanism for its therapy. The unique pathological mechanism of DNP is still unclear and may be related to the pathological mechanism of diabetic neuropathy. In this study, the mechanisms of exercise therapy for DNP were reviewed to understand better the role of exercise therapy in treating DNP.

KEYWORDS

exercise, diabetic neuropathic pain, mechanism, therapy, review

Introduction

The incidence rate of diabetes worldwide is very high and the number of individuals with diabetes will increase to 642 million by 2040 (Ng et al., 2021). Diabetes affects 8.3% of Americans, and the annual treatment cost of diabetes is US$ 174 billion (Feldman et al., 2019). Diabetic neuropathy is the most common chronic complication in patients with type 1 or 2 diabetes (Javed et al., 2015; Melese et al., 2020) and accounts for 54–59% and 45% of type 1 and type 2 diabetic patients (Zilliox and Russell, 2011), respectively. Pain, abnormal sensation, and decreased stability are the typical clinical symptoms of diabetic neuropathy (Goldberg et al., 2008; Marcovecchio et al., 2010).

The diabetic neuropathic pain (DNP) associated with diabetes is gradually increasing with the prevalence of diabetes (Tesfaye et al., 2010). It is reported that 25% of patients with type 2 diabetic neuropathy will experience pain (Callaghan et al., 2015). In general, symptoms related to DNP are burning, lacerating, tingling and shooting pain, loss of protective sensation, and hyperalgesia (Kirk et al., 2019). DNP hurts patients' quality of life compared with painless diabetic neuropathy (Van Acker et al., 2009).

Currently, there are no treatments available to completely cure DNP; however, drugs and exercise are its common symptomatic treatments (Pop-Busui et al., 2017). There are three main categories of drugs used to treat DNP: antiepileptics, antidepressants,

and non-specific analgesics (Feldman et al., 2019). However, the severe side effects and high cost of drug therapy have greatly limited the treatment of DNP (Tölle et al., 2006). Exercise for pain has received increasing attention in recent years, i.e., exercise for low back pain (Peng et al., 2022). Research on mechanisms related to exercise for pain has also been favored by researchers, i.e., effects of exercise-induced hypoalgesia (Wu et al., 2022). Meanwhile, the effectiveness and safety of exercise have been proven for people with diabetes (Lemaster et al., 2008; Chiang et al., 2016). According to the American Diabetes Association proposal, at least 150 sessions of moderate to vigorous aerobic exercise for adults with diabetes (60 min for children and adolescents) and 2–3 sessions per week of resistance training are need (American Diabetes Association, 2018). More randomized controlled trials are needed to further explore the mechanisms by which exercise reduces DNP in order to select the appropriate exercise prescription for treatment. This review describes the pathological mechanisms associated with exercise for DNP based on recent studies on exercise for DNP.

Mechanisms of exercise in improving diabetic neuropathic pain

Exercise is an integral part of DNP management plan, and it improves blood glucose control, reduces cardiovascular risk factors, reduces obesity, and promotes good health (American Diabetes Association, 2018). Doing exercise for treatment of DNP is increasingly favored by public-health worker. This paper summarizes studies related to the pathological mechanisms of exercise therapy for DNP (**Table 1**). This is different between exercise can reduce pain and exercise can reduce neuropathic pain in diabetes. Given that the unique mechanism of pain production is unclear, the pathological mechanism of diabetic neuropathy may be related to that of DNP (Calcutt, 2020). Therefore, it was concluded from the pathological mechanism of diabetic neuropathy that exercise may relieve pain related to DNP by affecting blood glucose and intra-epidermal nerve fibers (IENFs), inflammatory response, miRNA, apoptosis, deficit in oxide synthase (NO) synthesis, and dysregulation of voltage-gated calcium channels (VGCCs) (**Figure 1**).

The role of exercise in glucose control and intra-epidermal nerve fibers

It is known that hyperglycemia is an essential factor that causes diabetes, and that extended hyperglycemia can cause cellular damage (Callaghan et al., 2012). The pathogenesis of DNP remains to be unknown, and hyperglycemia leading to production of advanced glycation end products (AGEs) may be one of the mechanisms for the emergence of pain (Sugimoto et al., 2008). In this signal pathway, glycation of extracellular matrix protein laminin leads to impaired regenerative activity in diabetic neuropathy (Sugimoto et al., 2008). AGEs connect reactive carbohydrate groups to proteins, lipids, or nucleic acids to affect cellular functions (Duran-Jimenez et al., 2009), and AGEs bind to their receptor, initiating NADPH oxidases and generating oxidative stress further damaging neurons, vascular endothelial cells, and thus, leading to reduced IENFs (Vincent et al., 2007; Boric et al., 2013; Do et al., 2020). To quantify intraepidermal nerve fiber density, biopsy of the hairy skin in the lower extremities is a more commonly accepted method (Peltier et al., 2014; Lauria et al., 2010).

A test was conducted to clarify the effects of exercise on controlling the glucose level of diabetic patients. Jensen et al. (2019) conducted 12 weeks of exercise on 50 diabetic patients with musculoskeletal pain, and the results indicated that exercise reduced pain, and that HbA1c (mmol/mol) was decreased from 60 ± 15 to 54 ± 11. These results suggest that exercise effectively improves glucose control in diabetic patients' neuropathy. Therefore, it is theoretically feasible that exercise can reduce IENF damage by improving blood glucose. Ten weeks of aerobic and resistance exercise interventions on 17 patients with diabetic peripheral neuropathy was conducted by Kluding et al. (2012) After the program, the patients were processed for immunohistochemistry of the right leg proximally at the lateral thigh and distal part of the lateral ankle using a rabbit anti-PGP9.5 primary antibody, and the IENF density was quantified. It was found that exercise significantly reduced pain, lowered HbA1c, and increased PGP 9.5 in the epidermis of the patients, and that the number of branches per fiber in the proximal biopsy site had improved. However, there was no significant increase found in the distal IENF measures or proximal IENF density, and this may be due to some subjects being pain-free before the exercise intervention, limitations of current guidelines on IENF quantification, and testing of IENF density at different time points before and after the exercise intervention (Kluding et al., 2012). Therefore, the specific role of IENFs in DNP needs further study or guidelines to quantify the IENF density to be more detailed and understood. Contradictory findings regarding IENFs in patients with DNP have been reported (Smith et al., 2001; Polydefkis et al., 2003). Another study explained the pathological mechanism of exercise intervention in DNP in terms of neurotrophin and absence of significant change in IENFs in DNP. Groover et al. (2013) developed a DNP mouse model by giving the male C57Bl/6 mice a high-fat diet and then quantifying the IENFs using a rabbit anti-PGP9.5, and the growth factor using an ELISA kit. The quantification of IENF density showed that the high-fat diet and exercise changed the number of PGP9.5-immunopositive fibers. However, the percentage of TrkA/PGP9.5 fibers was 30% lower in the exercise group than in the sedentary control group. The related growth factor and nerve growth factor (NGF) were significantly decreased. Meanwhile, brain-derived neurotrophic

TABLE 1 The possible pathological mechanism of exercise in the treatment of DNP.

Reference	Model	Exercises types	Related gene/ cytokines/ protein/ion	Involved in pathways/ channel	Functions	Change
Nadi et al. (2019)	DNP Patients model	Resistance and peripheral neuropathy exercise	TNF-α, IL-10, CRP, HbA1c		Inflammation, Glucose	↓
Heidari et al. (2021)	DNP Patients model	Integrated exercise	HbA1c		Glucose	↓
Yoo et al. (2015)	DNP Patients model	Aerobic exercise	HbA1c		Glucose	↓
Ma et al. (2019)	DNP rat model	Treadmill exercise	IL-1β, IL-6, TNF-α		Inflammation	↓
Nascimento et al. (2012)	DNP rat model	Treadmill exercise	Calcitonin gene-related peptide		Apoptosis	↑
Shankarappa et al. (2011)	DNP rat model	Treadmill exercise	$Ca2^{+}$	LVA T-/HVA N-type	Dysregulation of VGCC	↑
Aghdam et al. (2018)	DNP rat model	Swimming exercise	NaV1.3	VGS	miR-96	↓
Ma et al. (2020)	DNP rat model	Treadmill exercise	p-S6K1, p-4E-BP1, IL-6	IL-6-mTOR	Inflammation	↓
Jensen et al. (2019)	DNP patient model	Aerobic and resistance exercise	HbA1c		Glucose	↓
Chen et al. (2013)	DNP rat model	Swimming exercise	TNF-α, IL-6, Hsp72		Inflammation	↓
Olver et al. (2014)	DNP rat model	Treadmill exercise	eNOS	PI3k-Akt	NO synthesis	↑
Yoon et al. (2015)	DNP rat model	Treadmill exercise	TNF-α, IL-1β, Enkephalin, Hsp70	TRPM8, TRPV1	Inflammation	↑
Kluding et al. (2012)	DNP patient model	Aerobic and resistance exercise	HbA1c, PGP9.5		IENF	↑
Groover et al. (2013)	DNP mice model	Treadmill exercise	PGP9.5, TrkA, GDNF, NGF, BDNF		IENF	↑
Lohmann et al. (2010)	DNP patient model	Physical activities	HDL, HbA1c		Apoptosis, Glucose	↓
Chen et al. (2015)	DNP rat model	Treadmill exercise	IL-10, IL-6, TNF-α		Inflammation	↓

