THE COGNITIVE EFFECTS AND THE UNDERLYING NEUROPHYSIOLOGICAL MECHANISMS OF QIGONG IN DEPRESSED OLDER ADULTS：A RANDOMIZED CONTROLLED TRIAL

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The Cognitive Effects and the Underlying Neurophysiological Mechanisms of Qigong in Depressed Older Adults：A Randomized Controlled Trial

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Certificate of Originality

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Abstract

Background: Depression is one of the most common geriatric mental disorders. Approximately one third of older population worldwide have depressive symptoms. The depressed older adults are commonly found to exhibit cognitive deficits that can further affect daily functioning and mood disorders. However, current available antidepressant treatments show limited effects in alleviating cognitive symptoms in depression. Therefore, identifying innovative and effective interventions to improve cognitive function is urgently needed for these individuals. The study aims to examine the cognitive effects of qigong and to further the understanding of neuroscientific mechanisms of its beneficial effects in older adults with depressive symptoms.

Methods: A pilot randomized controlled trial was performed to primarily examine the effect of Baduanjin qigong intervention on global cognitive function, to evaluate the effects on attention, inhibitory control, and working memory, and to explore possible neurophysiological mechanisms underlying the effects. Older adults with depressive symptoms were recruited from community and randomly allocated into the intervention group or waitlist control group. The intervention group received a 12-week Baduanjin qigong training. The primary and secondary outcomes were assessed at baseline and post-intervention.

Results: This study identified statistically significant improvement of global cognitive function in the Baduanjin group as the primary outcome compared to the waitlist groups. As to secondary outcomes, there were between group differences in cognitive performance of attention and inhibitory control. The results did not identify significant changes in working memory. ERP investigation revealed that P3 amplitudes were enhanced after intervention and was observed to mediate the relationship between Baduanjin training and cognitive improvements related to inhibitory control.

Discussion and Implications: The main study provides feasible and efficacious evidence for the cognitive effects of qigong exercise. Our results support that qigong has positive effects on cognitive ability which might be associated with corresponding neural changes in older adults with depressive symptoms. Therefore, the findings recommend that Baduanjin is a safe and suitable intervention for older adults with depressive symptoms to helps bring cognitive and brain function improvement. These therapeutic effects might be explained by physical exercise and mindfulness elements of qigong practice. Despite some positive findings in this pioneering study, conclusions on the cognitive effects and underlying brain mechanisms of qigong in depression cannot be fully confirmed. The findings need to be further tested in better designed and larger scale research.

Publications arising from the thesis

Journals

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Conference

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Chapter 1: Introduction

1.1 Background

Depression is the most prevalent mood disorder worldwide and one of the most important public health problems. In Hong Kong, the overall prevalence of depressive symptoms was about 50% in older adults (Jin et al., 2022). Patients with depressive disorders commonly suffer from emotional, neurovegetative, and neurocognitive symptoms (APA, 2013; Diniz et al., 2013). Cognitive deficits are reported to affect about two-thirds of individuals with depression (Rock et al., 2014a). The remediation of cognitive dysfunction is important for improving social and health functioning in depressed adults (Rock et al., 2014a). Despite antidepressants are generally effective in improving depressive symptoms, they are costly and without effects on cognitive function (Cuijpers et al., 2008; Nebes et al., 2003; Rosenblat et al., 2016). According to another large clinical trial, antidepressants were not effective in improving cognition in patients with major depressive disorder (MDD), even if their affective symptoms remitted (Shilyansky et al., 2016). Recently, there is increased attention in identifying non-pharmacological treatments that can enhance cognitive function in individuals suffering from depression.

The Cochrane systematic review and meta-analysis in both clinical and nonclinical populations by Cooney et al. documented that exercise can alleviate depressive symptoms effectively (Cooney et al., 2013). Furthermore, the effects of exercise on cognition have been revealed in healthy or cognitively impaired adults (Smith et al., 2010). It is also a promising option for enhancing cognitive function in people with depression (Malchow et al., 2013). Exercise might impact on various brain regions positively, according to previous studies, which involved in both cognitive function and depression (Erickson et al., 2014; Voss et al., 2013). Hence, it is reasonable to propose that exercise may positively affect mood and cognitive function through neural activity and function.

Mind-body exercise is a specific type of exercise which incorporates controlled breathing and mental focus into physical movements (Hempel et al., 2014; Yeung et al., 2018b). It was identified to have health benefits in both depressive symptoms and cognitive outcomes. Therefore, mind-body exercise is a promising treatment option for depressed individuals. Among different modalities of mind-body exercise, Baduanjin is one of the most commonly accepted low-to-moderate practice (Tsang et al., 2002). It can help to enhance harmony of physical movements, breathing, and meditative state state of mind (Chan & Tsang, 2019). In addition, Baduanjin practice involves only eight smooth and simple movements. Since the physical and cognitive demands are relative lower in Baduanjin, it is easier to learn and practice than tai chi (Chan & Tsang, 2019; Koh, 1982). Accordingly, Baduanjin qigong is particularly suitable for older adults, especially for older adults with depressive symptoms and chronic conditions.

Baduanjin practice has been demonstrated to reduce depression and enhance psychological well-being in older adults (Zou et al., 2017). There are also evidence supported that Baduanjin can slow cognitive decline in community elderly (Ge & Anli, 2008; Song-tao, 2007). Baduanjin was shown to have a significant effect on overall cognitive function of older adults with declined cognitive function (Tao et al., 2019; Yu et al., 2021). Therefore, Baduanjin exercise is plausible to benefit global cognitive function in older adults who are depressed, while high-quality study to evaluate this potential health benefit of Baduanjin is warranted.

In addition, to our best knowledge, qigong has not been thoroughly studied for its beneficial effects on specific cognitive function domains in addition to global cognition. Currently, limited studies have investigated the impact of mind-body exercises on neurocognitive functions for depressed individuals, and the results are largely ambiguous and limited (Chan et al., 2013; Lavretsky et al., 2022a). Lavretsky and colleagues reported tai chi presented non-significant impact on attention or executive functions in older adults (Lavretsky et al., 2022a). Chan and colleagues found that Dejian mind-body intervention, outperformed waitlist control in improving attentional ability (Chan et al., 2013). Therefore, it is worthwhile to examine the benefits of Baduanjin exercise on individual subdomains of cognitive function in depressed older adults.

Systematic reviews have suggested exercise may reduce vascular risk factors, attenuate neurodegenerative processes, and facilitate neurotrophic factor production, thereby improving cognition (Ahlskog et al., 2011). The positive effects of mindfulness meditation and physical exercise on cognition have been supported by previous studies (Barnes, 2015; Marciniak et al., 2014; Zeidan et al., 2010). According to these findings, it is possible that the intervention which combines the two components (i.e. mind-body exercise) can be also effective for cognitive function in depressed individuals. It has been demonstrated that tai chi mind-body practice may enhance neural plasticity in the frontal cortex (Audiffren & André, 2019; Sungkarat et al., 2018). Another study of mind-body intervention in patients with MDD found improved attention and neural connectivity following the intervention (Chan et al., 2013). Event-related potentials (ERPs) are electroencephalographic (EEG) indices, which are non-invasive recordings of brain evoked potentials. N2 and P3 are two important ERP components, with their amplitudes often reflecting conflict monitoring and neural resources allocation (Ghin et al., 2022; Näätänen, 1988). A greater amplitude of N2 component was observed in patients with MDD after exercise training which indicates an improvement in cognitive control (Olson et al., 2017).

Besides, studies have hypothesized that the benefits on cognitive function could be maximized if mental and physical training are combined. For example, Ladawan and colleagues have found that the combined physical and mental intervention had a greater impact on cognitive function than single-component interventions (Ladawan et al., 2017). Alderman and colleagues' study also support this finding. They observed that among individuals with MDD, the N2 and P3 amplitudes increased following the intervention which combined mental training with physical training (Alderman et al., 2016). Baduanjin qigong integrates body postures and movements, coordinated deep breathing and intermingles mindfulness meditation (Greten, 2007). Therefore, it is considered as a promising approach to improve specific cognitive functions through the enhanced brain activation, marked by increased N2 and P3 amplitudes (Chang et al., 2014).

Despite the previous findings that physical exercise and mind training in combination benefits both cognitive function in various populations, and the understanding of the neurophysiology underlying such benefits remains limited. To our knowledge, no studies have investigated the effects of qigong on ERPs in depressed older adults during cognitive tasks. Therefore, whether qigong is associated with enhanced brain activation related to improvement in specific cognitive domains in depressed individuals needs to be explored by more research.

1.2 Aims of the study

The thesis aims primarily to determine the efficacy of Baduanjin qigong exercise on global cognitive function among older adults with depressive symptoms in Hong Kong. Further, the thesis secondarily aims to explore possible neural mechanisms of qigong on depressive and cognitive symptoms in this population. Data for this pilot study was drawn from a 12-week Baduanjin intervention evaluating cognitive effects and neurophysiological mechanisms of Baduanjin qigong among older adults with depressive symptoms. We first examined whether Baduanjin exercise was effective in benefiting depressive symptoms and cognitive performance. The analysis could provide evidence to support limited data about the possible effects of qigong on cognitive function in depression. And to the best of our knowledge, this is one of the first studies to test the cognitive effects of Baduanjin qigong in older adults with depressive symptoms. Second, we used the EEG data to explore whether qigong exercise affect brain activity in addition to the antidepressant and cognitive effects. Addressing these aims might provide a preliminary understanding of the possible mechanism of qigong effects on depressive and cognitive symptoms.

1.3 Objectives

Primary objectives

Objective 1: To synthesize the empirical evidence of non-pharmacological intervention on cognitive function of individuals with depressive symptoms as found in previous randomized controlled trials. A systematic review (SR1) was done to achieve this objective.

Objective 2: To synthesize the empirical evidence of neurobiological changes in people with depressive symptoms following mind-body exercise or physical exercise as found in previous randomized controlled trials. A systematic review (SR2) was done to achieve this objective.

Objective 3: To test the efficacy of a 12-week Baduanjin qigong intervention in enhancing global cognitive function in older adults with depressive symptoms at post-intervention (i.e., 12 weeks after baseline), in comparison to 12-week waitlist control. A randomized controlled trial (Main Study) was done to achieve this objective.

Secondary objectives

Objective 4: To explore the benefit of a 12-week qigong training (Baduanjin) in enhancing attention, inhibitory control, and working memory of older adults with depressive symptoms at post-intervention (i.e., 12 weeks after baseline), in comparison to 12-week waitlist control.

Objective 5: To explore the benefit of a 12-week qigong training (Baduanjin) in enhancing brain activation (indicated by increased anterior N2 amplitude and posterior P3 amplitude) of older adults with depressive symptoms during cognitive tasks at post-intervention (i.e., 12 weeks after baseline), in comparison to 12-week waitlist control.

Objective 6: To explore the correlations between the changes in brain activity (anterior N2 amplitude and posterior P3 amplitude) and changes in cognitive performance (attention, inhibitory control and working memory).

Objective 7: To explore the mediating roles of the changes in brain activity (anterior N2 amplitude and posterior P3 amplitude) that unpack the qigong-related enhancement in cognitive function compared with waitlist control.

1.4 Hypotheses

Primary Hypothesis

Hypothesis 1 ***(****Referring to Objective 3****)***: Compared with the waitlist control group receiving no intervention for 12 weeks, the qigong group that received 12 weeks of Baduanjin training would have significantly more improvement in global cognitive function after the completion of the training (i.e., 12 weeks after baseline).

Secondary Hypothesis

Hypothesis 2 ***(****Referring to Objective 4****)***: Compared with the waitlist control group receiving no intervention for 12 weeks, the qigong group that received 12 weeks of Baduanjin training would have significantly more improvement in attention (2a), inhibitory control (2b), and working memory (2c) after the completion of the training (i.e., 12 weeks after baseline).

Hypothesis 3 ***(****Referring to Objective 5****)***: Compared with the waitlist control group receiving no intervention for 12 weeks, the qigong group that received 12 weeks of Baduanjin training would have significantly more enhancement in anterior N2 amplitude (3a) and posterior P3 amplitude (3b) after the completion of the training (i.e., 12 weeks after baseline).

Hypothesis 4 ***(****Referring to Objective 6****)***: Changes in at least one of the specific cognitive functions (attention, inhibitory control and working memory) would be significantly correlated with the changes in either of the brain activity indicators (anterior N2 amplitude or posterior P3 amplitude).

Hypothesis 5 ***(****Referring to Objective 7****)***: Changes in either of the brain activity indicators (anterior N2 amplitude or posterior P3 amplitude) significantly would mediate the qigong-related enhancement in at least one of the cognitive outcomes (global cognitive function, attention, inhibitory control and working memory).

1.5 Significance

Cognitive dysfunctions are commonly seen in late-life depression. Our research is one of the first studies to explore how qigong affects cognitive function in older adults with depressive symptoms. Further, this pilot study is a preliminary attempt to investigate the neurophysiological changes in depressed older adults after practicing qigong. The findings from the current study might shed light on possible neurophysiological mechanisms underpinnings the therapeutic effects associated with qigong, which will inform its application as a treatment for depressed elderly population. Moreover, qigong is a simple and easy intervention that may reduce both depressive and cognitive symptoms of older adults with depressive symptoms in Hong Kong. This, in turn, may lead to better functioning in their daily life and increase overall quality of life for them.

Chapter 2: Literature Review

2.1 Depression and cognitive impairment

Depression is a prevalent mood disorder and one of the most important public health problems. According to the World Health Statistics, over 280 million people worldwide suffer from depression in 2019 and it was the largest contributor to disability (WHO, 2023). Liu and colleagues investigated the global burden of depression and found that the incident cases increased from 172 million to 258 million during the past 30 years (Liu, He, et al., 2020). It should be noted that depression was not only widespread but often underdiagnosed and undertreated (Kessler & Bromet, 2013). In Hong Kong, according to a recent study, about 40% of older community dwellers had exhibited depressive symptoms (Zhang et al., 2018). It was also reported that 43.7% of males and 54.8% of females in Hong Kong suffered from depression symptoms (Jin et al., 2022).

There are significant high costs related to depression on a global scale. In the United States, depression leads to lost productivity and healthcare expenses amounting to over $210 billion per year (Greenberg et al., 2015). Similarly, in the United Kingdom, it has been estimated that depression costs the economy approximately £105 billion per year (Health, 2010). Importantly, individuals suffering from depression often experience impaired social relationships, increased risk of other physical and mental health issues, further decreased overall quality of life (Sivertsen et al., 2015; Teo et al., 2013). Additionally, depression also increases rates of disability, healthcare utilization, and the strain on social support systems.

Depressive disorders are characterized by affective, somatic, interpersonal, and cognitive symptoms (APA, 2013; Diniz et al., 2013). Impaired ability to think or concentrate, or indecisiveness are important symptoms for the diagnosis of depressive disorders (APA, 2013). Due to the profound implications on patients' quality of life, the cognitive aspects of depression have received considerable attention recently. Approximately two-thirds of depressed individuals were estimated to suffer from cognitive deficits (Rock et al., 2014a). And due to the cognitive impairment, their daily functioning can be negatively affected significantly (Baune et al., 2010; Cambridge et al., 2018). In depression, impaired cognitive functioning may exhibit as forgetfulness, inability to concentrate, indecision, difficulties in planning and carrying out activities (Hammar & Årdal, 2009; Koenig et al., 2014).

Various cognitive domains are impaired in patients with depression. According to meta-analyses and neurophysiological studies, many cognitive functions might be impaired during the course of depression, including alertness, attention, memory and executive functions (Rock et al., 2014a; Semkovska et al., 2019; Vanderhasselt et al., 2012). Importantly, these cognitive decline observed to be related to the changes in anatomical abnormalities and reduced brain activities (Drevets et al., 1997) in depression. According to a cross-sectional survey conducted in 2010 by Baune and colleagues, they found that compared with healthy control, significant deficits in immediate memory and attention were presented in depressed patients (Baune et al., 2010). More recently, a study conducted in 2021 examined treatment-resistant depression and concluded that worse cognitive performance, particularly in attention, memory, and executive functions, was significantly associated with severer depression and lower daily functioning (Vancappel et al., 2021). It has been shown in another large cross-sectional study that depression patients 60 years or older performed worse on varies cognitive domains, including attention, processing speed, executive functions, memory functions, spatial and verbal abilities, compared to older adults with health mood condition (Koenig et al., 2015). Moreover, there is evidence that reduced working memory capacity might be a key mediator of the late life depression related cognitive impairment (Sheline et al., 2006). According to a study by Snyder, depressed patients often exhibit impairment in executive function compared to healthy control. Specifically, the deficits in response inhibition, cognitive flexibility, and abstract reasoning were most significant (Snyder, 2013). Interestingly, these impairments have been associated with functional abnormalities in the brain.

It was documented that ERPs are closely associated with cognitive activities, such as attention, memory, and executive function (Boutros et al., 2011). Therefore, it was suggested that the relationship between neural activity and stimulus processing can be identified by ERPs (Blair et al., 2008). Several previous studies have shown that the ERPs of depressed patients are significantly different healthy individuals. Cui and colleagues studied the association between mood and cognitive function using ERPs, and the results found that negative mood might impact working memory significantly, as measured by a reduction in late positive potential amplitude (Cui et al., 2017). In conclusion, ERP studies have also demonstrated cognitive impairment in depression.

A systematic review with 27 studies included found cognitive deficits in all subdomains, including attention, executive function, memory function, and processing speed, persist even during times of remission (Rock et al., 2014a). Among these, inhibitory control was observed to present the most striking differences. Since cognitive impairment is closely associated with poor psychosocial functioning, remediation of cognitive impairment plays an essential role in improving social and health functioning for patients with depression. Importantly, substantial evidence have demonstrated that the risk of dementia increased significantly among older adults with co-occurrence of depression and cognitive impairment (Diniz et al., 2013; Vu & Aizenstein, 2013). According to another meta-analysis published recently, included 26 studies revealed a significant pooled relative risk of 1.82 for the development of dementia (Fernández et al., 2024). Therefore, cognitive function should be an important target for future interventions for depressed population.

2.2 Interventions for cognitive impairment in depression

2.2.1 Overview of existing interventions

Given the high prevalence of late life depression and associated personal and social burden, there is an essential need to improve the management of depressive symptoms and cognitive deficits. Typically, first-line treatments include pharmacological, psychological, behavioural, or combination approaches. The use of pharmacological treatment can offer relief of symptoms, but it may also come with dependency risks and unpleasant side effects, including weight gain, dry mouth, nausea, insomnia, fatigue, and headache (Santarsieri & Schwartz, 2015). Although preliminary studies suggested that a novel antidepressant, vortioxetine, may have potential cognitive effects, the usage of common antidepressants was evidenced to be associated with cognitive decline, especially in older adults (Moraros et al., 2017). Psychological interventions have been proven to be effective for benefiting certain mental health problems by dealing with underlying thinking patterns and behaviours. However, psychological therapies can be labour-intensive, leading to challenges in providing adequate support for all patients in need. Studies have revealed that while antidepressants and psychological interventions are on the whole effective for treating depression (Cuijpers et al., 2008), many patients encountered difficulties in adherence (Dimidjian et al., 2006) and remission (Thase, 2016). Additionally, the effects of antidepressant on cognitive symptoms were found to be limited. A large randomized clinical trial observed no effect of antidepressants on cognition in MDD patients, even when clinical symptoms of depression were remitted (Shilyansky et al., 2016). Besides, another review of cognitive function in depression reported that attention and executive function impaired persisted throughout treatment (Douglas & Porter, 2009). As a result, identifying and developing interventions that may enhance cognitive function in depression has gained attention in recent years.

2.2.2 Exercise effects on depression

Exercise has been documented as an effective non-pharmacological intervention for depression, either as adjunctive or standalone therapy, with benefits similar to other first line treatments (King et al., 2019). The association between physical activity and severity of depression has been noted from studies three decades ago. According to a classic study with the analysis of 31,000 questionnaires from Harvard graduates conducted by Paffenbarger and colleagues, people with self-reported regular exercise had lower levels of depression than those without regular exercise (Paffenbarger Jr et al., 1994). Exercise has been evidenced as an effective antidepressive intervention across the lifespan for both clinical and subclinical individuals. In a meta-analysis that included 35 studies, Cooney and colleagues revealed that exercise could reduce depressive symptoms moderately, compared to any control conditions, including active controls (other types of intervention) and non-active controls (waitlist or treatment-as-usual) (Cooney et al., 2013). Eight trials provided follow-up data, showing a smaller, but still significant reduction in symptoms with exercise. In addition, exercise intervention showed comparable effects with psychological therapy or pharmacological treatments in reducing depression as no significant difference was detected in subgroup analysis. Additionally, exercise was found alleviate depressive symptoms effectively in both major and minor depression.

Importantly, exercise is also reported as an effective intervention for alleviating depressive symptoms in older adults. While many of the currently available evidence was examined in young or middle-aged population, there were meta-analysis of RCTs in older adults indicated exercise might be particularly useful in treating depression among this population. There was a systematic review of eight meta-analysis, which involving 134 RCTs, assessed the antidepressant effect of exercise across different age groups (Hu et al., 2020b). Six of the eight meta-analytic results showed significant reductions in depressive symptoms among children, adolescents, adults, and older adults. Specifically, for older adults, one meta-analysis included high quality studies reported a significant reduction with effect size of -0.36, indicating the promising benefits of exercise in older adults. The evidence from previous studies suggested that low-intensity exercise was as effectively in reducing depressive symptoms as exercise with high-intensity (Conn, 2010; Larun et al., 2006). The major types of exercise, including aerobic, resistance, and mind-body exercises, have been shown to be effective treatments for clinical depressed older adults, according to a recent meta-analysis; mind-body exercises showed to have the most significant reduction in depression among the three types of exercise with high compliance and tolerance (Miller, Gonçalves-Bradley, et al., 2020).

Furthermore, a recent meta-analysis of forty-one studies, comprising 2264 participants, demonstrated large effects favouring exercise interventions than control conditions (Heissel et al., 2023). It has also been reported in another meta-analysis that exercise intervention reduced mild depressive symptoms compared to no treatment in adults with subclinical depression symptoms (Rethorst et al., 2009). It was evidenced that exercise treatment for depression could significantly reduce depression symptoms in 12 weeks (Stanton & Reaburn, 2014). According to these methodologically rigorous meta-analyses, exercise has moderate-to-large positive effects on depressive symptoms in both clinical and subclinical depression throughout adulthood.

2.2.3 Exercise effects on cognitive function

Exercise has been positively associated with healthy ageing. According to a meta-analysis of 23 follow-up studies (Daskalopoulou et al., 2017), exercise was related to improvements in healthy ageing with significant large overall effect size. While cognitive functions decline with aging, studies have demonstrated that the neuroplasticity might be maintained throughout life by various activities, and cognitive functions can be even enhanced (Voss et al., 2013). It has been shown that physical activity can lead to physiological and metabolic changes, which in turn may contribute to specific cognitive improvements through adaptations in brain structure and function (Bherer et al., 2013; Gomez-Pinilla & Hillman, 2013). Therefore, exercise interventions are often considered to be an effective intervention to improve cognitive functioning and can be used to counteract cognitive decline that occurs with age. Another meta-analysis concluded that regardless of cognitive status, physical activity could benefit cognitive function for those over 50 (Northey et al., 2018).

The findings of one meta-analysis with 80 RCTs of older adults with healthy cognition indicates that exercise significantly benefits overall cognitive performance, attention, executive function and memory (Ludyga et al., 2020). Hishikawa and colleagues evaluated and analyzed the effects of yoga in 385 older adults (Hishikawa et al., 2019). They found that long term training improved cognitive function, daily activities, and self-regulation in older adults. Another study examined the effects of exercise on cognitive control and brain activation by cognitive control tasks and EEG (Chang et al., 2017). They included older adults over 60 and divided them into three groups by exercise habit: aerobic exercise, coordinated exercise, and control group. The results showed better cognitive performance in the two exercise groups than the control group, suggesting that exercise can modulate brain activation related to executive function. Taking together, the current evidence found in older adults with healthy cognition suggested that different types of exercise are potentially effective for cognitive function.

In recent years, Chinese traditional mind-body exercise has received attention from researchers worldwide. With the long history and growing popularity around the world, Chinese mind-body exercises have demonstrated both physical and mental health benefits with accumulating scientific evidence (Ebner et al., 2021; Li et al., 2020; Yu et al., 2022). Chinese mind-body exercise is characterized by slow pace, low-to-moderate intensity, and unique combination of physical and mental components, it thus particularly suitable for older adults.

Practicing mind-body exercise was found to maintain and promote cognitive functioning and slow cognitive aging. For instance, a cross-sectional study observed that older practitioners of tai chi or aerobic exercise scored significantly better on the mental health assessment than stretching and no exercise groups (Lam et al., 2009). Another study by Lam et al. found better cognitive performance in the tai chi exercise group compared to the stretching group (Lam et al., 2011). Additionally, it was revealed that mind-body exercise (i.e. qigong and tai chi) significantly enhanced overall executive function and its subdomains of working memory and shifting in a recent meta-analysis involving 29 studies (Ren et al., 2021). The RCT by Yao et al. showed that tai chi mind-body intervention reduced levels of anxiety and depression, and it improved emotional regulation in both clinical patients and healthy adults (Yao et al., 2021).

It is also evident from empirical studies that exercise improves cognitive function in older adults with cognitive dysfunction. Aerobic exercise has shown significant moderate beneficial effects on both depression and overall cognition for older adults with mild cognitive impairment (Ahn & Kim, 2023). Another meta-analysis by Biazus-Sehn and colleagues also investigated how physical exercise affected cognition in older adults with MCI. In total, it included 2,077 participants from 27 studies. Physical exercise was shown to benefit overall cognitive function and executive function significantly with moderate effect sizes. The most significant cognitive effects appeared to arise from mind-body exercises (Biazus-Sehn et al., 2020). Recent studies also found improved cognitive function after tai chi intervention in older adults (Chen et al., 2023; Park et al., 2023). In conclusion, for older adults with impaired cognition, exercise can be an effective treatment strategy in terms of cognitive function based on current evidence.

A number of studies evidenced that exercise reduces depressive symptoms. However, according to previous reviews, studies only primarily evaluated how exercise affects depressive symptoms, without focusing on its cognitive effects (Bross et al., 2002; Lawlor & Hopker, 2001). Kubesch and colleagues assessed the cognitive effects of exercise by measuring their reaction times of completing a variety of cognitive tasks in depressed individuals. It was found that there was a significant reduction in reaction time on cognitive tasks among depressed patients engaged in exercise (Kubesch et al., 2003). Another RCT showed that tai chi could enhance executive function and physical fitness in middle-aged adults with depression (Zhang et al., 2022a). In two published meta-analysis examining the potential cognitive effects of exercise among depressed patients, no significant effects were observed (Brondino et al., 2017; Sun et al., 2018).

In summary, exercise was found to be beneficial to the brain health and cognitive function for older adults. According to these evidence presented so far, exercise has a potential to benefit depressive symptoms and cognitive function in older adults with depression. However, the current evidence is limited and ambiguous, which emphasizes the necessity of additional high-quality trials to further examine these findings.

2.2.4 Non-pharmacological interventions for cognitive outcomes in depression

We conducted a systematic review and meta-analysis with a view to evaluate and compare cognitive effects of non-pharmacological interventions, including exercise and psychotherapy interventions, on cognitive performance in individuals with depressive symptoms. The full text of the systematic review (SR1) is reported in sub-section **2.5.1** of Chapter 2.

We searched the electronic databases *PubMed*, *EMBASE*, *CINAHL* and *PsycINFO* to identify relevant RCTs published up to 1st March 2024. Inclusion criteria were based on the PICO model: participants (adults with depressive symptoms or depression), intervention (an arm of non-pharmacological intervention), comparison, outcome (reported at least one pre- and post-intervention cognitive measurement). The interventions were categorized into three types for subgroup analysis: mind-body exercise, physical exercise, and structured psychological interventions.

For overall cognitive function, the meta-analysis of 22 RCTs showed that non-pharmacological interventions had overall significant improvement in comparison with controls. The difference of the pool effects was not significant among the three subgroups.

For single cognitive domains, meta-analysis was also performed to assess effects of non-pharmacological interventions on attention/concentration, memory function, and executive function. Our pooled results indicated that mind-body exercise significantly enhanced attention/concentration and executive function relative to controls, while physical exercise and psychological intervention showed significant improvement memory function and attention/concentration, respectively. Additionally, the sensitivity analysis that excluded a study with high risk of bias showed mind-body exercise also exhibited a potential beneficial effect of subjects' memory function.

However, although mind-body exercise is a promising intervention to provide cognitive benefits for older adults with depressive symptoms, previous studies did not test the cognitive effects of qigong in this vulnerable population.

2.3 Qigong for cognitive function in older adults with depressive symptoms

2.3.1 Qigong exercise and Baduanjin

Qigong, a traditional Chinese exercise that integrates physical movements, controlled breathing, meditation, and mental focus to cultivate "Qi" within the body (Cohen, 1999; Kemp, 2004). "Qigong" refers to the combination of "Qi", which refers to vital energy, and "Gong," which refers to skills or training (Yang, 1997). Therefore, English translation of Qigong can be "energy cultivation." Qigong is rooted in Chinese traditional medicine (TCM) for promotion of health and well-being through the harmonization of the flow of Qi (Jahnke et al., 2010). Known for its gentle movements and meditative elements, qigong is suitable for all ages and provides physical and psychological relaxation.

Qigong has had a long history dating back over 5,000 years in ancient China, evolving through the country’s diverse spiritual and cultural traditions (Akman, 2018). It was originated from five primary traditions: Confucianism, Buddhism, Daoism, martial arts, and medicine, each leaving a unique imprint on the practices we recognize today (Deadman, 2014). Throughout history, Qigong remained a closely guarded family secret, passed down through generations as esoteric knowledge. It was primarily practiced by small groups of elite scholars, monks, and martial artists. The Chinese government officially recognized Qigong in 1949, consolidating various forms under a single term. The term "qigong" emerged in the mid-20th century, and by then, around 200 million Chinese were practicing it to prevent illness (Yeung et al., 2018a). Following the standardization of the qigong by the Chinese Health Qigong Association in 2001, qigong began to attract global attention and interest (Chen et al., 2019).

Qigong can be generally categorized into two forms: static and dynamic. These two forms of qigong use different approaches to promote relaxation and the flow of Qi and provide various health benefits (Jiménez-Martín & Liu, 2018). Static qigong focuses on a state of stillness through meditation, which usually involves sitting, standing or lying postures. This form of qigong help people to achieve internal harmony by deep relaxation, visualization, and mental focus. Dynamic qigong usually involves gentle and flowing movements. They are designed to maintain balance, flexibility, and mobility while promoting the flow of Qi throughout the whole body. Practitioners need to coordinate their movements with controlled breathing and concentration. Dynamic qigong is a progressive approach with high degree of adaptability and therefore suitable for different fitness levels.

As a form of dynamic qigong, Liu et al. described health qigong as an exercise characterized by slowness and coherence (Liu et al., 2016). It is believed that the best way to practice health qigong is regulating the body, breath, and mind in the present moment (Chan & Tsang, 2019; Zhang, 2007). As a most popular form of health qigong, Baduanjin has over 1000 years of history. It focuses on the internal harmony of the body, breathing techniques, and mindfulness meditation (Cheng, 2015; Tsang et al., 2002). The name of Baduanjin implies that the movements are delicate as a brocade, a richly patterned fabric. Baduanjin consists of eight movements that target different areas of the body, promoting physical flexibility, coordination, and Qi flow (Chan & Tsang, 2019). Many of its movements can be found in the illustrated Daoyin in the Han Dynasty. Until the end of Ming and early Qing Dynasties, the designations of the routines in Baduanjin were basically finalized and are still in use even nowadays (Chen et al., 2019). Each of these movements is practiced with coordinated breathing and visualization to improve energy flow and release tension throughout the body. The simplicity of Baduanjin makes it accessible to practitioners of all ages and fitness conditions, serving as an ideal entry level of Qigong practice (Yeung et al., 2018a) (Koh, 1982; Tsang et al., 2002). The General Administration of Sport promoted the rearranged Baduanjin as a part of Health Qigong in 2003 (*Health Qigong Management Center of General Administration of Sport of China* 2003). It has become increasingly popular among the public due to its certain effects on health and disease prevention. Baduanjin is currently one of the most practiced ancient Chinese qigong for life nurturing and rehabilitation internationally (Cheng, 2015). It's known as its smooth and elegant movements, especially with a focus on spine and the practice techniques of keeping the left-right symmetry, the front-back harmony and the up-down coordination. Through the continuous and overall training of the body, it can promote the circulation of qi and blood throughout the body, strengthen the body and thus achieve the purpose of life nurturing and rehabilitation. The slow movements and controlled breathing stimulate relaxation and nonattachment to stressful thoughts (*Chinese Health Qigong Association*, 2007). As a kind of physical exercise, Baduanjin provides low- and medium-intensity physical training, which is conducive to improving cognitive function (Bherer, 2015). Studies have shown that Baduanjin may effectively improve cognitive function in older adults through improving the self-regulation ability of the brain (Chen et al., 2017), increased the volume of grey matter, and modulated functional connectivity in cognitive control network (Liu et al., 2019; Tao et al., 2017). In conclusion, qigong provides a holistic approach to improve physical and mental well-being.

2.3.2 Mental health benefits of Baduanjin

Mind-body intervention is a type of non-pharmacological intervention and recognized as a complementary alternative therapy (Carlson & Bultz, 2008). Mind-body exercise, or exercise-based mind-body intervention, was found to enhance mind-body awareness and coordination through controlled movements and concentration practice (Kwok et al., 2016; Wu et al., 2019). Mind-body exercise has a significant impact on brain health due to its physical movement and mental focus. The most commonly practiced mind-body exercises include qigong, tai chi, and yoga (Kwok et al., 2016). Baduanjin qigong practice has shown to have beneficial effects of psychological well-being in a growing body of research. A meta-analysis revealed that practicing qigong has been associated with decreased depressive symptoms and anxiety, and improved mood (Wang et al., 2013). These benefits were observed in studies involving healthy adults and individuals with chronic conditions, indicating that Baduanjin may be effective for mental health in diverse populations.

2.3.3 Baduanjin for cognitive function

In addition to mental health benefits, previous evidence also suggests the possible cognitive effects of qigong (Chan & Tsang, 2019; Jin et al., 2020; Wang et al., 2022). Regular Baduanjin could slow cognitive decline in older adults with healthy condition (Ge & Anli, 2008; Song-tao, 2007). Besides, previous studies also showed the significantly benefit of Baduanjin on global cognitive function in MCI (Yu et al., 2021) and frailty (Tsang, Lee, et al., 2013; Ye et al., 2024). Therefore, Baduanjin is proposed to effectively enhance global cognitive function in depressed older adults. However, the evidence is limited in older adults with depressive symptoms. To address this research gap, a single-blinded RCT is proposed for the main study. The present study aims to examine the effects of a 12-week Baduanjin training on global cognitive function of older adults with depressive symptoms by comparing with wait-list control **(Primary Objective)**. It was hypothesized that the qigong group that received 12 weeks of Baduanjin training would have significantly more improvement in global cognitive function after the completion of the training.

Additionally, the possible benefits of qigong training on specific cognitive domains have not been explored thoroughly. The current available evidence is limited and mixed. The study by Ladawan found qigong intervention enhanced attentional ability in healthy subjects, while executive functions did not change significantly (Ladawan et al., 2017). Besides, Baduanjin was reported to improve attention, memory and executive ability of older adults with MCI (Tao et al., 2019; Xia et al., 2019). Furthermore, the findings of a cluster RCT demonstrated that qigong significantly improved memory and visuospatial abilities compared to stretching, but no significant effect was found for attention (Jin et al., 2020). Importantly, despite these encouraging research findings, no research has examined possible effects of qigong practice on attention, working memory, and inhibitory control among older adults with depressive symptoms. According to our literature review, the effects of mind-body exercises on neurocognitive functions have been investigated in limited number of studies which have yielded equivocal results. Lavretsky and colleagues found that in older adults, the changes in attention and executive functions were not significant following the training (Lavretsky et al., 2022a). Chan and colleagues evaluated the cognitive effect of Chinese Chan-based Dejian mind-body interventions (DMBI) as an augmentation strategy for depressed patients (Chan et al., 2013). Participants who received 10-week DMBI exhibited improved measures of attentional ability than waitlist control. These previous studies have provided important preliminary evidence towards establishing qigong mind-body exercise as a neurobehavioral intervention in individuals with depression. Collectively, although qigong may present itself as a promising intervention in enhancing attention and executive functions, little research has studied these cognitive benefits of Baduanjin in depressed older adults. Therefore, our main study also intended to explore the benefit of a 12-week qigong training (Baduanjin) in enhancing attention, working memory, and inhibitory control, in older adults with depressive symptoms at post-intervention (i.e., 12 weeks after baseline), in comparison to 12-week waitlist control **(Secondary Objectives)**.

2.4 Possible explanation for effects of qigong

Current empirical evidence of neurobiological changes in people with depressive symptoms after qigong intervention is still limited, and relevant findings of other exercises might inform the possible explanation of qigong's effect. Therefore, we conducted a systematic review on possible neurobiological mechanism pathways underpinning the effects of exercises, including both mind-body and physical exercises. The sub-section **2.5.2** of Chapter 2 presented the full text of the systematic review (SR2). According to our review, the antidepressant effect of mind-body exercise might be explained by regulation of the hypothalamic-pituitary-adrenal (HPA) axis activity, enhancement of neurogenesis, and decrease of pro-inflammatory cytokines. Among the included RCTs in the review, only one study explored the brain activity and observed enhanced frontal alpha asymmetry following the mind-body exercise training. Given that no previous RCT was identified to explore neurophysiological mechanism of qigong mind-body exercise in depressed population, it should be further explored and tested by future studies.

Depression is one of the most common psychiatric diseases in later life. These individuals are typically over-sensitive and over-reactive to surrounding environment negatively, along with persistence of negative thoughts (Zhu et al., 2017). It was suggested that the rumination in patients with depression can be attributed to their difficulty in disengaging attention (i.e. attentional biases) from negative information (Donaldson et al., 2007). In addition to the attentional biases, late life depression is often related to impaired executive function, both are keys to the neuropsychology of frontal lobe problem (Tam & Chiu, 2011). In fact, abnormalities and reduced activities in the prefrontal cortex were found in patients with mood disorders (Drevets et al., 1997) (Henriques & Davidson, 1990). Together, previous research has indicated that alterations of brain functions might be important for the possible neural mechanism of depression.