factor (BNDF) and glial cell line-derived neurotrophic factor (GDNF) were significantly increased (Groover et al., 2013). The increase in TrkA axons in the DNP mouse model can mediate the increase in NGF (Kashiba et al., 1996), and NGF has an important role in pain management (Pezet and McMahon, 2006). Therefore, this is one of the pathological mechanisms of DNP, and exercise also reduces pain related to DNP by decreasing NGF and TrkA axons. In addition, TrkA-expressing fibers are peptidergic fibers that express nociceptive neuropeptides (Kashiba et al., 1996), and non-peptidergic fibers are sensitive to GDNF (Groover et al., 2013). Therefore, the absence of change in IENFs after exercise intervention in DNP may be due to a decrease in peptidergic fibers and increase in non-peptidergic fibers. However, to determine specific non-peptidergic fibers changes, they should be quantified by markers.

The role of exercise in inflammatory response

Under normal physiological conditions, inflammatory response is the immune system's response when a harmful stimulus causes damage to the body (Weiss, 2008). In recent years, evidence has been emerging from related research that inflammatory response has a significant role in the pathogenesis of DNP (Pop-Busui et al., 2016). For example, increased pro-inflammatory factors tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and C-reactive proteins (CRPs) lead to an inflammatory response associated with neuropathy in diabetes (Shoelson et al., 2006; Pop-Busui et al., 2016). Galloway and Chattopadhyay (2013) constructed the DNP rat model and observed the expression of pro-inflammatory factors and found that compared to rats with no pain, overexpression of a large number of pro-inflammatory factors in NDP rats such as TNF-α, IL-1, 6, 13, and 17, chemokines such as MIP1 and 3, Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), Fractalkine, and cell adhesion molecule sICAM in dorsal root ganglion (DRG) that are associated with pain phenotype remarkably increased. These results suggested that the pro-inflammatory factors in DRG play a non-negligible role in DNP (Galloway and Chattopadhyay, 2013).

Exercise inhibits inflammatory response by reducing pro-inflammatory factors, thus, reducing pain in DNP, which is the common activity mechanism in treating DNP. Ma et al. (2019) established a DNP rat model by intraperitoneal injection of streptozotocin (STZ) and made DNP rats perform

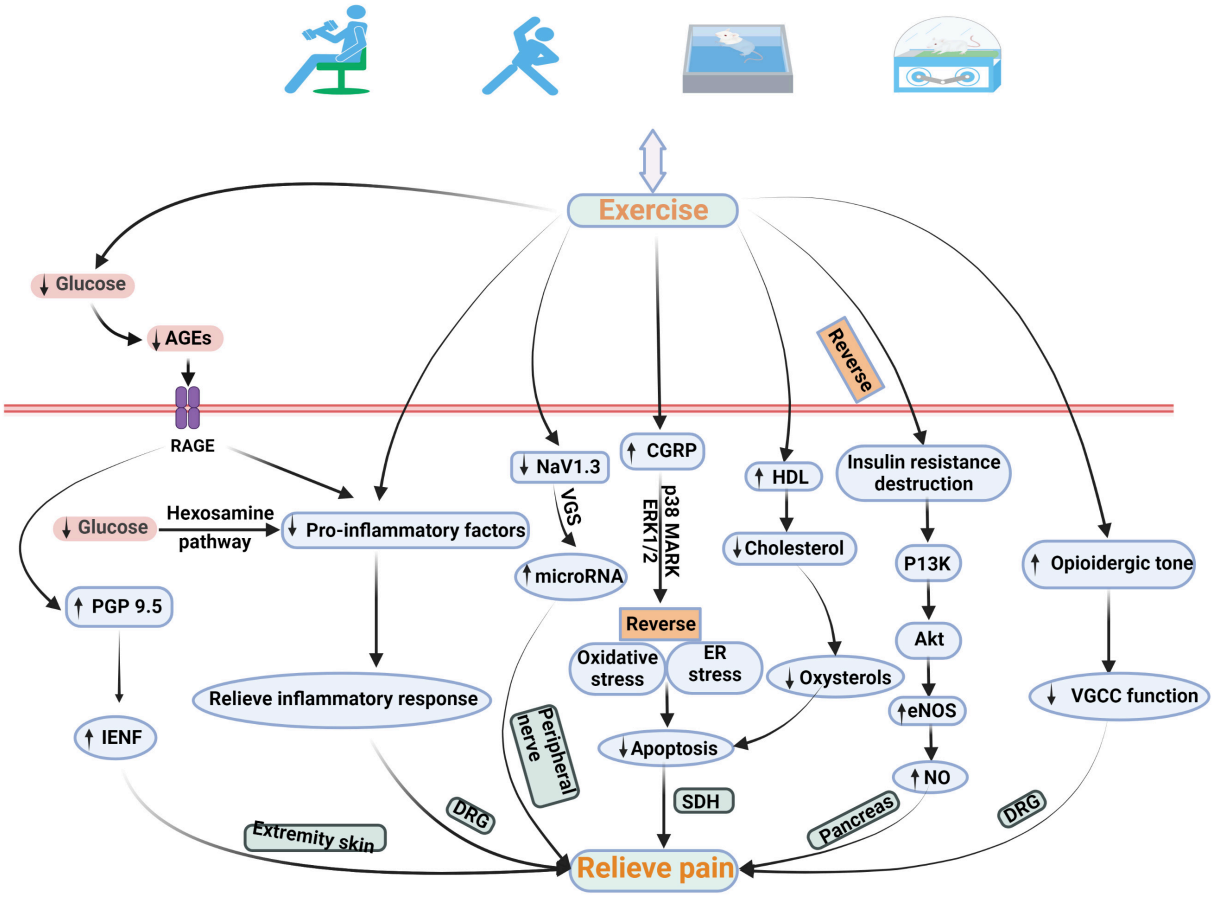


FIGURE 1
Schematic diagram of the possible pathological mechanism of exercise in the treatment of DNP. Exercise relieves DNP by changing the quantity of IENFs, expression of pro-inflammatory factors, NaV1.3, CGRP, HDL, and eNOS, and VGCC function. AGEs, advanced glycation end products; IENF, intra-epidermal nerve fiber; CGRP, calcitonin gene-related peptide; ASK1, apoptosis signal-regulating kinase 1; p38 MARK, p38 mitogen-activated protein kinase; ERK 1/2, extracellular signal-regulated kinase ½; ER, endoplasmic reticulum; PI3K, phosphatidylinositol-3-kinase; eNOS, endothelial nitric oxide synthase; VGCC, voltage-gated calcium channel.

exercise on a treadmill. Paw withdrawal thresholds (PWTs) were significantly increased in the STZ rats by the exercise compared to the control group, and relief of pain was accompanied by decreases in levels of IL-1β, IL-6, and TNF-a. This suggests that exercise modulates pro-inflammatory factor signaling pathways, hence reducing the inflammatory response and further inhibiting DNP. Furthermore, blocking individual pro-inflammatory factor receptors elevated PWTs. This result illustrated the side effects of inflammatory response on regulation of DNP (Ma et al., 2019). Similarly, Yoon et al. (2015) exerted moderate-intensity exercise on DNP rats and they used the level of TNF-α and IL-1β in the DRG as the observations. The results showed that the exercise inhibited hyperalgesia and recess the development of cold allodynia through the TRPM8 and TRPV1 ion channels. Meanwhile, immunohistochemical studies on DRG also showed a significant decrease in TNF-α and IL-1β in the diabetic exercise group. It is an important mechanism in changing the pain threshold in DNP test animals (Yoon et al., 2015). Interestingly, an exercise intervention study on hyperalgesia and allodynia in DNP rats showed that exercise reduced diabetic-associated thermal hyperalgesia and increased heat shock protein 72 (Hsp72) (Chen et al., 2013). Hsp72 has a neuroprotective role in neuropathic pain in rats after peripheral nerve injury (Chen et al., 2012). However, unlike the above study, the expressions of TNF-α and IL-6 have no difference between the exercise and sedentary groups after the exercise intervention, which may be due to the acute pro-inflammatory effect of the short-term exercise (only 2 weeks of exercise intervention). This is because the acute pro-inflammatory effect after each exercise session causes a transient increase in pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 (Nemet et al., 2002; Galassetti et al., 2006; Chen et al., 2013). However, further investigation is needed to know the specific mechanistic relationships among

exercise duration, pain, and pro-inflammatory factors. In conclusion, exercise can modulate DNP inflammatory factors and suppress inflammatory responses, consequently reducing pain in DNP.