Although researchers have applied mind-body exercise such as Qigong and tai chi in older adults with MCI, this type of exercise has not been widely promoted as an treatment for cognitive impairment in depressed older adults due to limited research findings (Chan et al., 2016; Siu & Lee, 2018). Researchers have proposed that exercise may improve cognitive function by slowing the neurodegeneration, promoting the neurotrophic production, or decreasing inflammatory markers (Ahlskog et al., 2011). It was found that physical exercise and tai chi can increase neural plasticity in the hippocampus and frontal cortex, which might be related to the changes in brain activity and further play important roles in cognitive function (Audiffren & André, 2019; Marinus et al., 2019; Sungkarat et al., 2018). Mind-body exercise might induce brain changes more than conventional physical exercise. Cui and colleagues implemented an eight-week training of tai chi and brisk walking intervention in a group of college students. In their study, tai chi had a greater effect on brain plasticity (Cui et al., 2019), that shown in increased functional connectivity between the left middle frontal gyrus and the left superior parietal lobule. It is believed that combining physical exercise and mental focus might generate a synergistic effect on neuroplasticity, and thus the promotion of neurogenesis may explain the potential benefits of qigong on cognitive function in people with depressive symptoms.

However, the neurophysiological evidence on qigong-related enhancement in on brain activation is very limited. Traditionally, behavioural performance, such as accuracy and response time, was assessed to determine the cognitive function after exercise intervention. With the development of advanced technologies and tools, more and more evidence has shown an association between mind-body exercise and brain activity. It was demonstrated that the ERPs represent brain voltage fluctuations for specific events, such as onset of stimulus (Luck & Kappenman, 2013). The two ERP components, N2 and P3, were suggested to help better understand cognitive process (Patel & Azzam, 2005). It was showed that the N2 component is a negative deflection at the frontocentral scalp site approximately 200–350 ms after stimulus onset, while the P3 component is a positive deflection with a centroparietal scalp distribution approximately 250–500 ms after stimulus onset (Folstein & Van Petten, 2008; Friedman et al., 2001). Both N2 and P3 are considered to be positively correlated with attention (Polich, 2007), working memory (Gevins & Smith, 2000), inhibitory control (Jackson et al., 1999; Larson et al., 2014), as well as general cognitive abilities (Gevins & Smith, 2000). Therefore, previous findings suggest that measuring N2 and P3 components would be promising for furthering our understanding of qigong on cognitive and brain functions.

Several studies explored the possible neural basis for cognitive improvements after mind-body practice. Chan et al. investigated the neurophysiological changes after the mind-body intervention in MDD patients. The participants showed improved attention and related neural connectivity following the intervention (Chan et al., 2013). The effects of exercise on cognitive control in MDD were studies in another RCT (Olson et al., 2017). They observed greater N2 amplitudes after the intervention, indicating an improvement in cognitive control processes. Moreover, previous research has also suggested that the cognitive effects are greater in the combination of physical and mental training than single intervention (Ladawan et al., 2017). Alderman et al. observed increased N2 and P3 amplitudes related to cognitive control following the combined mental with physical training, especially among the MDD patients (Alderman et al., 2016). Despite that previous research suggested that both physical exercise and meditation can effectively increase cognitive function individually, this study added further evidence that combined intervention may be highly effective for cognitive function in depressed population.

Since qigong incorporates body movements, coordinated breathing, and induces a kind of mental state of 'attention' (Greten, 2007), the cognitive effects of qigong might due to its multi-modal nature as a mind-body exercise (Chang et al., 2014). Considering qigong could give rise to positive affect and improve cognitive function, it is plausible to hypothesize that the neurophysiological changes associated with this intervention may also involve enhanced brain activity. However, whether qigong is associated with changes in brain activity related to cognitive improvement in specific or global cognitive functions in depressed individuals should be explored by more studies. Therefore, our main study also aimed to explore possible effects of a 12-week Baduanjin qigong training in enhancing anterior N2 amplitude and posterior P3 amplitude of older adults with depressive symptoms at post-intervention (i.e., 12 weeks after baseline), in comparison to 12-week waitlist control; we will also explore their potential roles as mediators that unpack the qigong-related cognitive benefits **(Secondary Objectives)**.

2.5 Systematic reviews on qigong studies

2.5.1 SR1: Non-pharmacological interventions for cognitive outcomes in depression: A systematic review and meta-analysis of randomized controlled trials

There are studies showed that non-pharmacological interventions, including exercise and psychological interventions, might be useful in improving cognitive function in depression. We therefore performed a systematic review to summarize and compare the effects of mind-body exercise, physical exercise, and psychological interventions on cognitive function among adults with depression.

2.5.1.1 Introduction

Depression is a prevalent mood disorder that significantly impacts global health. It was estimated that over 280 million younger and older adults worldwide suffer from this chronic relapsing and remitting condition in 2019 (WHO, 2021). Cognitive deficits, a common and important aspect of depression, including impaired memory, attention, and executive function (Monastero et al., 2009; Rock et al., 2014c). Importantly, psychosocial functioning and overall quality of life of depressed individuals could be further impaired significantly (Cambridge et al., 2018).

Cognitive deficits were hypothesized to closely related to the development and maintenance of affective symptoms, according to the cognitive models of depression (Beck, 2008). In individuals with depression, they usually exhibit biased attention to negative stimuli and negative interpretation for ambiguous information (Castaneda et al., 2008; Tavares et al., 2007). In addition, they also show impaired working memory and cognitive flexibility, and this makes them hard to adapt the situation changes and find alternative way to solve problems (Clark et al., 2009; Grahek et al., 2018). Consequently, depression can persist by a cycle of negative thinking and rumination. In severe cases, they can have exacerbated feelings of hopelessness and suicidal ideation (Bortolato et al., 2014). Therefore, cognitive function is considered an important therapeutic target for depressed population, and effective interventions are needed urgently.

Although pharmacological intervention remains important in depression treatment, the effect on cognitive symptoms is not clear. Some patients maintain cognitive deficits while their mood improved after antidepressant treatment (Pan et al., 2019). This limitation of pharmacological intervention highlights the need for alternative or complementary interventions to address cognitive symptoms in depression. Currently, non-pharmacological interventions, such as exercise and psychological interventions, were found to benefit cognitive and mental wellness (Cuijpers et al., 2008). These interventions are considered as promising strategies for enhancing cognitive function in depressed individuals without medication-related adverse effects (de Asteasu et al., 2017; Hofmann et al., 2012).

Exercise was shown to improve both depressive symptoms and cognitive performance in healthy population and patients with cognitive impairment(Barth et al., 2016; Falck et al., 2019; Gutkin et al., 2021; Knapen et al., 2015; Stillman et al., 2020). Mind-body exercise is a special form of exercise that combined physical with mental components, and is considered a promising intervention for depression (Bo et al., 2017; La Forge, 2016). Furthermore, previous studies showed that regular mind-body practice might delay cognitive decline among healthy older adults (Ge & Anli, 2008; Song-tao, 2007), and also benefit the overall cognitive function in older adults with frailty and MCI (Liu, Seah, et al., 2020; Tao et al., 2019; Tsang, Lee, et al., 2013).

There are various types of psychological intervention for depression treatment, including mindfulness, cognitive behavioral therapy, interpersonal therapy, psychodynamic therapy. Mindfulness meditation is an effective psychological treatment that helps develop nonjudgmental awareness of present moment by focusing on body awareness, attention and emotion regulation (Kabat-Zinn, 2003). Individuals with depression may benefit from mindfulness-based intervention by reducing rumination, improving attention and working memory (Kraines et al., 2022). Moreover, other psychotherapies were also shown to associated with improvements in memory and attention, providing valuable alternative strategies in addition to pharmacological treatments (Barth et al., 2016).

Taken together, cognitive impairments are strongly related to the development and maintenance of depressive episodes and functional symptoms. Considering the increasing global burden of depression, it is therefore important to study the effectiveness of interventions that target cognitive dysfunction in depression. Non-pharmacological interventions, such as exercise and psychotherapy, can be employed to enhance cognitive performance as more comprehensive and effective options for people with depressive disorders. The present systematic review and meta-analysis synthesized recent evidence on the cognitive effects of non-pharmacological interventions for individuals with depressive symptoms. This review aims to elucidate the most effective strategies for cognitive enhancement in this population. The results would inform clinical practice and future research, thus ultimately contribute to the development of holistic and effective treatment approaches for depression (Godlewska & Harmer, 2021; Rock et al., 2014b).

2.5.1.2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was applied to conduct and report this systematic review and meta-analysis. The study was pre-registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022329926).

Literature search

The electronic databases, including *PubMed*, *EMBASE*, *CINAHL* and *PsycINFO* were searched to identify relevant studies published up to 1st March 2024. Following terms were used for literature search: depress* AND (psychotherapy* OR "psychological intervention" OR "psychological treatment" OR "cognitive behavioral therapy" OR CBT OR "dialectical behavior therapy" OR "interpersonal therapy" OR "mindfulness-based" OR MBCT "acceptance and commitment therapy" OR "problem-solving therapy" OR psychodynamic OR "behavioral activation therapy" OR "mind body" OR yoga OR "tai chi" OR "taiji" OR qigong OR "qi gong" OR exercise OR aerobic* OR walk* OR jog* OR run* OR cycl* OR swim* OR danc* OR anaerobic OR resistance OR strength OR endurance OR stretch*) AND (cognition OR "cognitive function") AND (randomized controlled trial OR controlled clinical trial OR controlled clinical study OR controlled trial OR controlled study OR randomiz* OR randomis* OR randomly). In addition, the reference list of each of the included studies was checked to identify additional relevant studies.

Eligibility criteria

The inclusion criteria of this study were based on the Population, Intervention, Comparison, Outcome (PICO) model: 1) Participants: older adults with depressive symptoms or depression as measured by diagnostic criteria (International Classification of Diseases, Diagnostic and Statistical Manual for Mental Disorders), or recognized depression inventories; 2) Intervention: at least one arm of non-pharmacological intervention. The included interventions were classified into three subtypes: physical exercise (PE), mind-body exercise (MBE), structured psychological interventions (PI); 3) Comparison: any different type of intervention or non-active control; 4) Outcomes: baseline and post-intervention measure of global or at least one single-domain cognitive outcome; and 5) RCT design. A study was excluded if 1) its participants had comorbid psychiatric conditions; 2) it was a conference abstract; or 3) it was not in English and not published in a peer-reviewed journal.

Study selection

The literature search records were managed by EndNote 21 (Thompson ISI Research Soft, Philadelphia, PA, USA). Two independent reviewers (WS and JH) first screened titles and abstracts taken from electronic database sources for the initial inclusion of potentially relevant studies after excluding duplicates. In order to determine eligibility for systematic review, two reviewers then retrieved the fulltext of identified studies, and any inconsistencies were addressed by discussion with another reviewer (CW).

Data extraction

The two reviewers (WS and JH) independently extracted information on the author, year of publication, country, subject characteristics, sample size, intervention specifics, and cognitive function measures at baseline and post-intervention from each individual study. The outcome data were primarily extracted from intention-to-treat analysis; otherwise, the outcome data were obtained from available cases.

Risk-of-bias assessment

The reviewers (WS and CW) evaluated risk of bias for all the included studies using the revised Cochrane Risk of Bias assessment tool (RoB 2.0) . The following domains were considered: 1) bias arising from the randomization process, 2) bias due to deviations from the intended interventions, 3) bias due to missing outcome data, 4) bias in measuring the outcome, and 5) bias in selecting the reported results. Each domain was classified as being at risk of bias, with some concerns, or with high risk of bias.

Data Synthesis

Meta-analysis was conducted to estimate a combined measure of effect when two or more studies reported a comparable outcome (Deeks et al., 2021). For each individual cognitive measurement, the mean changes pre- to post-intervention were computed and entered for meta-analysis. Due to different tests of cognitive function being used in the included studies, we obtained the pooled effect using standardized mean difference (SMD) by Hedges' g method and also calculated the 95% confidence intervals (CIs) and the p-value.

For studies that reported multiple measures for an individual cognitive domain, the mean effect size within that domain was computed thereby only a single effect size was obtained for each cognitive domain within each study (Borenstein et al., 2009). This approach was taken to restrict artificial inflation, potential interdependence of observations, and to avoid error due to redundancy. Furthermore, the overall cognitive change was also measured by averaging the changes in all cognitive subdomains.

In studies with multiple intervention or control groups, the data of the primary intervention and non-active control conditions were extracted. Random-effects model was employed in the meta-analysis in order to account for the study variability regarding the effect of different interventions. I^2 statistic was used to estimate the heterogeneity across studies and divided into three levels: small (25%), moderate (50%), and high (75%). Publication bias was tested by detecting the asymmetry of funnel plot and analyzing the significance of Egger's regression. We evaluated the impact of publication bias on the results by applying the trim-and-fill method. Subgroup meta-analyses explored the differences in effect sizes and CIs by type of intervention, age groups, depression severity, baseline cognitive function, and control conditions. A sensitivity analysis was conducted by excluding studies with high risk of bias from the analysis. Stata version 17 (STATA corporation, College Station, TX, USA) was used for all the statistical analysis.

2.5.1.3 Results

Study selection and characteristics

Figure 1 describes the process of literature search and study selection. A total of 4,608 studies were initially identified from the five databases searched, and 42 studies were identified from relevant systematic reviews and meta-analyses, resulting in 2,613 studies after the removal of duplicates. After the screening of titles and abstracts, 228 studies were subjected to full-text review. Of these, 22 RCTs with 1,721 participants finally met the inclusion criteria and were selected for this systematic review.

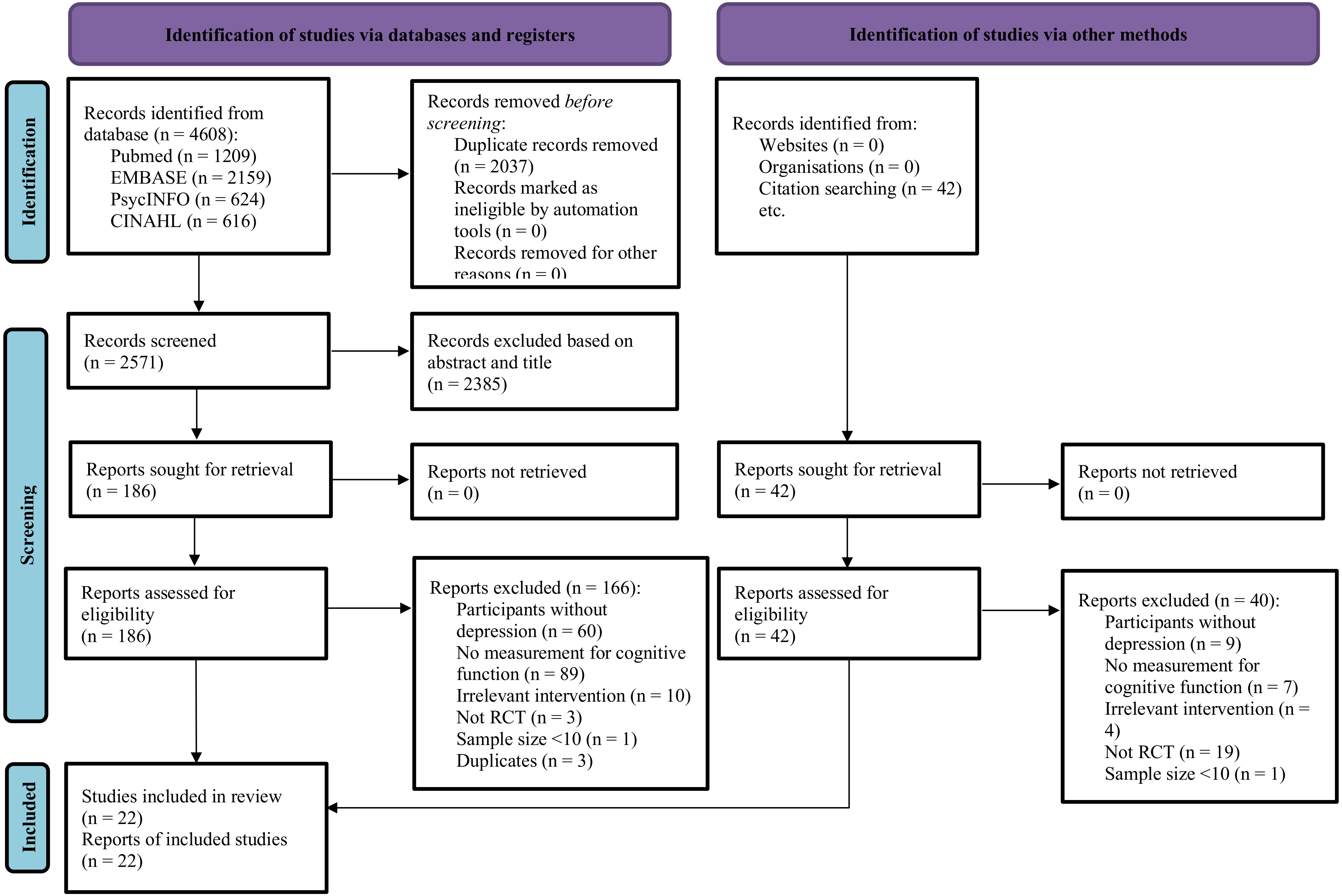


Figure 1. PRISMA flowchart

Table 1. Summary of included exercise studies (*s*=22)

Study	Country/ Region	Sample size	Age (mean±sd)	Gender (M/F)	Intervention	Frequency Duration	Control	Depression measures	Cognitive measures
Khatri (2001)	UK	I: 42 C: 42	56.7±6.5	20/64	Aerobic exercise	3 sessions/week 16 weeks	Medication	HAMD	WAIS-R digit-span WMS logical memory immediate & delayed recall WMS visual reproduction immediate & delayed recall TMT - A & B Stroop WAIS-R digit symbol
Sharma (2006)	India	I: 15 C: 15	I: 31.9±8.8 C: 31.7±8.5	19/11	Sahaj Yoga plus conventional anti-depressant	3 sessions/week 8 weeks	Conventional anti-depressant	HAMD	Letter cancellation test Digit Span Test TMT - A & B Ruff figural fluency test
Krogh (2009)	Denmark	I: 55 C: 55	I: 38.1±9.0 C: 36.7±8.7	I: 12/43 C: 21/34	Strength or Aerobic training	2 sessions/week 16 weeks	Relaxation	HAMD-17 MADRS BDI	Digit Span Test Subtracting Serial Sevens Buschke Test RCFT - 3-min recall TMT - A & B VFT - animal, S words
Lavretsky (2011)	US	I: 36 C: 37	I: 69.1±7.0 C: 72.0±7.4	I: 13/23 C: 15/22	Tai Chi	2 hours/week 10 weeks	Health education	HAMD-24	MMSE CVLT long delayed recall TMT-A
Krogh (2012)	Denmark	I: 56 C: 59	I: 39.7±11.3 C: 43.4±11.2	I: 16/40 C: 22/37	Aerobic exercise	3 sessions/week 12 weeks	Stretching	HAMD-17 BDI	Digit span - forwards Digit span - backwards Subtracting Serial Sevens Buschke Test RCFT - 3 min recall Stoop TMT - A & B Digit symbol VFT - animal, S words
Bastos (2013)	Brazil	I: 90 C: 91	I: 29.9±2.4 C: 29.6±2.2	I: 39/61 C: 37/63	Long-term psychodynamic psychotherapy	1 session/month 24 months	Medication	BDI	WAIS-III - Digit span WAIS-III - Matrices WAIS-III - Similarities