The role of exercise in micro-ribonucleic acids

Micro-ribonucleic acids (microRNAs) are short categories of non-coding RNAs and they regulate the expression of their target genes by repressing protein translation (Bartel, 2004; Winter et al., 2009). Previous studies have shown that abnormal expression of microRNAs in white blood cells, the sural nerve, and skin is associated with painful peripheral neuropathies (Leinders et al., 2017). Chen et al. (2014) showed that enhanced NaV1.3 expression exacerbated neuropathic pain, and that among microRNAs, miR-96 alleviated neuropathic pain by decreasing the expression of NaV1.3.

Aghdam et al. (2018) established a DNP rat model by intraperitoneal injection of STZ and with a high-fat diet for 1 month to elucidate the effect of exercise on miR-96 and NaV1.3. Rats were subjected to 10 weeks of swimming exercise, after which real-time quantitative PCR was conducted to measure the expression of miR-96 and NaV1.3. The results showed that the swimming exercise group's thermal pain threshold was remarkably prolonged compared with that of the control group. The swimming exercise reversed the enhanced expression of NaV1.3 caused by diabetes, whereas increasing expression levels and the swimming exercise decreased NaV1.3 expression in the healthy rats. These results indicated that miR-96/NaV1.3 mRNA is a possible mechanism for a protective effect of swimming exercise on diabetic thermal hyperalgesia. In healthy rats, exercise can regulate pain related to DNP through gene regulation pathways (Aghdam et al., 2018).

The role of exercise in apoptosis

Apoptosis is an automatic, evolutionarily conserved, and genetically determined form of programmed cell death that is necessary for maintaining homeostasis and growth in animal tissues (Cheng and Ferrell, 2018). Pancreatic β cells, which are responsible for insulin production, are associated with ER stress-induced apoptosis caused by oxidative stress in diabetic neuropathy. The main action pathway is the apoptosis signal-regulating kinase 1 (ASK1)/p38 mitogen-activated protein kinase (MAPK) signaling pathway (Callaghan et al., 2012; Yamaguchi et al., 2013). Inhibition of the ASK1 signaling pathway reduces the chances of apoptosis pancreatic β cell death (Pepin et al., 2014). In general, the role of calcitonin gene-related peptide (CGRP) in diabetic patients is to control blood glucose, thus reducing the release of insulin (Russell et al., 2014), and insulin increase in diabetic rats is accompanied by loss of CGRP-containing fibers (Hashikawa-Hobara et al., 2012). In an earlier study, CGRP was localized in pancreatic β cells (Westermark et al., 1987), and CGRP prevented apoptosis of vascular smooth muscle cells caused by oxidative stress by activating the extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 MAPK signaling pathways (Schaeffer et al., 2003). Therefore, the mechanism of apoptosis associated with CGRP is involved in the pathological mechanism of DNP. An STZ injection-induced diabetic rat model was established by Nascimento et al. (2012) to research on the role of exercise in DNP and CGRP levels in DRG. A tail-flick apparatus was used to assess nociceptive injury changes. Meanwhile, the immunohistochemical procedure and optical densitometry were performed to measure the level and intensity of CGRP. The results showed that exercise reduced the hyperalgesia and reversed the diabetes-induced decrease in CGRP in the DRG levels of diabetic rats (Nascimento et al., 2012). Therefore, the exercise mechanism for nociceptive hyperalgesia may be increase in CGRP, which reverses the pancreatic β-cell death induced by oxidative and ER stresses through ASK1, p38 MARK, and ERK1/2. That is to control the release of insulin, and then control blood glucose, and finally reduce pain related to DNP. In addition, compared with before the exercise intervention, another study has found an 8.6% increase in HDL cholesterol after the exercise intervention (Lohmann et al., 2010). HDL decrease and LDL increase are inducing factors of oxidative stress, and cholesterol can lead to apoptosis when oxidized to oxysterols (refer to Callaghan et al., 2012 for details). Therefore, exercise may alleviate pain by improving the apoptosis caused by dyslipidemia.

The role of exercise in the deficit of nitric oxide synthesis

Nerve dysfunction is a common complication of experimental diabetes caused by reduced endothelial function and defective neural blood flow (Mrugacz et al., 2021). This may present clinically as DNP (Callaghan et al., 2012; Calcutt, 2020). Reduced diabetic neural blood flow is caused by hyperglycemia leading to reduce nitric oxide (NO) in vascular endothelial cells and further affecting impaired nitric oxide synthase (NOS). Insulin can increase NO by activating intracellular enzymes phosphatidylinositol-3 kinase (PI3K) and protein kinase B (Akt) to further activate endothelial NOS (eNOS) to increase NO, and restore neurological reactivity associated with neural blood flow (Callaghan et al., 2012). This insulin effect of improving vascular reactivity is disrupted by insulin resistance (Wallis et al., 2002). However, a related study has found that exercise can reverse this damage (Rattigan et al., 2001). To verify that exercise ameliorates decreased vascular

nerve reactivity and reduced NO signaling that contributes to peripheral nerve dysfunction, Olver et al. (2014) established a diabetic rat model by STZ injection, performed insulin treatment and exercise training, and then observed motor nerve conduction velocity (MNCV) and eNOS expression in the rat's sciatic nerve. The results revealed that the diabetes sedentary (DS) rats had lower MNCV than the control sedentary (CS) and diabetes exercise-trained (DX) rats, and that the eNOS expression of the DX rats was remarkably higher than that of the DS rats. These results suggested that motor nerve and vascular nerve functions are impaired in diabetic rats, and that exercise can improve this impairment. The effect of the exercise was found to be higher in the CX rats than in the DX rats in terms of MNCV and eNOS expression. In addition, the expression of MNCV and eNOS was higher in the CX rats than in the DX rats. This suggests that medium to high blood glucose reduces vasa nervorum and nerve function in rats (Olver et al., 2014). Therefore, exercise maybe can reverse the deficit of NO synthesis by reversing the reduction of eNOS expression in nerves caused by diabetes, thus partially restoring peripheral nerve dysfunction and reducing pain.

The role of exercise in the dysregulation of voltage-gated calcium channel

Pain related to DNP can be relieved by following strict glycemic control (refer to section "The role of exercise in glucose control and IENF" for details). However, in some cases, strict glycemic control alone does not relieve pain (Calcutt, 2002). Dysregulation of ion channel function is thought to be a cellular mechanism of DNP (Gooch and Podwall, 2004). Among them, VGCCs help in mediating neuropathic pain (Julius and Basbaum, 2001; Zamponi et al., 2009). T-type VGCCs involved in the modulation of neuronal excitability (Todorovic and Jevtovic-Todorovic, 2006) have an important role in DNP (Jagodic et al., 2007). Unlike T-type VGCCs, N-type VGCCs are primarily involved in the release of injurious neurotransmitters like glutamate and substance P, thus propagating the pain. To investigate the mechanisms associated with treatment of DNP by exercise through high- and low voltage-activated Ca2 + channel function in DRG neurons, a DNP rat model was established by Shankarappa et al. (2011) by STZ injection and administration of forced exercise. The results showed that the forced exercise remarkably delayed the tactile hypersensitivity (a semiquantitative behavioral measure of painful neuropathy) in DNP rats, and that this may be due to an analgesic mechanism independent of glycemic control because altering blood glucose levels does not change tactile sensitivity in exercising rats. In addition, this study found that exercise significantly increased the dose of naloxone required to achieve tactile hypersensitivity and attenuated diabetes-related changes in the function of VGCCs. Previous studies have shown that the analgesic mechanism of opioid receptors is related to inhibition of VGCC function (Pettinger et al., 2013). These results suggested that exercise may alter the function of VGCC for analgesic purposes in part by altering opioidergic tone.