Chan (2013)	Hong Kong	I1: 25 I2: 25 C: 25	I1: 47.1±9.5 I2: 46.9±6.5 C: 45.4±8.3	I1: 2/15 I2: 4/13 C: 4/12	I1: Dejian Mind-Body Intervention I2: CBT	1 session/week 10 weeks	Waitlist	HAMD BDI-II	Digit Vigilance Test (DVT)
Groves (2015)	New Zealand	I: 23 C: 25	I: 37.2±12.7 C: 35.0±13.0	I: 12/11 C: 13/12	Metacognitive therapy	8-15 sessions within 12 weeks	CBT	QIDS MADRS	Rapid Visual Information Processing (RVP) Groton Maze Learning Task COWAT
Luttenberger (2015)	Germany	I: 25 C:26	I: 42.7±11.9 C: 45.0±12.1	I: 10/12 C: 10/15	Bouldering	1 session/week 8 weeks	Waitlist	BDI-II	D2-R
Neviani (2017)	Italy	I: 42 C: 42	I: 75.0±6.2 C: 75.6±5.6	I: 13/29 C: 10/32	Medication plus aerobic exercise	3 sessions/week 24 weeks	Medication	HAMD	MoCA
Olson (2017)	USA	50	I: 21.0±1.9 C: 21.2±2.2	I: 4/11 C: 2/13	Aerobic exercise	3 sessions/week 8 weeks	Stretching	BDI-II	Behavioral Performance
Halappa (2018)	India	I: 16 C: 23	I: 37.1±8.1 C: 31.0±5.9	I: 9/7 C: 13/10	Yoga	Daily 12 weeks	Medication		Digit Span Test RAVLT TMT - A & B
Buschert (2019)	Germany	I: 18 C: 20	I: 47.3±6.8 C: 47.5±8.5	I: 6/9 C: 5/10	Physical exercise	2-3 sessions/week 3-4 weeks	Occupational therapy	BDI-II HAMD-7	TAP - tonic alertness TAP - divided attention WMS-R working memory WMS-R short-term memory Rey VLMT learning total Rey VLMT recall SPM logical thinking
Dannehl (2019)	Germany	I: 34 C: 30	I: 37.2±12.5 C: 37.9±13.5	I: 15/19 C: 17/13	CBT emphasizing pleasurable low-energy activities	1 session/week 16 weeks	Waitlist	BDI-II	Rey VLMT learning total Rey VLMT recall Rey VLMT recognition
Dias (2019)	India	I: 91 C: 90	69.6±7.2	67/114	Problem-solving therapy	30-40min/session 6-8 weeks	Usual care	GHQ-12	MMSE
Yan (2019)	China	I: 41 C: 41	I: 39.1±3.6 C: 38.4±4.6	I: 22/19 C: 20/21	CBT plus medication	2 sessions/week 12 months	Medication	HAMD	WCST

Imboden (2020)	Switzerland	E: 22 C: 20	E: 41.3±9.2 C: 38.3±13.4	E: 12/10 C: 10/10	Aerobic exercise	3 session/week 6 weeks	Stretching	BDI HAMD-17	TAP - Alertness TAP - Working memory TAP - Flexibility TAP - Go / nogo
Makizako (2020)	Japan	I: 30 C: 29	I: 73.1±5.3 C: 73.0±5.9	I: 14/16 C: 14/15	Exercise	1 session/week 20 weeks	Health education	GDS-15	WMS - Story immediate & delay Wordlist memory tasks - immediate & delay TMT - A & B VFT - animal
Lavretsky (2021)	US	I: 89 C: 89	I: 69.2±6.9 C: 69.4±6.2	I: 27/62 C: 22/67	Tai Chi	60 min/week 12 weeks	Health education and wellness training	HAMD	CVLT-II - long delayed recall TMT - A & B Stroop Interference COWAT VFT - animal Boston Naming Test
Katayama (2022)	Japan	I: 19 C: 19	I: 38.0±7.4 C: 36.9±10.1	I: 9/10 C: 9/10	CBT	1 session/week 16 weeks	Talking control	HAMD	VFT Digit symbol substitution test
Zhang (2022)	Hong Kong	I: 20 C:19	50.6±7.4	4/35	Tai Chi	2 sessions/week 12 weeks	Waitlist	BDI-II	Stoop WCST TOL
Dong (2023)	China	I: 30 C: 30	I: 19.8 C: 19.6	I: 20/10 C: 17/13	Mindfulness training	1 session/week 8 weeks	Waitlist	SDS	Stroop N-back More-odd shifting switch

I: Intervention group; C: control group; CBT: cognitive-behavioural therapy;
BDI: Beck Depression Inventory; GDS, Geriatric Depression Scale; HAMD: Hamilton Depression Rating Scale; QIDS: Quick Inventory of Depression Symptomatology;
MADRS: Montgomery-Asberg Depression Rating Scale; GHQ: General Health Questionnaire; SDS: Self-Rating Depression Scale;
AVLT: Auditory Verbal Learning Test; COWAT: Controlled Oral Word Association Task; CVLT: California Verbal Learning Test; MMSE: Mini-Mental State Examination;
MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey-Osterrieth Complex Figure Test; SPM: Standard progressive matrices;
TAP: Testbatterie zur Aufmerksamkeitsprüfung; TMT: Trail Making Test; VFT: Verbal Fluency Test; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin card sorting Test; WMS: Wechsler Memory Scale.

The included studies were published between 2001 and 2023. The mean age of patients ranged from 19.7 to 75.3 years, and the sample size ranged from 30 to 181. The interventions were categorized into four non-exclusive types: PE (n=9), MBE (n=6), PI (n=8). The intervention sessions ranged from eight to seventy-two sessions and the duration of the interventions ranged from two to twenty-four months. An active comparator was used in 13 studies and a treatment-as-usual control group was used in the remaining nine studies. **Table 1** summarizes participants' demographics, intervention and control conditions, and outcome measurements of the included studies.

Risk of bias and quality assessment

As evaluated by the Cochrane risk of bias tool, 12 (55%) studies had overall low risk of bias, 6 (27%) had some concerns, and 4 (18%) had high risk of bias. Most of the included studies were of low risks in randomization process (77%), deviations from the intended interventions (82%), missing outcome data (82%), measurement of the outcome (95%), incomplete outcome data selection of the reported result (95%). The four studies with a high risk of bias were removed in the sensitivity analysis. **Table 2** provides the risk of bias for all the included studies.

Table 2. Version 2 of the cochrane risk of bias tool (RoB 2) for included RCT studies.

Source	Bias arising from the randomization process	Bias due to deviations from the intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Khatri (2001)	Some concerns	Low	Low	Low	Low	Some concerns
Sharma (2006)	Some concerns	Some concerns	Low	Low	Low	Some concerns
Krogh (2009)	Low	Low	High	Low	Low	High
Lavretsky (2011)	Low	Low	Low	Low	Low	Low
Krogh (2012)	Low	Low	Low	Low	Low	Low
Bastos (2013)	Some concerns	Low	Low	Low	Low	Some concerns
Chan (2013)	Low	Low	Low	Low	Low	Low
Groves (2015)	Some concerns	Some concerns	High	Low	Some concerns	High
Luttenberger (2015)	Low	Some concerns	Low	Some concerns	Low	Some concerns
Neviani (2017)	Low	Low	Low	Low	Low	Low
Olson (2017)	Low	Low	High	Low	Low	High
Halappa (2018)	Low	Low	Low	Low	Low	Low
Buschert (2019)	Low	Low	Low	Low	Low	Low
Dannehl (2019)	Low	Low	Low	Low	Low	Low
Dias (2019)	Low	Low	Low	Low	Low	Low
Yan (2019)	Low	Some concerns	Low	Low	Low	Some concerns
Imboden (2020)	Low	Low	Low	Low	Low	Low
Makizako (2020)	Low	Low	Low	Low	Low	Low
Lavretsky (2021)	Low	Low	High	Low	Low	High
Katayama (2022)	Low	Low	Low	Low	Low	Low
Zhang (2022)	Some concerns	Low	Low	Low	Low	Some concerns
Dong (2023)	Low	Low	Low	Low	Low	Low

Global cognitive function

Meta-analysis of 22 RCTs was conducted to evaluate the pooled effect of non-pharmacological interventions and revealed a significant improvement in global cognitive function (SMD=0.24, p=0.001, I^2=87.1%) compared to control groups (**Figure 2**). Further subgroup meta-analyses were conducted to study the effect of different types of intervention on cognitive function. Six studies examined the effect of MBE on global cognition (Chan et al., 2013; Halappa et al., 2018; Lavretsky et al., 2011a; Lavretsky et al., 2022b; Sharma et al., 2006; Zhang et al., 2022b) and demonstrated significant differences between the MBE group and the control group (SMD=0.25, p=0.013, I^2=62.9%). Non-significant pooled effects were found from the subgroup of the nine studies on PE (Buschert et al., 2019; Imboden et al., 2020; Khatri et al., 2001; Krogh et al., 2009; Krogh et al., 2012b; Luttenberger et al., 2015; Makizako et al., 2020; Neviani et al., 2017; Olson et al., 2017) and the eight studies on PI (Bastos et al., 2013; Chan et al., 2013; Dannehl et al., 2019; Dias et al., 2019; Dong et al., 2023; Groves et al., 2015; Katayama et al., 2022; Yan et al., 2019) (PE: SMD=0.08, p=0.130, I^2=48.1%; PI: SMD=0.44, p=0.079, I^2=94.3%). However, there was no significant difference in the pool effects among the three subgroups (p=0.683). The results of Egger's test (p=0.153) indicated non-significant publication bias for the included non-pharmacological studies. Further analysis with the trim-and-fill test showed unchanged pooled estimates and indicated that no adjustment for publication bias was needed.

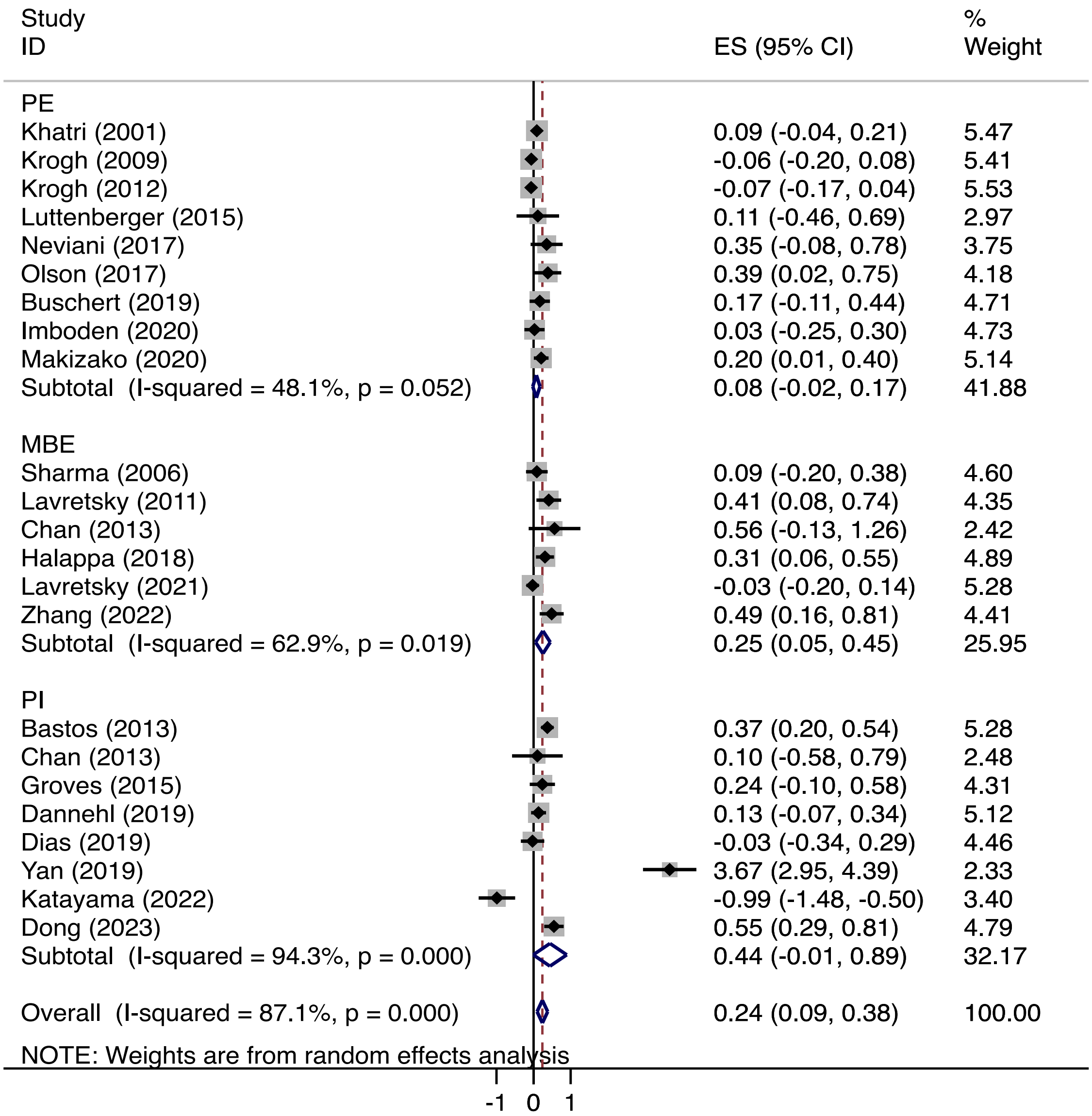


Figure 2. Pooled effects for overall cognitive function by intervention type

Single cognitive domains

Meta-analysis was also performed to assess cognitive effects of non-pharmacological interventions, including attention/concentration, memory function, and executive function.

Data on attention/concentration were extracted from six PE studies (Buschert et al., 2019; Imboden et al., 2020; Khatri et al., 2001; Krogh et al., 2009; Krogh et al., 2012b; Luttenberger et al., 2015), three MBE studies (Chan et al., 2013; Halappa et al., 2018; Sharma et al., 2006), and three PI studies (Bastos et al., 2013; Chan et al., 2013; Groves et al., 2015). The pooled overall result from meta-analysis demonstrated a non-significant increase in attention/concentration level (SMD=0.13, p=0.11, I^2=50.6%) (**Figure 3**). The further subgroup analysis by intervention type indicated that both MBE (SMD=0.33, p=0.021, I^2=0%) and PI (SMD=0.41, p<0.001, I^2=0%) showed significantly increased levels of attention/concentration, but PE (SMD=-0.04, p=0.497, I^2=5.9%) revealed non-significant results.

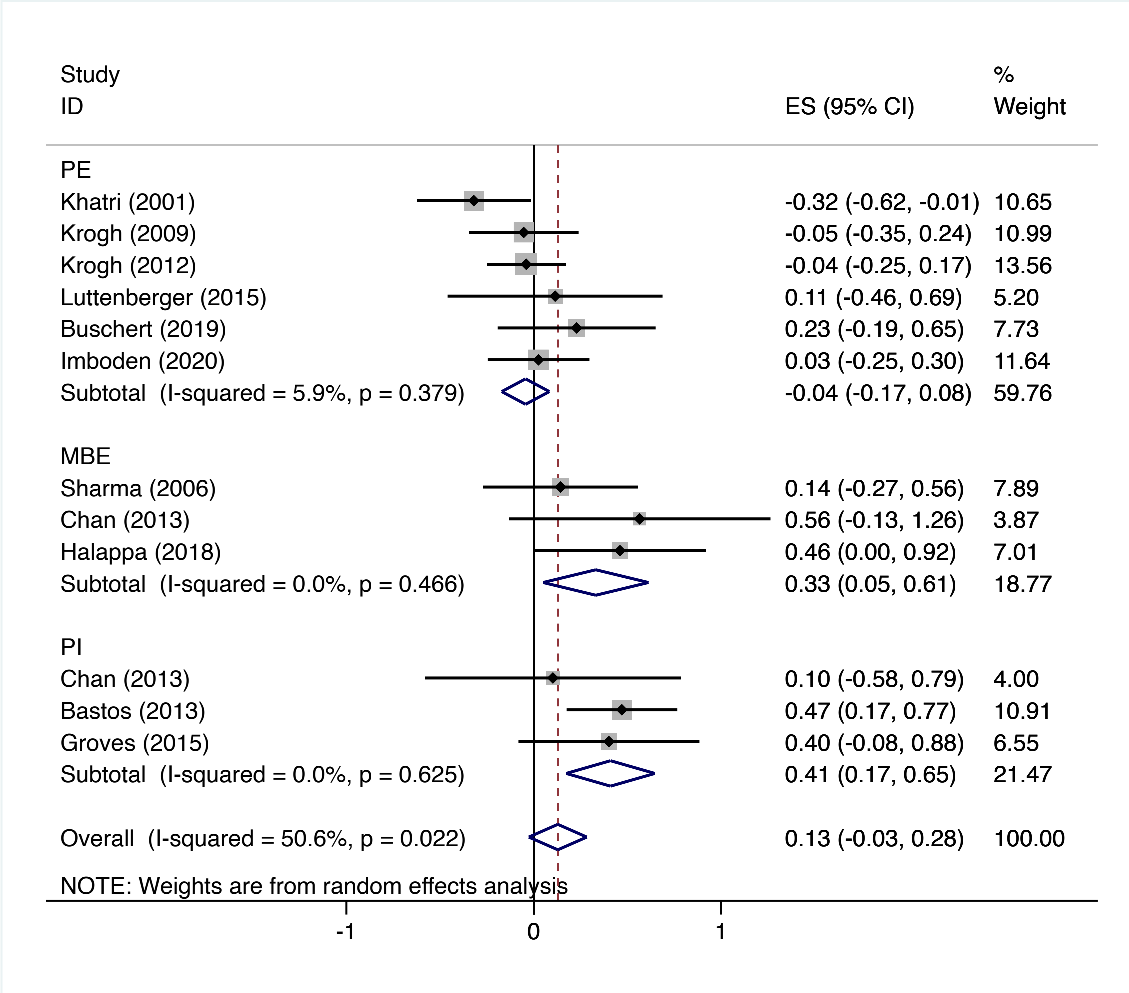


Figure 3. Pooled effects for attention/concentration by intervention type

Evaluable data on memory function from five PE studies (Buschert et al., 2019; Khatri et al., 2001; Krogh et al., 2009; Krogh et al., 2012b; Makizako et al., 2020), three MBE studies (Halappa et al., 2018; Lavretsky et al., 2011a; Lavretsky et al., 2022b) and one PI study (Dannehl et al., 2019) were pooled by meta-analysis. Overall, there was a significant improvement in memory function following these non-pharmacological interventions (SMD=0.15, p=0.005, I^2=19.8%) (**Figure 4**). Compared with the baseline, PE showed increased memory function relative to controls (SMD=0.19, p=0.003, I^2=0%), while non-significant effects on memory function were found in MBE (SMD=0.20, p=0.403, I^2=68.8%) and PI (SMD=0.13, p=0.191).

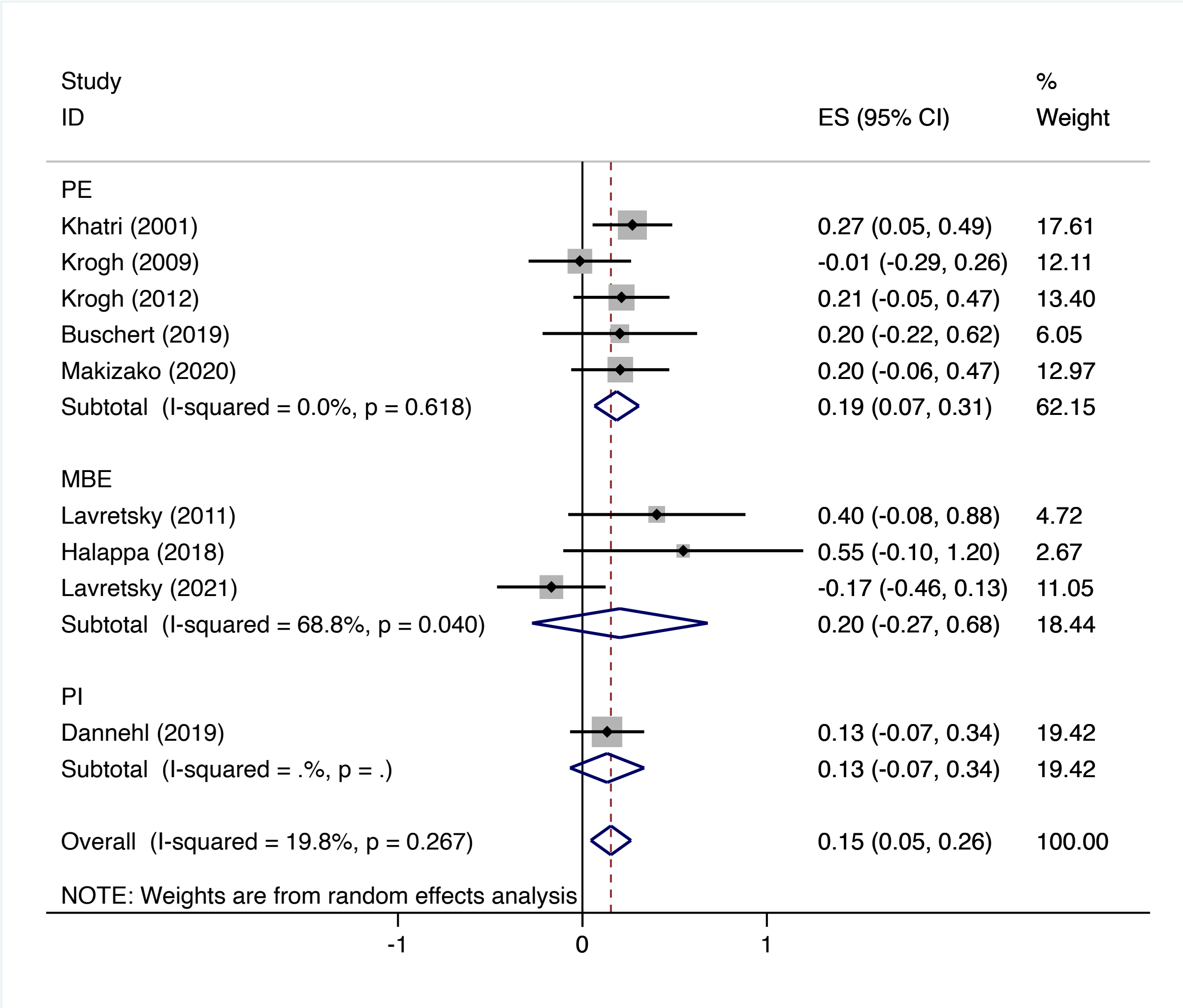


Figure 4. Pooled effects for memory function by intervention type

Meta-analysis was performed on executive function data from six PE studies (Buschert et al., 2019; Khatri et al., 2001; Krogh et al., 2009; Krogh et al., 2012b; Makizako et al., 2020; Olson et al., 2017), five MBE studies (Halappa et al., 2018; Lavretsky et al., 2011a; Lavretsky et al., 2022b; Sharma et al., 2006; Zhang et al., 2022b), and five PI studies (Bastos et al., 2013; Dong et al., 2023; Groves et al., 2015; Katayama et al., 2022; Yan et al., 2019), which showed a significant effect of non-pharmacological interventions in improving executive function (SMD=0.26, p=0.024, I^2=90.4%) (**Figure 5**). In the subgroup analysis, significant improvement in executive function performance was presented in MBE (SMD=0.21, p=0.030, I^2=38.9%), whereas the intervention effects on executive function were not statistically significant in PE (SMD=0.04, p=0.651, I^2=61.6%) and PI (SMD=0.68, p=0.137, I^2=96.5%).

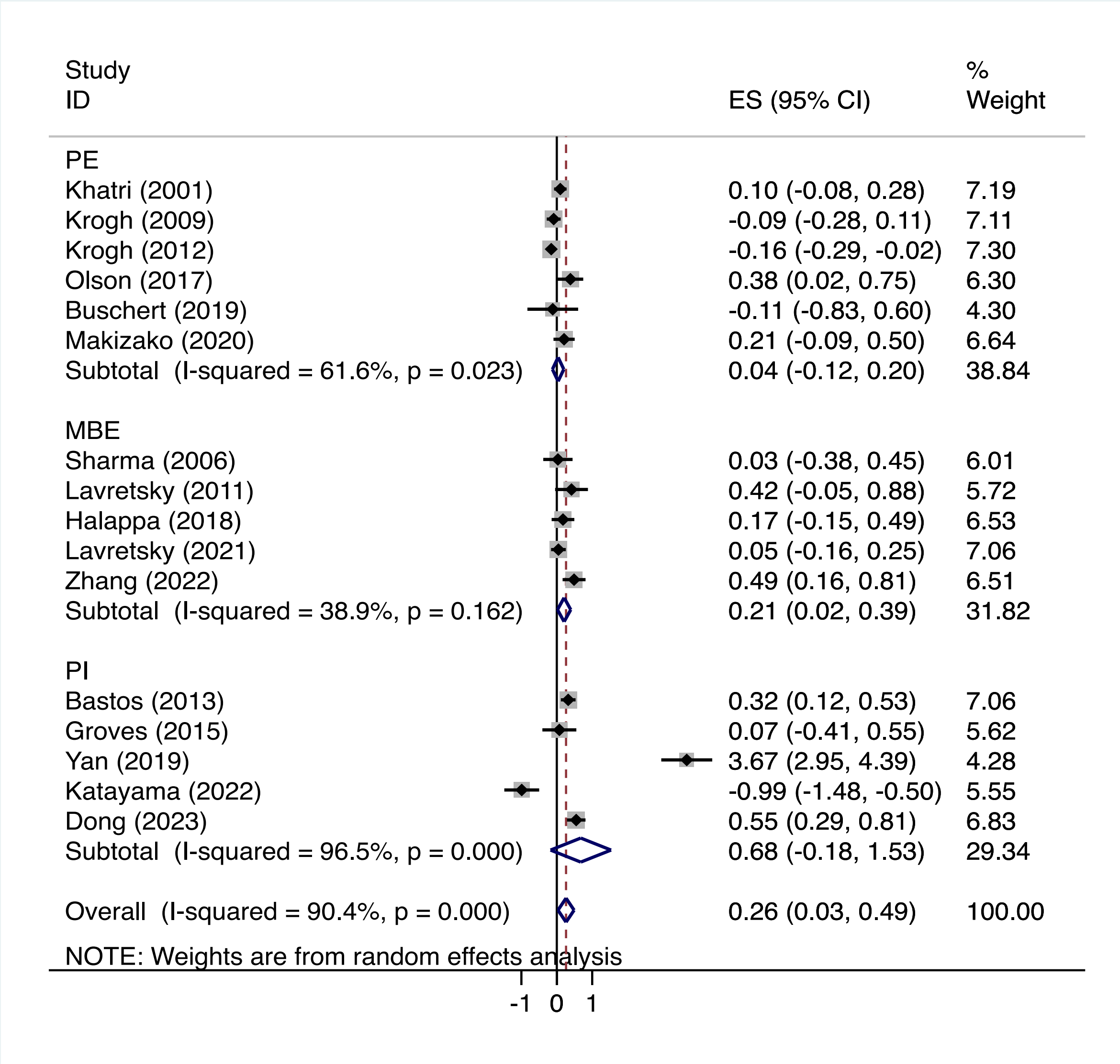


Figure 5. Pooled effects for executive function by intervention type

To further unpack the pooled effects of the non-pharmacological interventions in the studies, a meta-regression was conducted by considering the potential moderators, including participants age, sex, baseline cognition, length of intervention and control condition. None of the moderators was significant (*p*s>0.05).

Subgroup analysis

The subgroup meta-analysis was conducted for age groups, severity of depression, baseline cognitive function, and control conditions. It was shown that both older adults and young or middle-aged adults might benefit from exercise intervention on their overall cognitive function (**Figure 6**). Exercise intervention improved global cognitive function in MDD patients and adults with depressive symptoms (**Figure 7**). Individuals with cognitive impairment showed significantly greater improvement in cognitive function, while those with normal cognition at baseline also showed a good response trend to exercise training (**Figure 8**). While exercise intervention showed significant effects on global cognitive function compared with both active and non-active controls, the cognitive effects were greater in studies with non-active controls (**Figure 9**).

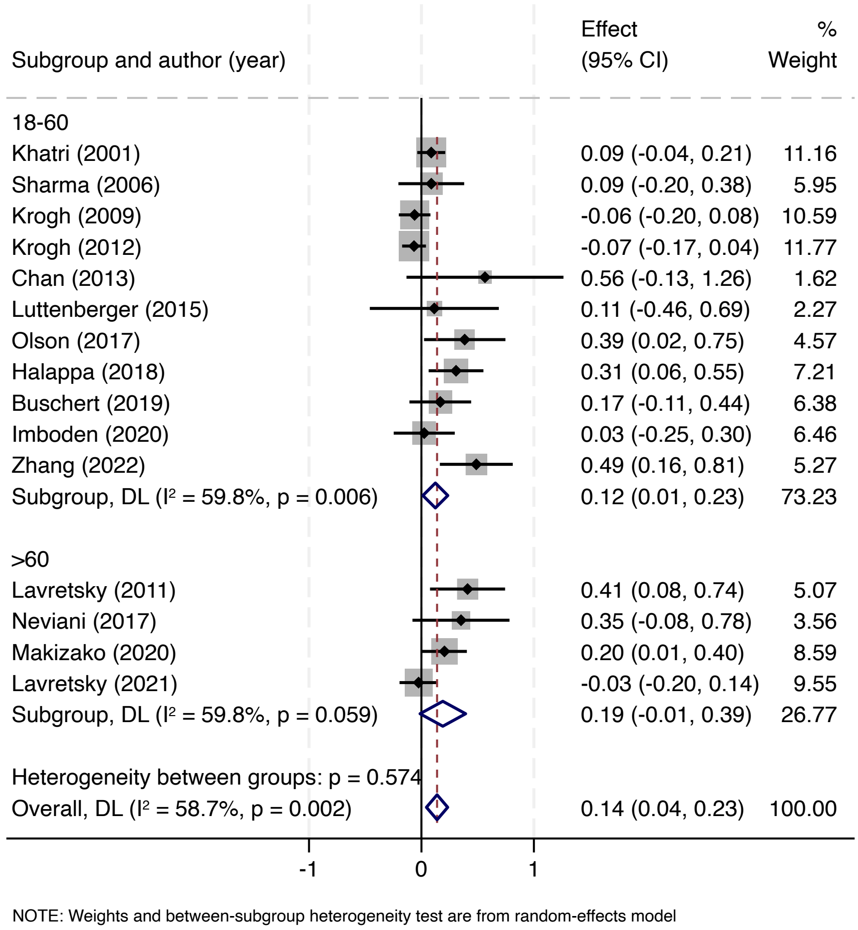


Figure 6. Pooled effects for global cognitive function by age groups

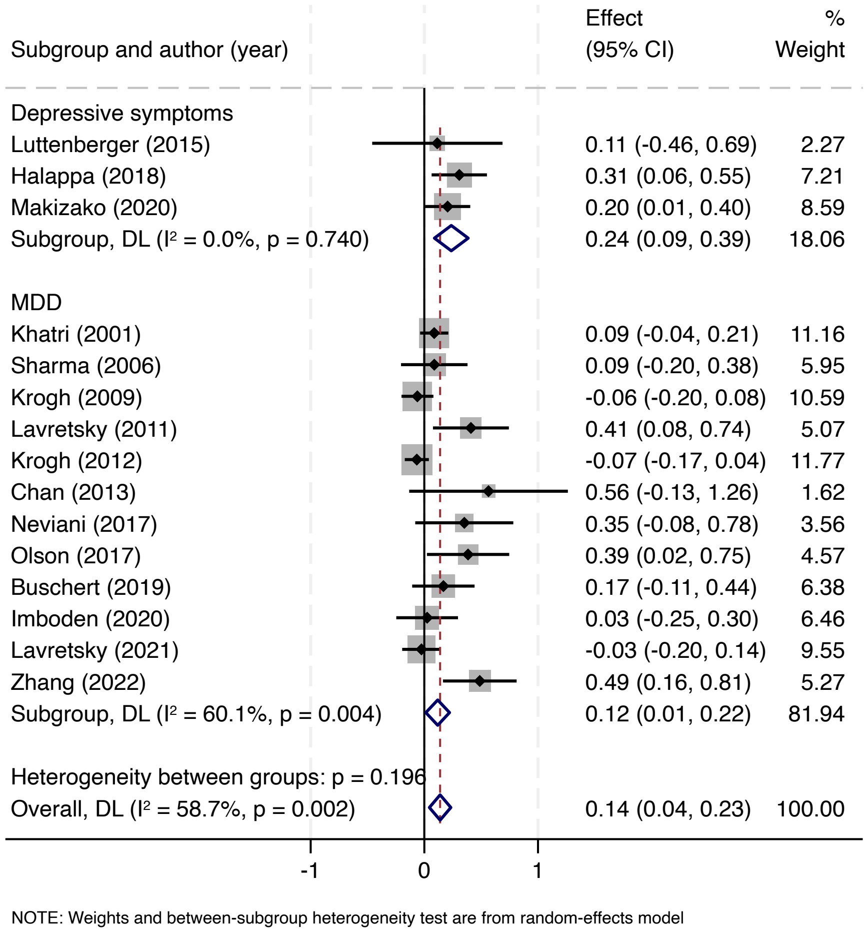


Figure 7. Pooled effects for global cognitive function by depression severity

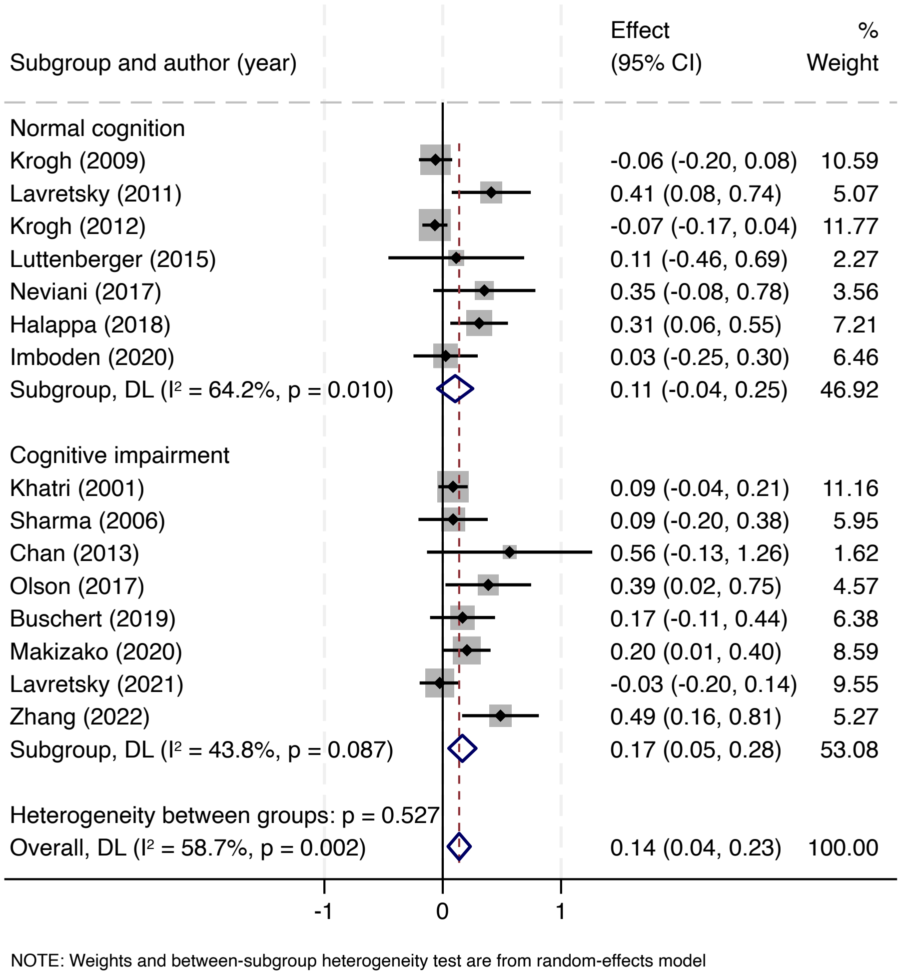


Figure 8. Pooled effects for global cognitive function by baseline cognitive function

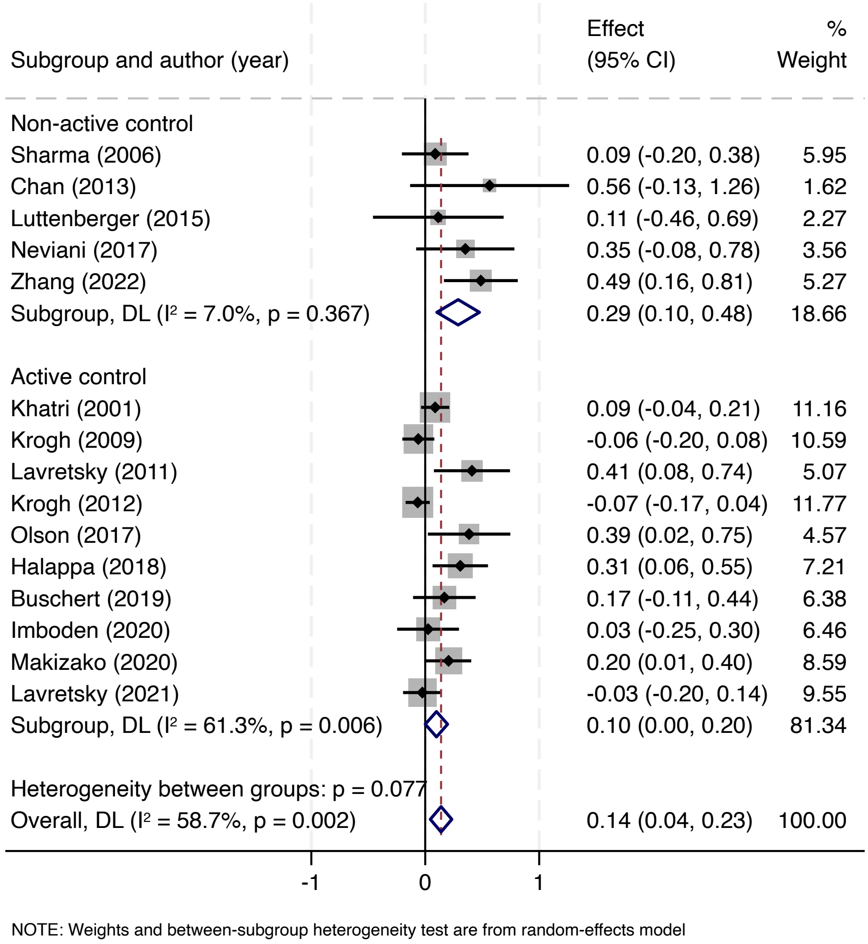


Figure 9. Pooled effects for global cognitive function by control conditions

Sensitivity analysis

Two PE studies (Krogh et al., 2009; Olson et al., 2017), one MBE study (Lavretsky et al., 2022b), and one PI study (Groves et al., 2015) had high risk of bias and contributed data to the meta-analysis. Therefore, sensitivity analysis was performed by excluding the studies at high risk of bias to evaluate the impact of the quality of the included studies on the findings. When excluding studies with high risk of bias, the significance of effects in both main and subgroup meta-analysis remained unchanged for overall cognitive function, attention/concentration, and executive function. When removing the study with inadequate quality, MBE showed a significant improvement in memory function (SMD=0.45, p=0.001, I^2=0%), while the effects of other types of intervention were retained in sensitivity analysis for this cognitive domain (**Figure 10**).