Conclusion and outlook

At present, the number of patients with diabetes mellitus is very large, and one-thirds of them present with DNP (Abbott et al., 2011). The pathological mechanism of DNP is still unclear, the above mechanisms have not been fully confirmed, and a large number of RCTs are needed to verify them in the future. Exercise therapy for DNP is receiving increasing attention. Various exercises are effective in improving DNP, including resistance exercise, aerobic exercise, swimming exercise, etc. Naturally, not all exercises have a good analgesic effect. For example, in terms of exercise duration, a short-term exercise may not improve DNP (Cheung et al., 2009); in terms of exercise intensity, a low-intensity exercise has a good analgesic effect (Johnson and Takemoto, 2019). However, excessive exercise intensity reduces IENF, thus leading to severe pain (Do et al., 2020). This review describes the possible mechanisms of exercise in treating DNP through a possible relationship of diabetic neuropathy with the pathological mechanisms of DNP, which provide a basis for future exercise treatment of DNP.

Author contributions

Y-LZ and BG: draft conception, project administration, and funding acquisition. JL, H-QZ, BG, and Y-LZ: writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of music-based movement therapy on the freezing of gait in patients with Parkinson's disease: A randomized controlled trial

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Background: Progression of freezing of gait (FOG), a common pathological gait in Parkinson's disease (PD), has been shown to be an important risk factor for falls, loss of independent living ability, and reduced quality of life. However, previous evidence indicated poor efficacy of medicine and surgery in treating FOG in patients with PD. Music-based movement therapy (MMT), which entails listening to music while exercising, has been proposed as a treatment to improve patients' motor function, emotions, and physiological activity. In recent years, MMT has been widely used to treat movement disorders in neurological diseases with promising results. Results from our earlier pilot study revealed that MMT could relieve FOG and improve the quality of life for patients with PD.

Objective: To explore the effect of MMT on FOG in patients with PD.

Materials and methods: This was a prospective, evaluator-blinded, randomized controlled study. A total of 81 participants were randomly divided into music-based movement therapy group (MMT, n = 27), exercise therapy group (ET, n = 27), and control group (n = 27). Participants in the MMT group were treated with MMT five times (1 h at a time) every week for 4 weeks. Subjects in the ET group were intervened in the same way as the MMT group, but without music. Routine rehabilitation treatment was performed on participants in all groups. The primary outcome was the change of FOG in patients with PD. Secondary evaluation indicators included FOG-Questionnaire (FOG-Q) and the comprehensive motor function.

Results: After 4 weeks of intervention, the double support time, the cadence, the max flexion of knee in stance, the max hip extension, the flexion moment

of knee in stance, the comprehensive motor function (UPDRS Part III gait-related items total score, arising from chair, freezing of gait, postural stability, posture, MDS-UPDRS Part II gait-related items total score, getting out of bed/a car/deep chair, walking and balance, freezing), and the FOG-Q in the MMT group were lower than that in the control group and ET group ($p < 0.05$). The gait velocity, the max ankle dorsiflexion in stance, ankle range of motion (ROM) during push-off, ankle ROM over gait cycle, the knee ROM over gait cycle, and the max extensor moment in stance (ankle, knee) in the MMT group were higher than that in the control group and ET group ($p < 0.05$). However, no significant difference was reported between the control group and ET group ($p > 0.05$). The stride length and hip ROM over gait cycle in the MMT group were higher than that in the control group ($p < 0.05$), and the max knee extension in stance in the MMT group was lower than that in the control group ($p < 0.05$). Nevertheless, there was no significant difference between the ET group and MMT group ($p > 0.05$) or control group ($p > 0.05$).

Conclusion: MMT improved gait disorders in PD patients with FOG, thereby improving their comprehensive motor function.

KEYWORDS

Parkinson's disease, freezing of gait, music-based movement therapy, gait disorders, randomized controlled trial

Background

Parkinson's disease (PD), a neurodegenerative disorder among the elderly population, was first described by James Parkinson in 1817 (Parkinson, 2002). The prevalence of PD is estimated as 0.3% in the general population and up to 1% for those aged over 60 years around the world (Balestrino and Schapira, 2020). Movement disorders (bradykinesia, resting tremor, rigidity, and postural instability) and non-motor symptoms (constipation, hyposmia, depression, and cognitive impairment) are frequently observed in patients with PD (Nemade et al., 2021). The incidence of PD exhibits a gradually increasing trend, making it urgent to find a treatment that could prevent or delay the progression of the disease (Tysnes and Storstein, 2017; Abbas et al., 2018).

Freezing of gait (FOG) is a serious gait disturbance that affected mobility and increased the risk of falling in people with PD in the middle and late stages (Gao et al., 2020). Patients with PD described FOG as feeling their feet were stuck to the ground when initiating gait, turning, or negotiating obstacles (Moore et al., 2020). Also, FOG contributes to the occurrence of disability, falls, and diminished mobility in patients with PD (Mazzetta et al., 2019). Therefore, it is critical to control the symptoms, reduce functional disability, and improve patient quality of life while treating PD with FOG. Previous studies have offered a number of hypotheses concerning pathological mechanisms, which could be summarized as the following four models: the threshold model (Plotnik et al., 2012), the interference model (Lewis and Barker, 2009), the cognitive model (Vandenbossche et al., 2012), and the decoupling model (Jacobs et al., 2009). Although these models and hypotheses have explained the development of FOG from different perspectives, they are incomplete and only partially explain the pathophysiology and clinical phenotype of FOG. Treatments used for the improvements of FOG warrant further exploration due to its complex mechanism, which involves many neural pathways and transmitter systems. In fact, the responsiveness of FOG to pharmaceutical treatment was limited and not always promising (Espay et al., 2012; Perez-Lloret et al., 2014; Nonnekes et al., 2020). Despite of benefits of symptom management, medication regimens do not necessarily improve gait disorders, like shuffling, step irregularity, freezing, and postural instability. The episodic, heterogeneous nature, and limited responsiveness of FOG to treatment make disease management difficult (Capecci et al., 2016). Thus, we hold a putative concept that long-term drug therapy might only play an adjunctive role in PD with FOG.

Music-based movement therapy (MMT) has become an effective tool to compensate for the indispensability of conventional treatment. Music therapy might be effective for treating damaged brains (Altenmüller et al., 2012; Moore et al., 2014). The goal of music therapy is to induce dramatic changes in brain function to systematically modified behavior (Wang and Agius, 2018). Rhythm, as well as melody, plays

a crucial role during music training (Karpati et al., 2017). Humans have the ability to synchronize their movements to auditory beats or rhythms spontaneously (Wright and Elliott, 2014). Cumulative evidence has demonstrated that music-based stimulation training could improve the gait of patients with PD (Ghetti et al., 2017; Ghai et al., 2018; Park et al., 2020, 2021). For a number of brain regions, neurons can respond to brief stimuli by spiking for a long period (Cui and Strowbridge, 2018). Repeated stimulation would strengthen the connection between the two neurons by causing biochemical and anatomical changes (Szelenberger et al., 2020). Hence, music could not only relax the brain but also link brain regions (Yang et al., 2012).

For its positive stimulatory effects on a range of brain regions, music therapy has been used to improve socialization and cognitive, emotional, and motor functions (Gramaglia et al., 2019). A systematic review showed that MMT is an effective treatment approach for improving motor function, balance, freezing of gait, walking velocity, and mental health for patients with PD (Zhou et al., 2021). Combining music therapy and physical therapies, MMT inherits the strengths of music therapy and physical therapies, indicating a more effective complementary treatment compared to traditional exercise and music therapy. With the advantages of simple operation and cost-save, MMT harbors potential research value and a wide range of application possibilities (de Dreu et al., 2012). By far, varieties of diseases have been found to be positively influenced by MMT. Patients could benefit from MMT in terms of their daily activities and motor function, as well as their quality of life. According to previous work, the combination of dance and music therapy improved walking function and the capacity of posture transition for PD (Pereira et al., 2019; Dos Santos Delabary et al., 2020). However, there is considerable research still recommending monotherapy (receiving music therapy or physical therapy only) for PD patients with FOG. In our prior trials, MMT improved limb function in patients with neurological disorders (stroke, spinal cord injury, PD). To sum up, MMT might have potential applications for PD with FOG. A further RCT of high quality was required for gaining further robust evidence for consideration. In the current study, we performed a prospective, randomized controlled trial to further evaluate the efficacy of MMT in PD patients with FOG.

Materials and methods

Study design

As a prospective randomized controlled trial, it complied with the Consolidated Standards of Reporting Trials recommendations and was approved by the institutional review board and the Ethical Committee (2018-01). We registered the clinical trial on the Chinese clinical trial registry (ChiCTR1900026063) prior to the first participant enrollment.