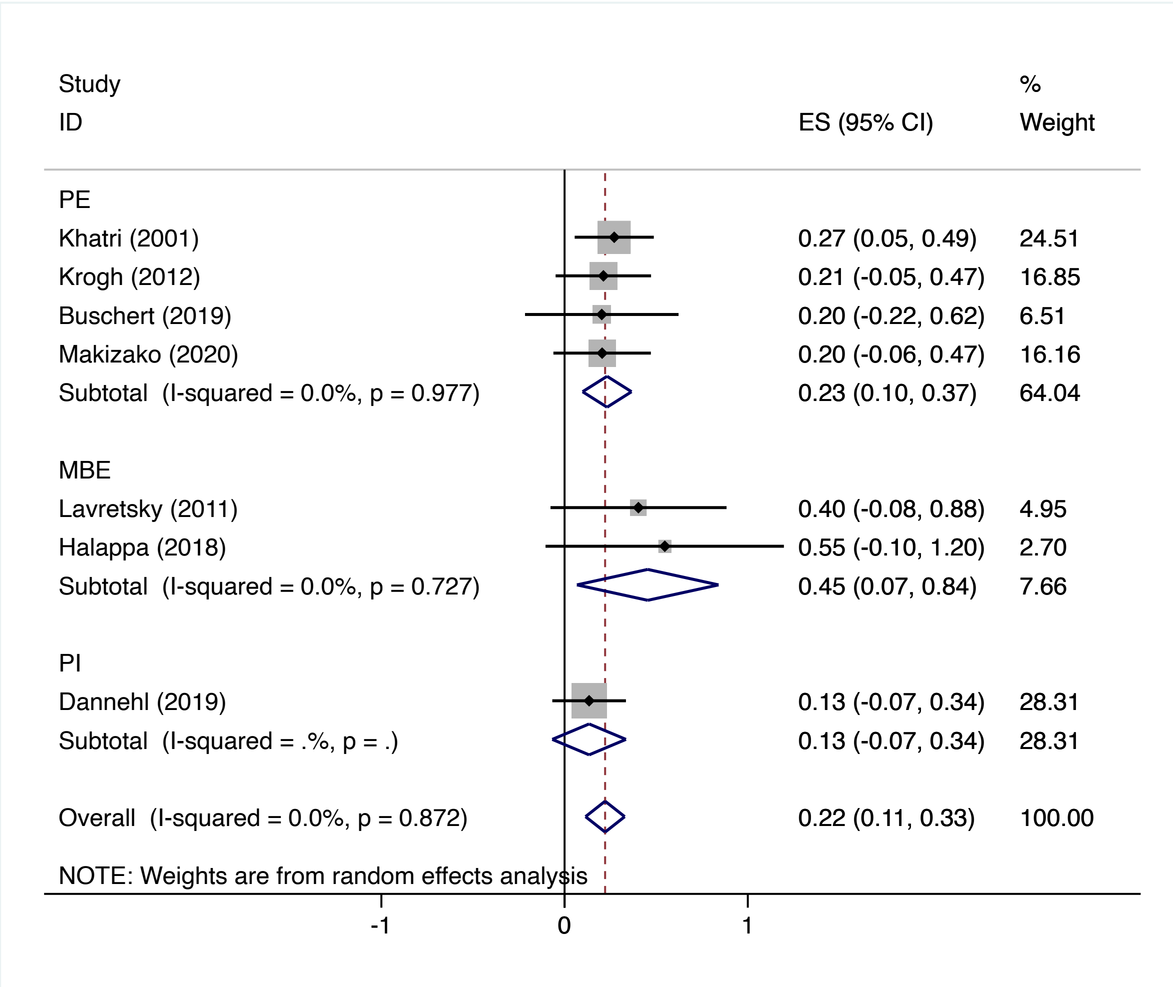


Figure 10. Forest plot of sensitivity analysis on memory function

2.5.1.4 Discussion

The present review synthesized findings from 22 RCTs with a total number of 1,721 participants with depressive symptoms. This study provides an updated and comprehensive summary on cognitive effects of recognized non-pharmacological interventions (i.e. exercise and psychological interventions) for individuals with depression. Our review of recent literature suggests that exercise and psychological interventions, can benefit global cognition, attention, memory and executive functions in depression. These results are in accordance with previous findings in other populations, including individuals with dementia or mild cognitive impairment, as well as in healthy adults (Carballo-García et al., 2013; Kim & Schneider, 2022; Xu et al., 2021; Yorozuya et al., 2019). However, the current meta-analysis are not entirely consistent with the findings from previous reviews on cognitive effects of exercise in depressed population (Brondino et al., 2017; Sun et al., 2018). The non-significant results observed in previous reviews might be due to the limited number of included studies, as well as the relatively small sample sizes. Another possible explanation is that the previous reviews further breakdown cognitive functioning domains into components, such as working memory, inhibitory control and information processing for executive function. The current review encompasses the broad domain of cognitive function, including attention, memory, and executive functioning, in order to facilitate a more streamlined and comparable analysis of studies with better statistical power.

The subgroup analysis revealed different cognitive effects by types of non-pharmacological interventions. We found that PE had an advantage on memory function, while MBE, which combines physical movements with cognitive activity, showed significant improvement in attention, executive functioning, and global cognitive function. In addition, the sensitivity analysis also exhibited a potential beneficial effect of MBE on memory function by excluding a study with high risk of bias. It is possible that the benefits of exercise interventions on cognitive function might be attributed to increased brain volume and modulated brain activity, and the acquisition of psychological techniques through intervention, such as relaxation and mindfulness.

The subgroup analysis showed significant pooled effects of PI on attention, while other domains were not significantly improved. Since limited studies available, the current knowledge of psychotherapy for improving cognitive function in depression is stringent. Only one study was identified to report the effects of CBT on attention and memory with non-significant results. It is conceivable that CBT may benefit executive function through the focus on the consideration of new information in decisions, alternative explanations, and correction of maladaptive thought patterns (Goodkind et al., 2016). Other psychological interventions, such as mindfulness that target cognitive and emotional processes, may produce better effectiveness in treating cognitive deficits (Kraines et al., 2022).

This meta-analysis reported generally small effect sizes for both overall cognitive function and individual cognitive domains. One potential explanation is the baseline cognitive function level in the included RCTs. It can be postulated that individuals with lower level of cognitive function at baseline might exhibit greater improvement after intervention (Smith et al., 2010). Cognitive impairment was not a criterion in any of the included studies, which may have led to an underestimation of the cognitive impact of the interventions, especially when compared to studies of cognitive decline. Another possible explanation is that the current findings might be because active conditions, such as other forms of intervention, might also change cognitive function. It was suggested that an active control group yielded smaller effect sizes than a non-active control group (Beserra et al., 2018).

In addition to our findings, several limitations should be taken into consideration. First, heterogeneity was presented due to different participant characteristics and intervention specifics. Subgroup and sensitivity analyses were conducted to evaluate the possible impact of heterogeneity on meta-analytic results. Second, we analyzed data from a range of cognitive measures belonging to a number of cognitive domains. These cognitive tasks may vary in their ability to detect changes and in their reliability, thus led to variability in estimates of the cognitive effects of interventions. Third, although RCTs provide the highest level of evidence, individual cognitive domains were measured in only a small number of studies, and most studies assessed cognition as a secondary outcome or were part of larger trials. As a result, the findings should be interpreted with caution since they are based on small samples and have insufficient power to draw valid conclusions.

Looking forward, more high-quality RCTs are needed in order to provide valid and convincing evidence to unravel the cognitive effects of non-pharmacological interventions in depression. Moreover, both exercise and psychological interventions are known to have positive effects on several mechanisms underlying neural plasticity and cognitive functioning (de Sousa Fernandes et al., 2020; Ludyga et al., 2020; Price & Duman, 2020), further investigation of the underlying mechanisms and predictors of response is required.

2.5.1.5 Conclusion

In conclusion, the current literature and analysis provide evidence to support the effects of non-pharmacological interventions for enhancing cognitive function in depression. In particular, attention appear to benefit from mind-body exercise and psychological interventions, while memory function might be improved by exercise interventions. Executive function was also observed to be enhanced by mind-body exercise. Given the limited studies and insufficient data published so far, the findings need to be further tested in future research. Consequently, more well-designed studies with sufficient subjects are warranted to provide clear and solid evidence for the cognitive effects of different types of non-pharmacological interventions for depression population.

2.5.2 SR2: Neurobiological mechanisms for the antidepressant effects of mind-body and physical exercises: A systematic review

There is evidence that both mind-body and physical exercises are effective in reducing depressive symptoms. However, the mechanisms underlying the antidepressant effect of exercise have rarely been examined. This article systematically reviewed and evaluated the existing evidence about neurobiological responses to mind-body and physical exercises in individuals with symptoms of depression.

2.5.2.1 Introduction

Depression is the most common psychological disorder and a major contributor to the overall global burden of illness (Liu, He, et al., 2020). In 2019, about 280 million people, representing 5 percent of adult population, suffered depression, indicating that it is a significant health issue worldwide (WHO, 2023). Depressive disorders are characterized by low mood, loss of interest or pleasure, and are often accompanied by symptoms such as disturbed sleep, changes in appetite, fatigue, and poor concentration (APA, 2013). Worst of all, patients with severe depression also exhibit increased suicide risk (Chesney et al., 2014). As a chronic condition with increasing prevalence and incidence (Meng et al., 2017; WHO, 2017), depression not only seriously affects health and quality of life, but also has a heavy economic burden on families and society. Consequently, the treatment of depression has attracted significant attention among researchers and remains a public health priority.

Exercise is well-documented to be beneficial to mental health. Accumulating findings reveal that exercise tends to have a moderate-to-large treatment effect on depression (Cooney et al., 2014; Kvam et al., 2016; Trivedi et al., 2011). The World Health Organization and the National Institute for Health and Clinical Excellence (NICE) both recommend the implementation of exercise as part of depression treatment (NICE, 2022; WHO, 2019). Importantly, exercise also has the advantages of cost-effectiveness, self-administered, and additional physical health benefits (Craft & Perna, 2004; Hallgren et al., 2017).

Mind-body exercise, also known as mindful exercise (La Forge, 2016), holistic movement practices (Taylor et al., 2021; Vergeer & Biddle, 2021), meditative movement (Larkey et al., 2009), or movement-based embodied contemplation (Schmalzl et al., 2014), has received recent attention in the scientific literature and have been shown to be effective for treating depression (Bo et al., 2017; Tsang et al., 2008; Weber et al., 2020; Zou et al., 2018). In spite of the fact that there is no universal consensus on the definition of mind-body exercise, it can be generally described as a form of exercise with elements of body movements, controlled deep breathing, proprioceptive body awareness (mental focus) and a meditative state of mind, which is similar to mindfulness practice that emphasizes noncompetitive, present-moment, and nonjudgmental introspection (Hempel et al., 2014; Kabat-Zinn, 2003; Khanna & Greeson, 2013; Yeung et al., 2018b). Therefore, mind-body exercise is distinct from physical exercise because of the above elements. Yoga, tai chi, and qigong are commonly practiced forms of mind-body exercise (National Cancer Institute, 2023; Wang et al., 2017), and these mind-body exercises are ranked as the top three complementary therapies among American adults in workplace in the National Health Interview Survey (Kachan et al., 2017). During the practice of yoga, tai chi and qigong, the abdominal breathing technique and the emphasis on body awareness are the mental component that helps to center the self in the present moment (Brisbon & Lowery, 2011; La Forge, 2016; Yeung et al., 2018b). And this present-focused sensory awareness is consistent with the Buddhist philosophy of mindfulness meditation (Kabat-Zinn, 2003). On the other hand, physical exercise refers to body activities without the emphasis on mental training, such as aerobic exercise, resistance exercise, and stretching. According to the evidence from recent reviews of RCTs, physical exercise has been shown to be effective in the prevention and treatment of depression (Hu et al., 2020a; Smith & Merwin, 2021; Stubbs & Schuch, 2019). Another network meta-analysis compared the effects of aerobic, resistance, and mind-body exercises in older adults with clinical depression, with a total of 15 randomized controlled trials (RCTs), and found that all three kinds of exercises had favourable effects on depressive symptoms, but mind-body practice showed the most significant improvement (Miller, Gonçalves-Bradley, et al., 2020). Since mind-body exercise is a relatively low intensity exercise that combines both physical and mental aspects, it is plausible that it can result in comparable antidepressant effects as higher intensity physical exercise (La Forge, 1997; Miller, Areerob, et al., 2020). The mental aspects involved in the mind-body exercise, such as an internally directed focus on breathing and proprioception, have shown to be associate with the resilience of depressive states and thus potentially contribute to the regulation of negative mood states (Avery et al., 2014; Li & Bressington, 2019; Paulus & Stein, 2010).

Despite extensive research on the efficacy of different types of exercise, the underlying neurobiological mechanisms of their anti-depressant effects remain unclear at present. Studies have reviewed the evidence and proposed several hypotheses to explain the effect of exercise on depression, including neuroendocrine, neurotransmission, neurogenesis, inflammation, and brain structure and activity (Schuch et al., 2016; So et al., 2019; Tsang & Fung, 2008). Though there are increasing numbers of trials to explore the possible mechanism outcomes of exercise on depression, few reviews have comprehensively summarized, synthesized, and compared the underlying mechanisms for the anti-depressant effect of both mind-body and physical exercises in RCTs. We performed this systematic review and meta-analysis to better understand how exercises have a beneficial effect on depressive symptoms through different plausible neurobiological pathways. The results of this study should help develop better exercise protocols and optimal treatment for maximizing the health benefits for depressed individuals, thereby facilitating more efficient use of available healthcare resources.

2.5.2.2 Methods

This systematic review and meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. This study was registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021239648).

Literature search

An electronic literature search in *PubMed*, *Web of Science*, *EMBASE*, *CINAHL*, *PsycINFO*, and *Cochrane Library* was performed to identify relevant studies published up to September 12, 2022. We used the following search terms: (depress* OR dysthymi*) AND (exercise OR yoga OR tai chi OR tai ji OR qigong OR qi gong OR mindful exercise OR mind body OR aerobic* OR walk* OR jog* OR run* OR cycl* OR swim* OR danc* OR anaerobic OR resistance OR strength OR endurance OR stretch* OR non mindful exercise) AND (neuroimag* OR neuroanatom* OR brain imag* OR brain region OR brain structure OR MRI OR MRS OR fMRI OR DTI OR PET OR functional near-infrared spectroscopy OR fNIRS OR electrophysiolog* OR EEG OR neurophysiolog* OR endocrin* OR hormone OR cortisol OR serotonin OR dopamine OR ACTH OR neurotransmitter) AND (randomized controlled trial OR controlled clinical trial OR controlled clinical study OR controlled trial OR controlled study OR randomiz* OR randomis* OR randomly). The search strategies for each database are shown in full in **Supplementary Table 1**. In addition, the reference list of each of the included studies was checked to identify additional relevant studies.

Eligibility criteria

The inclusion criteria included: 1) involvement of participants with depressive symptoms or depression as judged by each study using recognized criteria (International Classification of Diseases (ICD), Diagnostic and Statistical Manual for Mental Disorders (DSM)), or published depression inventories; 2) at least one arm of the intervention being mind-body exercise (yoga, tai chi, or qigong) or physical exercise; 3) the exercise intervention being compared with a different type of intervention or a non-active control; 4) baseline and post-intervention measurements for at least one neurobiological mechanism were reported; and finally 5) the study having an RCT design. A study was excluded if 1) its subjects had comorbid psychiatric conditions, 2) it was an animal study; 3) it had fewer than ten participants in any arm of the intervention; 4) it was an abstract from a conference or review paper; and 5) it was not published in an English-language peer-reviewed journal. Studies that presented data from the same sample but reported different mechanism outcomes were included.

Study selection

The literature search records were managed using EndNote X9 (Thompson ISI Research Soft, Philadelphia, PA, USA). After excluding duplicates, two independent reviewers first authenticated titles and abstracts extracted from electronic database sources for the initial inclusion of potentially relevant studies. Two reviewers retrieved the full text of the studies identified to determine systematic review eligibility, and any disagreements were resolved by achieving consensus with a third reviewer.

Data extraction and risk-of-bias assessment

Information on the first author and year, country, sample characteristics, sample size, specifics of intervention, control condition, measurement of depression at baseline and follow-up, neuroimaging and neurophysiological outcomes, and associations between changes in mechanism outcomes and depressive symptoms were extracted by the two reviewers independently. The outcome data were first obtained from the intention-to-treat analysis unless it was unavailable; otherwise, the data from the available cases were used.

The two reviewers assessed the risk of bias of the included studies by the Cochrane risk of bias tool (Higgins et al., 2019). The following items were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Each domain was classified as being at low, unclear, or high risk of bias. Any variation in data extraction and risk of bias assessment between the two authors was resolved by discussion.

Data synthesis

To qualitatively synthesize the findings of the included studies, we first tabulated relevant information as mentioned in Section 2.4 from each study. Narrative synthesis was performed on treatment-related changes in neurobiological outcomes after mind-body exercise and physical exercise, respectively. Evidence on associations between changes in neurobiological outcomes and depressive symptoms was also narratively synthesized to elucidate the current understanding of neurobiological mechanisms underlying the antidepressant effect of mind-body exercise and physical exercise.

Given the heterogeneity in type of exercise, duration, and frequency adopted in the included studies, random-effect model was adopted for meta-analysis of pooled effects on neurobiological outcomes. According to Jackson and Turner, at least 5 studies were needed for random-effect meta-analysis with satisfactory statistical power (Jackson & Turner, 2017). Similarly, subgroup analysis on neurobiological outcomes was performed comparing the effects of mind-body exercise and physical exercise if there were 5 studies within each subgroup. The effect sizes were calculated through the change of mean difference between exercise and control groups pre- to post-intervention, and the pooled effects were obtained from the standardized mean difference (SMD) with 95% confidence intervals (CIs). Where studies had multiple intervention or control groups, the primary exercise intervention and non-active control condition were extracted. For cross-over trials, the first phase was used to avoid the potential "carry-over" effect. Study heterogeneity was evaluated using I^2 statistics. Sensitivity analysis was employed by excluding studies with a high risk of bias, and by synthesizing outcome data if there were two studies within each subgroup. The statistical analysis was conducted using Stata version 15 (StataCorp LLC, College Station, TX, USA).