Participants

Participants were recruited from Shanghai's second rehabilitation hospital through the web platform, outpatient, and poster advertisements at inpatient clinics.

Eligibility criteria

Inclusion criteria

Eligible participants should fulfill the following criteria (Tang et al., 2019):

① Classified as Parkinson's disease (Daniel and Lees, 1993);

② Absence of organic disease;

③ Can stand at least 30 min without walking aids;

④ Aged 40–90 years and could walk independently for at least 3 meters;

⑤ Suffering FOG, with stage 2 or 3 Hoehn and Yahr;

⑥ Had a good to excellent response to L-dopa or other dopaminergic agents;

⑦ At a stable stage of disease and can communicate normally;

⑧ Provided full informed consent.

Exclusion criteria

Those participants meeting the following were excluded from the study:

① Secondary Parkinson's disease;

② No-response or intolerant to previous treatment;

③ Participated in a clinical trial related to PD in the last 3 months;

④ Received additional treatments.

Randomization and masking

Sequence generation

Randomization was administered by a trained research assistant *via* a random number generator function using Microsoft Excel (version 2016).

Concealment mechanism

After the informed consent was signed, the eligible participants were randomly assigned into three groups. This operation was conducted randomly, ensuring optimum allocation concealment. Random numbers used for participant grouping were placed into sequentially numbered, sealed, and opaque envelopes.

Blinding

Blinded outcome assessment and data analyses were implemented. The collected data were coded and kept using a

computer after removing unnecessary information. Unblinding will not be permissible throughout the trial.

Study interventions

All interventions were carried out by 10 skilled therapists with over a decade of clinical experience. The detailed interventions were described as follows.

Music-based movement therapy group

Intervention arm was provided with the MMT besides usual rehabilitation care. Regular exercise was modulated with respect to the musical tempo. There were five training sessions per week, with each session of 30 min.

Music selection

Before intervention, therapists selected the music with the following consideration: music preferences and personality, musical parameters such as rhythm, melody, harmony, dynamics, and timbre. Also, music with lyrics was not suitable because it may distract participants. Thereafter, therapists made a customized music playlist, which was loaded into a music player for each subject. In addition, participants had a choice of earplugs or headphones to achieve maximum comfort. The music was played repeatedly in order of the playlist, with a 2-min interval between music.

Exercise therapy

Participants underwent exercise training on a trail, which was 5 meters long and 1 meter wide (60 min at a time). Exercises, which were performed to the beat of the music, consisted of flat start walking, turning, narrow space walking, and step training. The participant took the first step with the toes as high as possible, then stepped forward with the heel touching the ground first and waited until the body was fully shifted to the foot before taking the next step. At the same time, swing the arms as far as possible. The participant first stepped with the foot on the same side as the direction of the turn, and then slowly shifted the body in place with small steps and angles as the body turned. After the direction was reversed, participants were instructed to take a step forward. Exercise intensity was judged by whether participants achieved a self-perceived exertion rating of 12–13 (easy) (Scharhag-Rosenberger et al., 2015). All subjects were asked to take a rest for about 10 min in case of fatigue during exercise training.

Exercise therapy group

Participants in this group were subjected to exercise therapy without music. Patients, wearing earphones but without music, were required to perform flat walking, turning, narrow space walking, and step training five times (1 h each time) every week for 4 weeks.

Control group

All participants were guaranteed conventional treatment including usual medical care and rehabilitation, comprising the following: ① basic drug treatment; ② physical factor treatment; and ③ daily life ability training. These treatments were performed five times (1 h each time) every week for 4 weeks.

Outcome measures

Clinical outcomes were evaluated by observers blinded to treatment allocation.

Primary outcome measurement

We adopted a three-dimensional gait analysis system to obtain gait information, including gait cycle (double support), kinematic parameters (stride length, gait velocity, cadence), joint angle parameters (ankle: max dorsiflexion instance, range of motion (ROM) during push-off, ROM over gait cycle; knee: max flexion instance, max extension in stance, ROM over gait cycle; hip: max hip extension, ROM over gait cycle), and kinetic parameters (ankle: max extensor moment in stance, knee: max extension moment in stance, max flexion moment in stance).

The 3D motion capture hardware equipment included 12 infrared light-sensitive cameras (Motion Analysis, Rohnert Park, CA, USA), 4 Bertec 3D force measurement tables, 80 A/D channel digital-to-analog converters (National Measuring Instruments, Austin, TX, USA), and 2 HD high-speed cameras. Software programs consisted of Cortex 1.1.0 data acquisition software and Orthotrack 6.6.1 gait data analysis software (Motion Analysis Corp., Rohnert Park, CA, USA). After applying the infrared light-sensitive marker ball to the corresponding body surface position, the participant was instructed to walk about 15 meters in the test area in a usual posture and speed, so that they could complete the adaptation training to the field-testing environment and the state of wearing the fluorescent ball. For static data collection, participants were instructed to stand naturally in the designated position with bilateral upper limbs held laterally for about 5 s. For dynamic data collection, participants were instructed to walk naturally on a dynamometer-lined walkway after the removal of the fluorescent balls from the bilateral medial ankles and medial femoral skeleton. Participants' gait data for a 5-meter walking distance needed to be collected in at least three sets. For each set, at least three whole gait cycles of the unilateral lower extremity were performed, and real-time kinematic and kinetic data for each joint of the

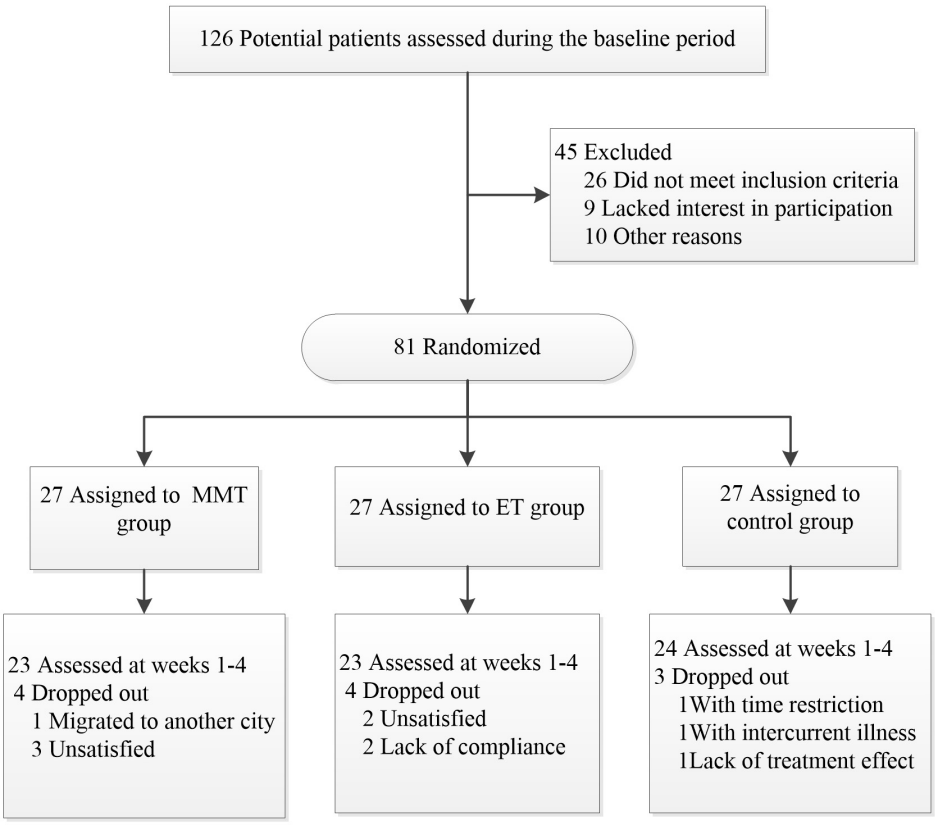


FIGURE 1
Flowchart of the screening, enrollment, and randomization.

lower extremity were collected. The 3D modeling analysis of the data was performed using the data acquisition software (Cortex 1.1.0) and the gait cycle was defined, processed, and analyzed using the gait analysis software (Motion Analysis Corp., Rohnert Park, CA, USA) to calculate the spatio-temporal parameters, kinematic and kinetic parameters of each joint of the lower limb.

Secondary outcome measures

The secondary evaluation indices included the evaluation of the comprehensive motor function and FOG-Questionnaire (FOG-Q) (Tambasco et al., 2015). We employed the Unified Parkinson's Disease Rating Scale Part II and III (UPDRS II, III) gait-related items scores to assess the motor function, while the FOG-Q was used to assess FOG.