2.5.2.3 Results

Study selection and characteristics

Figure 1 describes in detail the selection process of the systematic review. A total of 3,365 studies were initially identified from the five databases searched, and 46 from relevant systematic reviews and meta-analysis, resulting in 1,800 studies after the removal of duplicates. After screening these 1,800 titles and abstracts, 109 studies were subjected to full-text review. Of these, 32 publications comprising 28 RCTs with 1,820 participants finally met the inclusion criteria and were selected for this systematic review.

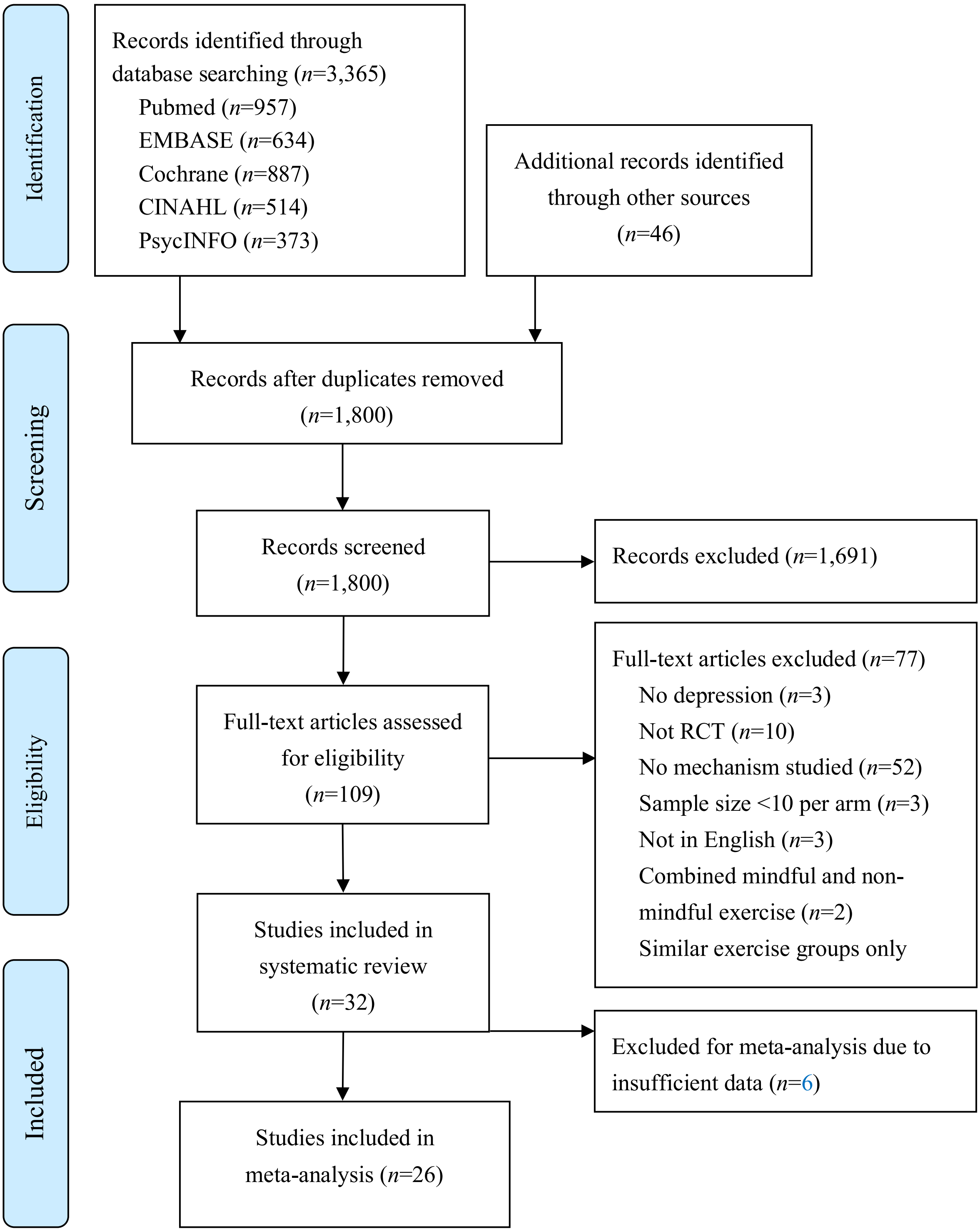


Figure 1. PRISMA flow chart of the study

The studies were published between 2004 and 2022. The mean age of participants ranged from 16.0 to 80.1 years, and the sample size ranged from 20 to 188. Four types of mind-body exercise were included: yoga (*n*=4), tai chi (*n*=1), qigong (*n*=3), and Nei Gong mind-body exercise (*n*=1). The non-mindful exercises included aerobic exercise (*n*=18) and combinations of aerobic, strength, flexibility, and stretching exercises (*n*=5). The duration of the interventions ranged from one to six months. **Table 1** summarizes the demographic, intervention, and outcome measurements of the included studies.

Table 1. Summary of included exercise studies (*s*=32)

Study	Country	Sample	Age (mean)	Sample size	Exercise intervention	Time, Frequency, Duration	Control (specific)	Depression Scales	Outcome changes	Associations between neurobiological outcomes and depressive symptoms
Mind-body exercise (*s*=9)										
(Woolery et al., 2004)	United States	Mildly depressed young adults	21.5	E: 13 C: 15	Iyengar yoga	60 mins/session, 2 sessions/week, 5 weeks	Wait-list control	↓ BDI**	↓ *Cortisol*	Not reported
(Lavretsky et al., 2011b)	United States	Older adults with MDD	70.6	E: 36 C: 37	tai chi Chih	120 mins/session, 1 session/week, 10 weeks	Health education	↓ HAMD-24*	↓ CRP	Not reported
(Chan et al., 2013)	Hong Kong SAR	Adults with MDD	46.3	E: 17 C: 16	Nei Gong mind-body exercise	90 mins/session, 1 session/week, 10 weeks	Wait-list control	↓ BDI-II*	↑ EEG alpha asymmetry and theta coherence in fronto-posterior region	Participants with improved depressive symptoms were significantly more likely to exhibit increased alpha asymmetry in the intervention group only.
(Tsang, Tsang, et al., 2013)	Hong Kong SAR	Depressed elders with chronic illness	80.1	E: 21 C: 17	Qigong (Eight-Section Brocades)	45 mins/session, 3 sessions/week, 12 weeks	Newspaper reading and discussion program	↓ GDS** ↓ HAMD-21	↓ Cortisol^ ↓ Serotonin	Not reported
(Sarubin et al., 2014)	Germany	Adults with MDD	40.3	E: 22 C: 31	Hatha yoga	60 mins/week, 5 weeks	Pharmacological treatment only	↓ *HAMD-21*	↑ Cortisol	The depressive symptoms was significant dependent of cortisol improvement status.
(Tolahunase et al., 2018)	India	Adults with MDD	38.0	E: 29 C: 29	Yoga- and meditation-based lifestyle intervention	120 mins/sessions, 5 sessions/week, 12 weeks	Routine drug treatment	↓ BDI-II***	↓ Cortisol*** ↑ BDNF*** ↓ IL-6***	The significant reduction in BDI-II was associated with the increase in BDNF in the yoga group.
(Nugent et al., 2019)	United States	Adults with MDD	45.2	E: 48 C: 39	Hatha Yoga	80 mins/session, 1 session/week, 10 weeks	Healthy Living Workshop	↓ *IDS-C*	↓ IL-6* ↓ CRP ↑ TNF-α	Not reported

(Lu et al., 2020)	Hong Kong SAR	Older adults with depressive symptoms	71.2	E: 14 C: 16	Qigong (Eight-Section Brocades)	60 mins/session, 2 sessions/week, 12 weeks	Cognitive training	↓ PHQ-9***	↓ Cortisol* ↑ Serotonin^ ↑ BDNF*	Changes in depressive symptoms were significantly correlated with changes in cortisol and serotonin, and marginally non-significantly correlated with changes in BDNF. Treatment-related changes in cortisol (but not serotonin or BDNF) fully mediated the beneficial effects of qigong on depressive symptoms.
(Ng et al., 2022)	Hong Kong SAR	Adults with depressive symptoms	55.3	E: 95 C: 93	Qigong	180 mins/week, 8 weeks	Wait-list control	↓ CES-D***	↓ IL-6*** ↓ IL-1β***	Changes in depressive symptoms were significantly correlated with changes in IL-6 and IL-1β.
Physical exercise (*s*=23)										
(Nabkasorn et al., 2006)	Thailand	Adolescent females with depressive symptoms	18.8	E: 28 C: 31	Group jogging below 50% HR reserve	50 mins/session, 5 days/week, 8 weeks	Usual daily activity	↓ *CES-D***	↓ Cortisol** ↓ Epinephrine* ↓ HR** ↑ VO_2peak**	Not reported
(Foley et al., 2008)	New Zealand	Depressed adults	/	E: 10 C: 13	Moderate intensity aerobic exercise	30–40 mins/session, 3 sessions/week, 12 weeks	Mild intensity stretching	↓ BDI-II ↓ MADRS	↓ Cortisol*	No significant association was found between depression severity and cortisol at baseline or post-intervention.
(Krogh et al., 2010)	Denmark	Adults with depression	38.9	E: 47 C: 48	Aerobic training at 70–90% maximal HR	40–60 mins/session, 2 sessions/week, 16 weeks	Relaxation exercise	↓ HAMD-17	→ *Cortisol* → *Growth hormone* → *Prolactin*	Not reported
(Hemat-Far et al., 2012)	Iran	Depressed female students	/	E: 10 C: 10	Moderate intensity aerobic exercises	40–60 mins/session, 3 sessions/week, 8 weeks	Normal life without physical activity	↓ BDI-21*	↑ Serotonin	Not reported

(Krogh et al., 2012a)	Denmark	Outpatients with MDD	41.6	E: 56 C: 59	Aerobic training at 65–80% VO_2max	45 mins/session, 3 sessions/week, 12 weeks	Attention control group (stretching exercise: bike, stretching, low intensity throwing and catching balls)	↓ BDI-II ↓ HAMD-17	↑ CRP ↓ Cholesterol ↓ HDL ↓ Triglycerides^ ↓ Glucose* ↑ Insulin ↓ BP ↑ VO_2max***	Not reported
(Krogh et al., 2013)	Denmark	Adults with MDD	41.9	E: 53 C: 58	Aerobic exercise on stationary bikes at 80% maximal HR	45 mins/session, 3 sessions/week, 12 weeks	Attention control group	*HAMD-17*	→ *Copeptin*	Not reported
(Krogh et al., 2014)	Denmark	Adults with MDD	41.3	E: 41 C: 38	Aerobic exercise on stationary bikes at 80% maximal HR	45 mins/session, 3 sessions/week, 12 weeks	Attention control group	*HAMD-17*	↑ VO_2max* ↑ BDNF ↓ VEGF ↓ IGF-1 → fMRI hippocampal volume	The decrease in depression was significantly correlated with the increase in right hippocampal volume. No significant correlations were found between the decrease in depression and changes in other neurobiological outcomes.
(Schuch et al., 2014)	Brazil	Severely depressed inpatients	42.7	E: 15 C: 11	Aerobic exercise at 59% HR reserve	3 times/week throughout hospitalization	Treatment as usual	↓ *HAMD-17**	↑ BDNF	Not reported
(Kerling et al., 2015)	Germany	Inpatients with MDD	42.6	E: 22 C: 20	Moderate intensity exercise training	45 mins/session, 3 sessions/week, 6 weeks	Treatment as usual	↓ BDI-II ↓ MADRS	↑ HDL*** ↓ Triglycerides ↓ Glucose ↓ BP ↑ VO_2peak** ↓ HR*	Not reported
(Vučić Lovrenčić et al., 2015)	Croatia	Type 2 diabetic patients with	58.1	E: 66 C: 69	Light-to-medium intensity flexibility,	90 mins/session, 1 session/week, 6 weeks	Treatment as usual	↓ CES-D	↓ CRP ↓ Adiponectin	Not reported

		subsyndromal depression			stretching, and strengthening				
(Abdelhamid et al., 2016)	Egypt	Older adults with mild depression	63.1	E: 50 C: 50	Aerobic exercise at 60–75% maximal HR	30–40 mins/session, 3 sessions/week, 24 weeks	Phoenix (three dates daily)	↓ *GDS*	↓ Serotonin***	Not reported
(Salehi et al., 2016)	Iran	Adults with MDD	29.7	E: 20 C: 20	Aerobic exercise training at 60–75% VO_2max	40–45 mins/session, 3 times/week, 4 weeks	Electroconvulsive therapy (ECT)	↓ BDI-21 ↓ HAMD-21	↑ BDNF	BDNF levels were not significantly associated with symptoms of depression at baseline or post-intervention.
(Siqueira et al., 2016)	Brazil	Adults with symptomatic MDD	38.8	E: 29 C: 28	Aerobic exercise at 60–85% VO_2max	4 times/week, 4 weeks	Anti-depressant only	↓ BDI ↓ HAMD	↑ VO_2max*	Correlation between the changes of depressive symptoms and VO_2max was not significant.
(Carneiro et al., 2017)	Portugal	Moderately clinical depressed patients	50.2	E: 13 C: 13	Aerobic exercise at 72% maximum HR	45–50 mins/session, 3 sessions/week, 16 weeks	Pharmacotherapy only	↓ BDI-II*	↓ Cortisol ↓ Serotonin ↓ Dopamine*	Not reported
(Euteneuer et al., 2017)	Germany	Adults with MDD	37.3	E: 36 C: 30	CBT emphasizing exercise (walking, jogging, swimming, gyms)	40 mins/sessions, 4 sessions/week, 16 weeks	Wait-list control	↓ BDI-II**	↓ CRP^ ↑ IL-6^ ↑ IL-10**	Not reported
(Kerling et al., 2017)	Germany	Depressed inpatients	42.6	E: 22 C: 20	Moderate intensity exercise	45 mins/session, 3 sessions/week, 6 weeks	Treatment as usual	↓ *BDI-II* ↓ *MADRS*	↑ BDNF*	Correlation between the changes of depressive symptoms and BDNF was not significant.
(Olson et al., 2017)	United States	Adults with MDD	21.1	E: 15 C: 15	Moderate intensity	3 sessions/week, 8 weeks	Light intensity stretching	↓ *BDI-II**	↑ EEG N2 amplitude*	Change in N2 amplitude was significantly correlated with change in depressive

					aerobic exercise					symptoms. However, the mediating effect of N2 amplitude was not significant.
(Patten et al., 2017)	United States	Female with moderate-to-severe depression	37.5	E: 15 C: 15	Vigorous intensity aerobic exercise	30–40 mins/session, 3 sessions/week, 12 weeks	Health education	↓ PHQ-9	↑ VO_2max** → *CRP* → *IL-6* → *TNF-α*	Not reported
(Rahman et al., 2019)	Sweden	Adults with mild to moderate depression	/	E: 38 C: 27	Physical exercise	60 mins/session, 3 sessions/week, 12 weeks	Treatment as usual	↓ MADRS*	↓ *Cortisol*	No association between the changes in depression severity and cortisol levels was found.
(Szuhany & Otto, 2020)	United States	Adults with MDD or persistent depressive disorder	34.2	E: 14 C: 15	Moderate intensity aerobic exercise plus behavioral activation	30 mins/session, 9 sessions in total, 12 weeks	Stretching plus behavioral activation	↓ BDI-II ↓ MADRS	↑ BDNF	Change in BDNF was not significantly correlated with change in depressive symptoms.
(Imboden et al., 2021)	Switzerland	Adults with MDD	39.9	E: 22 C: 21	Aerobic exercise on indoor bicycles at 60–75% maximal HR	40–50 mins/session, 3 sessions/week, 6 weeks	Active control activities	↓ *HAMD-17* ↓ *BDI-21*	↓ Cortisol ↑ BDNF ↑ TNF-α	Correlation between the change in VO_2max and depressive symptoms was significant.
(Wunram, Oberste, Hamacher, et al., 2021)	Germany	Depressed Adolescents	16.0	E: 20 C: 21	Vigorous aerobic activity treatment	30 mins/session, 3–5 days/week, 6 weeks	Treatment as usual	↓ DIKJ	↓ IL-6 ↓ TNF-α	No significant associations were found between IL-6 and TNF-α on depression scores at baseline or post-intervention.
(Wunram, Oberste, Ziemendorff, et al., 2021)	Germany	Depressed Adolescents	16.0	E: 20 C: 21	Vigorous aerobic activity treatment	30 mins/session, 3–5 days/week, 6 weeks	Treatment as usual	↓ DIKJ	↑*BDNF*** ↑*IGF*-1	Changes in BDNF and IGF-1 were not significantly correlated with depression-scores changes.

E: exercise intervention; C: control group; CBT: cognitive-behavioral therapy; BDI: Beck Depression Inventory; CES-D, Center for EpidemiologicStudies Depression Scale; DIKJ, Depressions inventar für Kinder und Jugendliche; GDS, Geriatric Depression Scale; HAMD: Hamilton Depression Rating Scale; IDS-C: Inventory of Depression Symptomatology-Clinician Rating; IDS-SR: Inventory of Depression Symptomatology-Self Report; MADRS: Montgomery-Asberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; SCL-90: Symptom Check List-90; BDNF: brain-derived neurotrophic factor; BP: blood pressure; CRP: C-Reactive Protein; EEG: Electroencephalography; fMRI: functional magnetic resonance imaging; HDL: high density lipoprotein; HR: heart rate; IGF-1: Insulin-like growth factor 1; IL: interleukin; LDL: low density lipoprotein; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor; VO_2max/peak: maximum/peak oxygen uptake.

↑ Increased in exercise group.

↓ Decreased in exercise group.

→ No change in exercise group.

Between group difference in changes: ^ $p<0.10$; * $p<0.05$; ** $p<0.01$; *** $p<0.001$

As evaluated by the Cochrane risk of bias tool, 18 (56%) studies had an overall unclear risk of bias, 1 (3%) had a low risk, and 13 (41%) had a high risk of bias (**Figure 2**). Notably, due to the nature of the intervention, trials assessing the effect of exercise interventions were rarely able to properly blind the participants and personnel. Participants were simply not told which intervention was considered an active treatment or the potential benefits of the intervention. Generally, 29 (91%) studies were not at high risk of bias in the remaining domains, and the three studies with a high risk of bias (Krogh et al., 2010; Rahman et al., 2019; Sarubin et al., 2014) were removed in the sensitivity analysis. The risk of bias was low for random sequence generation in 20 studies (63%), allocation concealment in 15 studies (47%), blinding of participants and personnel in 4 studies (13%), blinding of outcome assessment in 19 studies (59%), incomplete outcome data in 28 studies (88%), selective reporting in 31 studies (97%), and other bias in 31 studies (97%).