Statistical analyses

This was a randomized controlled trial, aimed at assessing the efficacy of three methods in the management of PD with FOG. The key observation index was gait parameters. As no studies performed the three-dimensional gait analyses to appraise the effect of MMT on FOG, we adopted results of the unified Parkinson's disease assessment scale (UPDRS III) from our exploratory trial for calculations. According to the pilot study, the mean value of UPDRS (III) score contraction in three groups after treatment was anticipated to be 20.7 ± 16.6, 7.9 ± 6.3, and 2.6 ± 2.2, respectively. We fulfilled a two-sided test, with α and assurance (test efficiency) of 0.05 and 90%, respectively. The sample size was calculated to be 66 cases using PASS software (version 15). Further, we calculated an overall sample size of no less than 84 cases enrolled assuming a dropout rate of 20%. However, only 81 patients completed the whole trial finally due to the influence of COVID-19.

Demographic characteristics of patients were described using descriptive statistics. When continuous variables conformed to normal distribution and chi-square, one-way ANOVA was used for comparison among the three groups, and multiple comparisons were performed using Bonferroni's adjustment method. For categorical variables, the chi-square test or Fisher's exact test was used. The rank sum test was used if data did not conform to normal distribution. P-values less than 0.05 represented a statistical significance. Notably, to avoid type I errors when making multiple comparisons, adjusted *p*-values were calculated as the *p*-value of 0.05 divided by the number of

comparisons. When the p-value was less than the corrected p-, statistical significance was present.

Results

Study participants

Of these 126 potential participants, 26 did not meet the inclusion criteria, nine were not interested in the study, and 10 could not participate in the study for other reasons (failure to sign the informed consent form, lack of musical rhythm to participate in MMT). So, a total of 81 subjects were enrolled in this study. **Figure 1** shows a flow chart of participants' screening, enrollment, and randomization. Baseline characteristics of the randomized subjects were comparable across the three treatment groups (**Table 1**). There was no significant difference in baseline characteristics among the three groups.

Primary outcome

Gait cycle

After 4 weeks of intervention, the double support time in the MMT group was lower than that in the control and ET groups (F = 6.647, p = 0.002). However, no significant difference was reported between the control group and ET group (p = 0.638) (**Table 2**; **Figure 2A**).

Kinematic parameters

The cadence in the MMT group was lower than that in the control and ET groups (F = 5.877, p = 0.005). The gait velocity in the MMT group was higher than that in the control and ET groups (F = 4.516, p = 0.015). However, no significant difference was reported between the control and ET group ($p > 0.05$). The stride length in the MMT group was higher than that in the control group (p = 0.030). Nevertheless, there was no significant difference between the ET and MMT groups (p = 0.248) or the control group (p = 0.587) (**Table 2**; **Figures 2B–D**).

Joint angle parameters

For the ankle, the max dorsiflexion in stance (F = 30.990, $p < 0.001$), ROM during push-off (F = 33.530, $p < 0.001$), and ROM over gait cycle (F = 28.340, $p < 0.001$) in the MMT group were higher than that in the control and ET groups. However, no significant difference was reported between the control group and ET group ($p > 0.05$).

As for the knee, the max flexion in stance (F = 4.999, p = 0.010) in the MMT group was lower than that in the control and ET groups, and the ROM over gait cycle (F = 8.145, p = 0.001) in the MMT group was higher than that in the control and ET groups. However, no significant difference was reported between control group and ET group ($p > 0.05$). The max extension in stance in the MMT group was lower than that in the control group (p = 0.001). Nevertheless, there was no significant difference between the ET group and MMT group (p = 0.054) or the control group (p = 0.309).

Regarding the hip, the max hip extension (F = 15.400, $p < 0.001$) in the MMT group was lower than that in the control and ET groups. However, no significant difference was reported between the control group and ET group (p = 0.479). The ROM over the gait cycle in the MMT group was higher than that in the control group (p = 0.031). Nevertheless, there was no significant difference between the ET group and MMT group (p = 0.159) or the control group (p = 0.747) (**Table 2**; **Figures 2E–L**).

Kinetic parameters

After 4 weeks of intervention, the max extensor moment in stance (ankle: F = 4.834, p = 0.011; knee: F = 4.435, p = 0.016) in the MMT group was higher than that in the control and ET groups, and the flexion moment of knee in stance (F = 5.094, p = 0.009) in the MMT group was lower than that in the control and ET groups. However, no significant difference was reported between the control group and ET group ($p > 0.05$) (**Table 2**; **Figures 2M–O**).

Secondary outcomes

Motor function

The comprehensive motor function of patients was evaluated by UPDRS Part II and III gait-related items. After 4 weeks of intervention, the comprehensive motor function in the MMT group was lower than that in the control and ET groups (total score of UPDRS Part III gait-related items: F = 6.740, p = 0.002; arising from chair: F = 5.644, p = 0.005; freezing of gait: F = 7.665, p = 0.001; postural stability: F = 6.435, p = 0.003; posture: F = 5.852, p = 0.005; total score of MDS-UPDRS Part II gait-related items: F = 6.492, p = 0.003; getting out of bed, a car, or deep chair: F = 6.785, p = 0.002; walking and balance: F = 7.542, p = 0.001; freezing: F = 6.410, p = 0.003). However, no significant difference was reported between the control group and ET group ($p > 0.05$) (**Table 3**; **Figures 3A–I**).

FOG-Questionnaire

The FOG-Q (F = 5.474, p = 0.006) in the MMT group was lower than that in the control and ET groups. Nevertheless, no significant difference was reported between the control group and ET group (p = 0.782) (**Table 3**; **Figure 3J**).

Discussion

This study evaluated the efficacy of MMT in improving gait disorders, including FOG, which severely reduced the QOL of

TABLE 1 Baseline characteristics.

Characteristics	MMT group (n = 23)	ET group (n = 23)	Control group (n = 24)	P value
Age, mean (SD), years	64.090 (11.000)	65.650 (8.716)	61.580 (10.730)	0.391
Duration of illness, mean (SD), month	43.480 (11.390)	44.830 (9.316)	41.080 (10.260)	0.458
Women, No (%)	11 (47.826)	12 (52.174)	13 (54.167)	0.906
Height, mean (SD), meter	1.660 (0.067)	1.653 (0.067)	1.650 (0.085)	0.907
Hoehn & Yahr stage, No (%)				
2	5 (21.739)	3 (13.043)	5 (21.739)	
2.5	9 (39.130)	11 (47.826)	10 (43.478)	0.95
3	9 (39.130)	9 (39.130)	9 (39.130)	

MMT, music-based movement therapy; ET, exercise therapy; CON, control. The baseline characteristics of the three groups were comparable.

TABLE 2 Gait parameters.

Gait parameters	CON	ET	MMT	F	P value	P value (*post hoc*)		
						CON *vs.* ET	CON *vs.* MMT	ET *vs.* MMT
Kinematic parameters								
Stride length (m)	0.915 ± 0.181	0.967 ± 0.174	1.050 ± 0.178	3.481	0.037*	0.587	0.030*	0.248
Gait velocity (m/s)	0.860 ± 0.177	0.900 ± 0.159	0.997 ± 0.174	4.516	0.015*	0.942	0.021*	0.048*
Cadence (steps/min)	136.000 ± 14.63	132.700 ± 14.040	122.700 ± 13.240	5.877	0.005*	0.703	0.005*	0.042*
Gait cycle								
Double support (%GC)	28.120 ± 3.388	27.330 ± 2.561	25.120 ± 2.778	6.647	0.002*	0.638	0.002*	0.031*
Joint angle parameters								
Max ankle dorsiflexion in stance	28.960 ± 3.037	30.390 ± 2.231	34.750 ± 2.575	30.990	<0.001*	0.162	<0.001*	<0.001*
ROM of ankle during push-off	18.960 ± 2.804	20.390 ± 2.330	24.790 ± 2.502	33.530	<0.001*	0.145	<0.001*	<0.001*
ROM of ankle over gait cycle	25.130 ± 3.494	27.130 ± 3.195	32.290 ± 3.420	28.340	<0.001*	0.117	<0.001*	<0.001*
Max knee flexion in stance	26.170 ± 3.128	25.700 ± 3.350	23.500 ± 2.813	4.999	0.010*	0.860	0.012*	0.047*
Max knee extension in stance	21.130 ± 3.334	19.700 ± 3.295	17.420 ± 3.269	7.592	0.001*	0.309	0.001*	0.054
ROM of knee over gait cycle	55.130 ± 3.829	56.650 ± 3.563	59.420 ± 3.694	8.145	0.001*	0.349	0.001*	0.033*
Max hip extension	9.522 ± 3.175	8.522 ± 2.842	5.042 ± 2.710	15.400	<0.001*	0.479	<0.001*	<0.001*
ROM of hip over gait cycle	33.220 ± 3.275	33.910 ± 3.103	35.670 ± 3.319	3.594	0.033*	0.747	0.031*	0.159
Kinetic parameters								
Max ankle extensor moment in stance	1.165 ± 0.192	1.183 ± 0.152	1.303 ± 0.153	4.834	0.011*	0.923	0.016*	0.042*
Max knee extension moment in stance	0.568 ± 0.109	0.577 ± 0.099	0.654 ± 0.117	4.435	0.016*	0.960	0.023*	0.048*
Max knee flexion moment in stance	0.255 ± 0.122	0.247 ± 0.095	0.172 ± 0.075	5.094	0.009*	0.957	0.014*	0.030*

Gait parameters were expressed in mean ± standard deviation. One-way ANOVA was used to compare the difference between CON, MMT and ET. Significance level was set at 0.05. *Showed significant difference. ROM, range of motion; MMT, music-based movement therapy; ET, exercise therapy; CON, control.

patients with PD. Results demonstrated the improvements in gait disorders as measured by gait analysis, UPDRS Part II, and Part III and FOG-Q. The key gait parameters findings in this study showed that MMT could significantly reduce the double support time and improve the joint angle, kinematic, and kinetic parameters.

For patients with PD, double support time reflects dynamic postural stability (Fasano et al., 2016). Increased double support time, a significant injury risk, may be an indicator of instability that had a significant impact on the gait pattern in PD patients with FOG (Zanardi et al., 2021). The preservation of dynamic stability in PD with FOG was accomplished by postural synergies (He et al., 2018). The extension of double support time during the gait cycle offers a longer time to achieve gait stability, thereby diminishing the requirements for the postural control system (LaPointe et al., 2010; Williams and Martin, 2019). Furthermore, participants surmount the dread of falling by boosting double support time to restore gait stability (Michalitsis et al., 2019). Thus, we concluded that MMT might increase gait stability in PD with FOG. Aside from the double support time, the kinematic parameters were an index of gait instability and fall risk (Thompson et al., 2017; Peppe et al., 2019). The kinematic features of gait in PD with FOG were characterized by slower velocity, shorter stride length, and higher cadence. PD with FOG undergoing MMT showed a notably slower cadence, longer stride length,

TABLE 3 Change in FOG-Q and the comprehensive motor function.

Secondary indicators	CON	ET	MMT	*F*	*P* value	*P* value (*post hoc*)		
						CON *vs.* ET	CON *vs.* MMT	ET *vs.* MMT
UPDRS Part III gait-related items total score	7.261 ± 2.220	6.522 ± 2.466	4.750 ± 2.541	6.740	0.002*	0.556	0.002*	0.038*
3.9 Arising from chair	1.739 ± 0.541	1.609 ± 0.656	1.167 ± 0.637	5.644	0.005*	0.752	0.006*	0.042*
3.11 Freezing of gait	2.217 ± 0.518	2.000 ± 0.674	1.500 ± 0.722	7.665	0.001*	0.492	0.001*	0.027*
3.12 Postural stability	1.696 ± 0.635	1.565 ± 0.662	1.042 ± 0.690	6.435	0.003*	0.784	0.003*	0.023*
3.13 Posture	1.609 ± 0.783	1.435 ± 0.788	0.875 ± 0.741	5.852	0.005*	0.725	0.005*	0.040*
UPDRS Part II gait-related items total score	6.261 ± 1.982	5.609 ± 2.426	4.000 ± 2.226	6.492	0.003*	0.582	0.002*	0.041*
2.11 Getting out of bed, a car, or deep chair	2.087 ± 0.668	1.870 ± 0.815	1.292 ± 0.807	6.785	0.002*	0.604	0.002*	0.032*
2.12 Walking and balance	2.130 ± 0.548	1.870 ± 0.757	1.375 ± 0.711	7.542	0.001*	0.398	0.001*	0.039*
2.13 Freezing	2.043 ± 0.878	1.826 ± 1.029	1.125 ± 0.850	6.410	0.003*	0.704	0.003*	0.030*
FOG-Q total score	13.170 ± 2.534	12.700 ± 2.458	10.960 ± 2.274	5.474	0.006*	0.782	0.007*	0.043*

Secondary indicators were expressed in mean ± standard deviation. One-way ANOVA was used to compare the difference between CON, MMT and ET. Significance level was set at 0.05. *Showed significant difference. MMT, music-based movement therapy; ET, exercise therapy; CON, control. UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; FOG-Q, Freezing of Gait Questionnaire.

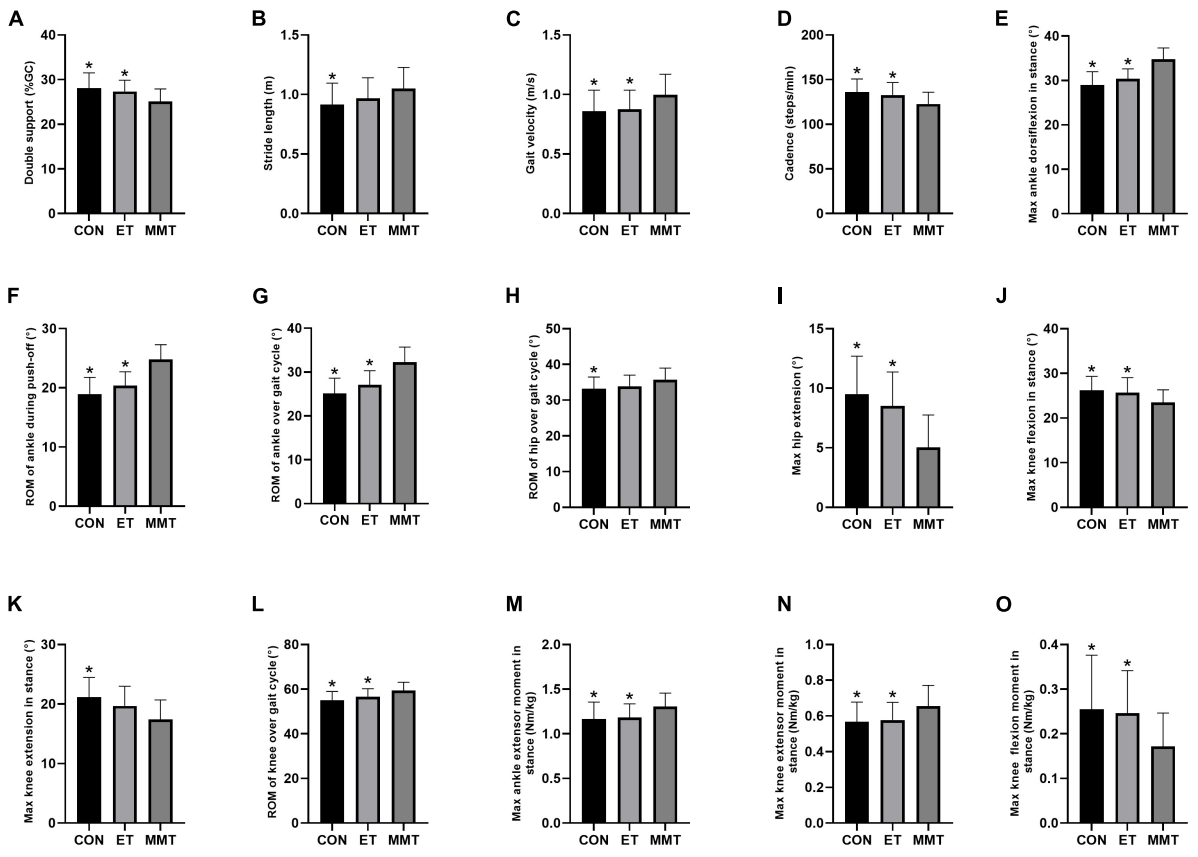


FIGURE 2
Gait parameters. Gait parameters were expressed in mean ± standard deviation. One-way ANOVA was used to compare the difference between CON, MMT, and ET. Significance level was set at 0.05. *$p < 0.05$, compared with the MMT group. ROM, range of motion; MMT, music-based movement therapy; ET, exercise therapy; CON, control. **(A)** Gait cycle, **(B–D)** kinematic parameters, **(E–L)** joint angle parameters and **(M–O)** kinetic parameters.

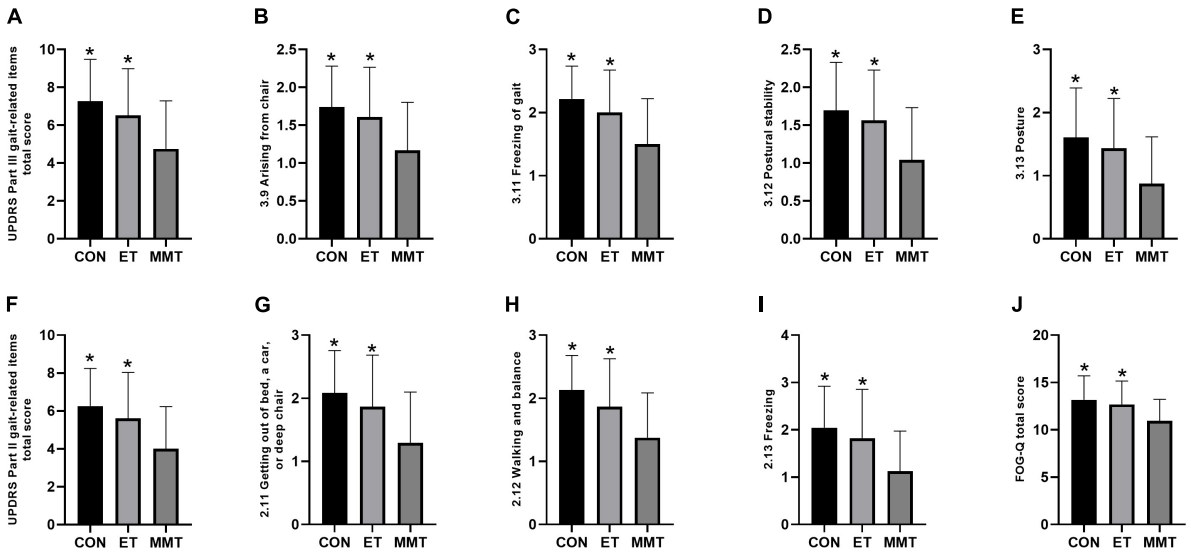


FIGURE 3
Change in FOG-Q and the comprehensive motor function. Secondary indicators were expressed in mean ± standard deviation. One-way ANOVA was used to compare the difference between CON, MMT, and ET. Significance level was set at 0.05. *$p < 0.05$, compared with the MMT group. MMT, music-based movement therapy; ET, exercise therapy; CON, control. UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; FOG-Q, freezing of gait questionnaire. **(A–I)** Motor function; **(J)** FOG-Q.

and faster velocity. Increased stride length and slower cadence were instrumental in PD with FOG for that they perhaps were conducive to avert the emergence of sequence effect, thereupon then contributing to ameliorating FOG. Significantly, lower ROM values of knee and ankle were found in patients compared to controls. In comparison, MMT prominently expanded joint angle offset. Research also indicated that gait disorder in PD with FOG derived from a discrepancy between cortically selected motion amplitude and the authentic proportion of leg movements implemented during walking (Morris et al., 2005; Miranda-Domínguez et al., 2020). MMT might enable participants to focus on walking tasks and mobilize sensitized motion control strategies which circumvented the damaged basal ganglia, therefore, giving rise to the legs' flexion-extension flexibility. The enhancement of lower limbs joints movement perhaps be the premise of the stride length lengthening (Struzik et al., 2016). Factors, for instance, the betterment of ROM at the ankle joint in the time of push-off, maximal hip, and knee extension in stance phase, presumably were conducive to lengthening the stride length. With the improvement of dynamics, the parameters of gait kinematics were also improved. Significant kinetic amelioration in the joints of lower extremities was also found in the MMT group. In addition, the tarsoptosis gait in PD with FOG perhaps was bound up with a lessened heel rocker, deficient knee extension, or insufficient hip flexion.

In spite of the promising effects of medical and surgical management, sequela of the movement disorders are not prevented and disabilities owing to mobility incommodiousness remain (Schootemeijer et al., 2020). Many gait defects in patients with PD, such as FOG, are relatively insensitive to drugs and surgical remedies (Ferrazzoli et al., 2016). Rehabilitation programs were important adjuncts to medical interventions that address residual motor deficits through task-oriented exercises. Exercise training was a significant therapeutic means in the rehabilitation setup. A prevalent and potential strategy to ameliorate gait performance and mobility is to apply external cue technology, especially rhythmic music (Harrison et al., 2018). Music probably touches off physiological enjoyment associated with reward and emotions, which probably draw attention from sensations for instance fatigue in turn and enhance therapy compliance over a long period of time (Jomori et al., 2013; Farbood et al., 2015). These active roles of music perhaps indicate the potentiality of incorporating music into exercise therapy in the management of PD. MMT, an integral part of cognitive assignment training, entails practitioners to remembering the name of each action as well as imitating the action. Ultimately, participants are required to complete a range of actions integrated with music, which ameliorate the cognitive functions of PD, such as visuospatial ability and executive ability. Thus, 4-week MMT was able to improve the gait performance of PD.

Various mechanisms have been proposed to explain the therapeutic effect of MMT on FOG in PD. One potential mechanism involves the alteration of neural pathways. Impaired basal ganglia function in patients with PD could impact their perception of rhythm, subsequently leading to gait freezing

(Jones and Jahanshahi, 2014). This could be compensated by the complement of the cerebellar network, which is usually spared in PD. In addition, the activation of the cerebellar network is dependent on external (e.g., auditory or visual) stimuli (Ashoori et al., 2015). Another potential mechanism involves rhythmic entrainment, which synchronized the auditory system with the motor system to facilitate movement (Thaut et al., 2014). In addition, the auditory environment and motivational effects of music might accelerate motor learning (Schaefer, 2014). Music might modulate the activity of specific brain regions by promoting the production of brain-derived neurotrophic factors (Clements-Cortes and Bartel, 2018).

In summary, PD with FOG was inclined to present with gait disturbance, including extended biphasic support time, shortened stride length, slower velocity, and shrunken ROM in lower extremities joints. These gait deficiencies gradually worsen along with the progression of disease, greatly reducing the quality of life. The present research revealed that abnormal gait characteristics in the MMT group were significantly improved. Thus, MMT can be used as a physical therapy method, which was conducive to the improvement of FOG in PD. Nevertheless, electromyography (EMG) activity in lower extremities was not investigated in the presented study. Future research is suggested to explore the effect of MMT on EMG of related muscle groups and its impacts on muscle power generation. Furthermore, the results did not provide clear evidence that whether the benefits of MMT will fade over time. Additionally, it is imperative to expand the sample size and carry out longer-term interventions and follow-up.

Conclusion

Music-based movement therapy improved gait disorders in PD patients with FOG, thereby improving their comprehensive motor function.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Shanghai Second Rehabilitation Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

K-PL, Z-QZ, and J-GX equally contributed to the design or implementation of the research. B-HS and X-HW were in charge of data collection. J-QS was responsible for data analysis and interpretation. Z-QZ, K-PL, and Z-LZ assisted in drafting the manuscript, which was critically revised by J-GX. All authors approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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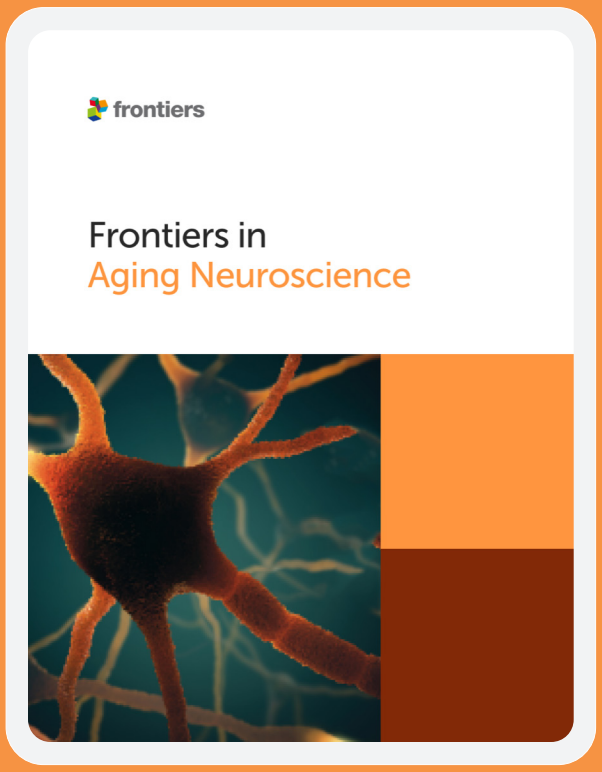
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