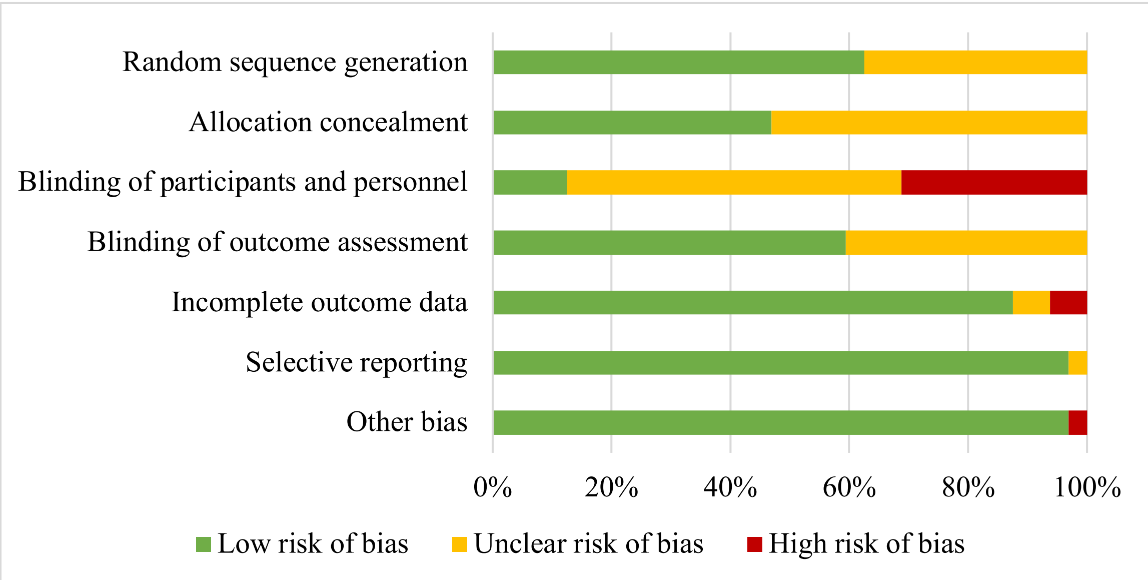


Figure 2. Risk of bias summary

Qualitative synthesis of effects on neurobiological outcomes

The included studies evaluated treatment-related effects on neurobiological outcomes that involved neuroendocrine system (cortisol, adiponectin, copeptin, growth hormone, and prolactin), neurotransmitters (serotonin and epinephrine), neurogenesis (BDNF, insulin-like growth factor 1 [IGF-1], and vascular endothelial growth factor [VEGF]), inflammatory functions (CRP, IL-1β, IL-6, IL-10, and TNF-α), the autonomic nervous system (blood pressure [BP] and heart rate [HR]), cardiorespiratory fitness (maximum/peak oxygen uptake [VO_2max/peak]), brain structure, and brain activity responses to exercise. Physiological outcomes (i.e., cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL], insulin, and glucose) were also included in this study.

Mind-body exercise

The levels of cortisol, serotonin, BDNF, CRP, IL-1β, IL-6, TNF-α, and neurophysiological changes were reported in the included studies on mind-body exercise. Among the five studies on cortisol (Lu et al., 2020; Sarubin et al., 2014; Tolahunase et al., 2018; Tsang, Tsang, et al., 2013; Woolery et al., 2004), two of these studies found significantly more decreases in cortisol concentrations in exercise group, compared with control group (Lu et al., 2020; Tolahunase et al., 2018). As the only two studies focused on serotonin, one of the studies found that qigong increased serotonin with a marginally non-significant effect compared to the control group (Lu et al., 2020), while no significant result was found in the other RCT (Tsang, Tsang, et al., 2013). Two studies focused on BDNF, and both found a significantly greater improvement in the mind-body exercise group than control group (Lu et al., 2020; Tolahunase et al., 2018). CRP was evaluated in two studies, and both showed a decreasing trend within mind-body exercise intervention, whereas such decrease was not found to be significantly more than control groups (Lavretsky et al., 2011b; Nugent et al., 2019). IL-1β was reported to decrease significantly in qigong participants with reference to the controls in one trial (Ng et al., 2022). Three studies presented data on IL-6, and all found significantly greater reductions in mind-body exercise group than control group (Ng et al., 2022; Nugent et al., 2019; Tolahunase et al., 2018). One RCT provided data on TNF-α and non-significant effect was exhibited (Nugent et al., 2019). Chan et al. found that after ten sessions of Dejian mind-body intervention, subjects exhibited significantly increased electroencephalogram (EEG) alpha asymmetry, which is an indication of left-side anterior activation .

Physical exercise

Cortisol was studied in six trials. Two found that physical exercise led to greater reduction in cortisol concentration compared with control group (Foley et al., 2008; Nabkasorn et al., 2006), while no significant differences were found in the other four studies (Carneiro et al., 2017; Imboden et al., 2021; Krogh et al., 2010; Rahman et al., 2019). Adiponectin was evaluated in one study, and non-significant change was found after six weeks of physical exercise (Vučić Lovrenčić et al., 2015). The study conducted by Krogh et al. showed that aerobic exercise did not change copeptin levels during rest or acute exercise (Krogh et al., 2013). One study indicated that the effects of aerobic training caused no changes in prolactin and growth hormone (Krogh et al., 2010).

Three studies focused on serotonin. Abdelhamid et al. found that the serum serotonin level decreased significantly in the exercise group compared with control group (Abdelhamid et al., 2016), while the other two RCTs showed no significant effects of exercise on serotonin (Carneiro et al., 2017; Hemat-Far et al., 2012). A significant effect of group jogging in significantly more reduction in epinephrine in physical exercise group than control group was found in one study (Nabkasorn et al., 2006). Carneiro et al. provided data on dopamine and showed that intervention group exhibited significantly higher dopamine level after physical exercise compared to control group (Carneiro et al., 2017).

BDNF was evaluated in seven studies. Two found that increased BDNF was related to exercise intervention (Kerling et al., 2017; Wunram, Oberste, Ziemendorff, et al., 2021), and five studies showed non-significant improvement compared with controls (Imboden et al., 2021; Krogh et al., 2014; Salehi et al., 2016; Schuch et al., 2014; Szuhany & Otto, 2020). Two trials that investigated the IGF-1 levels of the participants (Krogh et al., 2014; Wunram, Oberste, Ziemendorff, et al., 2021) found no effect of aerobic exercise intervention. Krogh et al. also reported no effect of add-on exercise therapies on vascular endothelial growth factor (VEGF) (Krogh et al., 2014).

CRP was studied in four trials. Euteneuer et al. revealed marginally non-significant reduction in participants practicing CBT with exercise compared to waitlist control (Euteneuer et al., 2017), but no significant changes were registered in the other three trials (Krogh et al., 2012a; Patten et al., 2017; Vučić Lovrenčić et al., 2015). Three studies observed non-significant effect for IL-6 (Euteneuer et al., 2017; Patten et al., 2017; Wunram, Oberste, Hamacher, et al., 2021). Euteneuer et al. (Euteneuer et al., 2017) also measured IL-10 and found significantly more increase after physical exercise, compared to control condition; while no differential effects between aerobic exercise and an active control condition were found by the other two RCTs on IL-10 (Imboden et al., 2021; Wunram, Oberste, Hamacher, et al., 2021).

Triglycerides, HDL, and glucose levels were evaluated by two studies and neither observed a significant effect of exercise (Kerling et al., 2015; Krogh et al., 2012a). Krogh et al. (Krogh et al., 2012a) suggested no significant difference in total cholesterol and insulin levels after 12 weeks of aerobic exercise compared to the attention control group.

Two studies reported that SBP and DBP decreased in both exercise and control groups with non-significant group difference (Kerling et al., 2015; Krogh et al., 2012a). Heart rate was studied in two trials and was found to show significantly more decreases in the aerobic exercise groups than control groups (Kerling et al., 2015; Nabkasorn et al., 2006). Cardiorespiratory fitness was evaluated by VO2max/peak in six trials (Kerling et al., 2015; Krogh et al., 2014; Krogh et al., 2012a; Nabkasorn et al., 2006; Patten et al., 2017; Siqueira et al., 2016) and participants showed significantly greater improvement after exercise interventions than control conditions.

One study involved EEG to record changes in brain activity following aerobic exercise intervention(Olson et al., 2017), and it found that the exercise group showed significantly more increase in N2 amplitude for incongruent trials than control group. An fMRI study by Krogh et al. (Krogh et al., 2014) demonstrated that hippocampal volume did not differ between exercise and control groups after intervention.

Associations between neurobiological outcomes and depressive symptoms

Mind-body exercise

Five of the nine included mind-body exercise RCTs reported results of the associations between changes in neurobiological outcomes and depressive symptoms after intervention. Improvement in cortisol was significant related to the antidepressant effects of Yoga (Sarubin et al., 2014) and qigong (Lu et al., 2020), while Lu et al. further reported that the changes in cortisol fully mediated the beneficial effects of qigong on depressive symptoms. Greater reduction in depressive symptoms was associated with increased BDNF level for both Yoga (Tolahunase et al., 2018) and qigong (Lu et al., 2020). Treatment-related changes in serotonin and the beneficial effects of qigong on depressive symptoms were correlated significantly (Lu et al., 2020). Ng et al. found that the between group change of IL-6 and IL-1β were significantly correlated with changes in depressive symptoms (Ng et al., 2022). One EEG study showed that participants with improved depressive symptoms were more likely to exhibit increased alpha asymmetry in the intervention group only (Chan et al., 2013).

Physical exercise

For physical exercise, twelve of the 23 included studies investigated the associations between in neurobiological outcomes and depressive symptoms. No significant correlation was found between changes in cortisol with regard to depression severity in two studies (Foley et al., 2008; Rahman et al., 2019). The relationship between depressive symptoms changes and BDNF after exercise was not significant in four studies (Kerling et al., 2017; Salehi et al., 2016; Szuhany & Otto, 2020; Wunram, Oberste, Ziemendorff, et al., 2021). No significant effects of IL-6, TNF-α and IGF-1 on depression scores were found (Wunram, Oberste, Hamacher, et al., 2021; Wunram, Oberste, Ziemendorff, et al., 2021). Two studies investigated the correlation between changes in depressive symptoms with VO_2max, one found a significant correlation (Imboden et al., 2021) while the other showed non-significant correlation (Siqueira et al., 2016). Olson et al. reported that the change in N2 amplitude was correlated with changes in depressive symptoms, however, the mediation effect of N2 amplitude underlying the antidepressant effect of physical exercise was not significant (Olson et al., 2017). An fMRI study found the increase in right hippocampal volume was associated with the decrease in depressive symptoms (Krogh et al., 2014).

Quantitative synthesis of effects on neurobiological outcomes

Data was pooled to study the five neurobiological outcomes: cortisol, serotonin, BDNF, CRP, and IL-6. Seven studies were excluded from quantitative synthesis due to insufficient data (Chan et al., 2013; Krogh et al., 2013; Krogh et al., 2010; Rahman et al., 2019; Woolery et al., 2004; Wunram, Oberste, Hamacher, et al., 2021; Wunram, Oberste, Ziemendorff, et al., 2021). Due to the limited number of the included studies, we could not identify five or more studies for each neurobiological outcome within either mind-body exercise subgroup or physical exercise subgroup. Hence, the quantitative synthesis of effects on neurobiological outcomes was performed with studies on both types of exercises pooled together (**Table 2**).

Table 2. Summary estimates for neurobiological outcomes of exercise intervention

Outcomes	No. of studies (MB/PE)	No. of participants	Effect size		Heterogeneity	
			SMD (95%CI)	*p*-value	I^2	*p*-value
Cortisol	8 (4/4)	304	-0.88 (-1.63, -0.13)	**0.022**	88.7%	<0.0001
Serotonin	5 (2/3)	193	-2.48 (-5.31, 0.35)	0.086	97.8%	<0.0001
BDNF	8 (2/6)	346	0.34 (-0.07, 0.76)	0.107	71.4%	0.001
CRP	5 (2/3)	453	-0.01 (-0.22, 0.19)	0.914	18.5%	0.297
IL-6	5 (3/2)	438	-0.51 (-1.08, 0.06)	0.077	86.7%	<0.0001
VO_2max/peak	6 (0/6)	368	1.20 (0.38, 2.02)	**0.004**	91.7%	<0.001

MB: mind-body exercise; PE: physical exercise; BDNF: brain-derived neurotrophic factor; CRP: C-Reactive Protein; IL: interleukin; VO_2max/peak: maximum/peak oxygen uptake.

Four mind-body exercise studies and four physical exercise studies provided data on cortisol (Carneiro et al., 2017; Foley et al., 2008; Imboden et al., 2021; Lu et al., 2020; Nabkasorn et al., 2006; Sarubin et al., 2014; Tolahunase et al., 2018; Tsang, Tsang, et al., 2013) and the pooled overall result demonstrated that cortisol level reduced significantly in exercise groups (SMD=-0.88, p=0.022, I^2=88.7%; **Figure 2**).

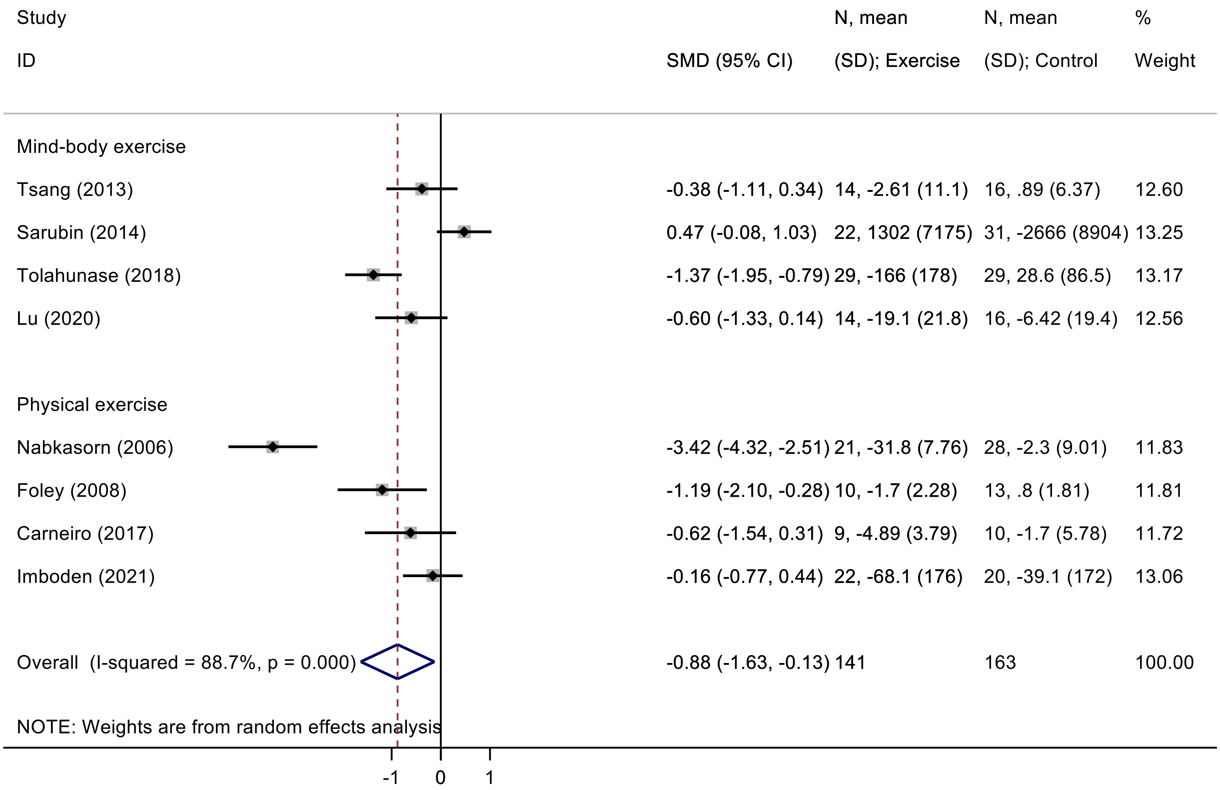


Figure 2. Effect of exercise on cortisol

Two mind-body exercise and three physical exercise studies presented the data of serotonin (Abdelhamid et al., 2016; Carneiro et al., 2017; Hemat-Far et al., 2012; Lu et al., 2020; Tsang, Tsang, et al., 2013). The pooled result showed that exercise intervention produced marginally non-significant reduction of serotonin levels (SMD=-2.48, p=0.086, I^2=97.8%; **Figure 3**).

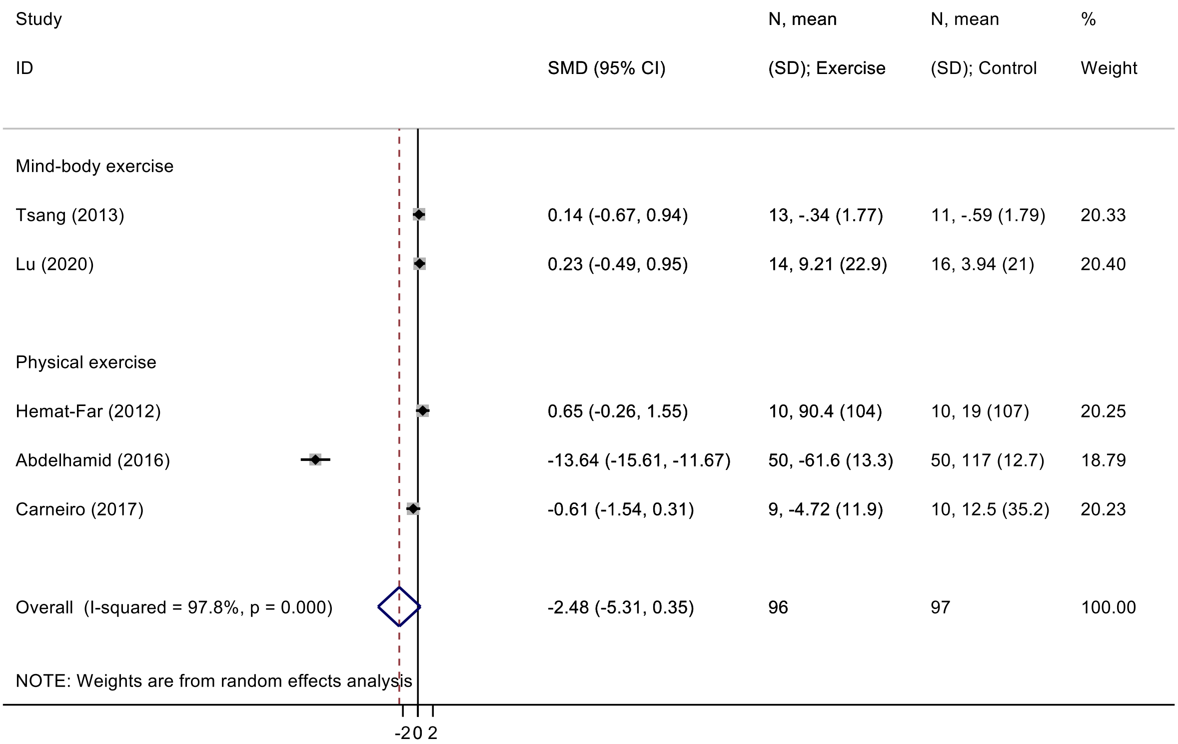


Figure 3. Effect of exercise on serotonin

Evaluable data on BDNF from two mind-body exercise studies (Lu et al., 2020; Tolahunase et al., 2018) and six physical exercise studies (Imboden et al., 2021; Kerling et al., 2017; Krogh et al., 2014; Salehi et al., 2016; Schuch et al., 2014; Szuhany & Otto, 2020) were pooled to present the effect of exercise intervention. Overall, there was non-significant improvement in BDNF following exercise (SMD=0.34, *p*=0.107, I^2=71.4%; **Figure 4**).

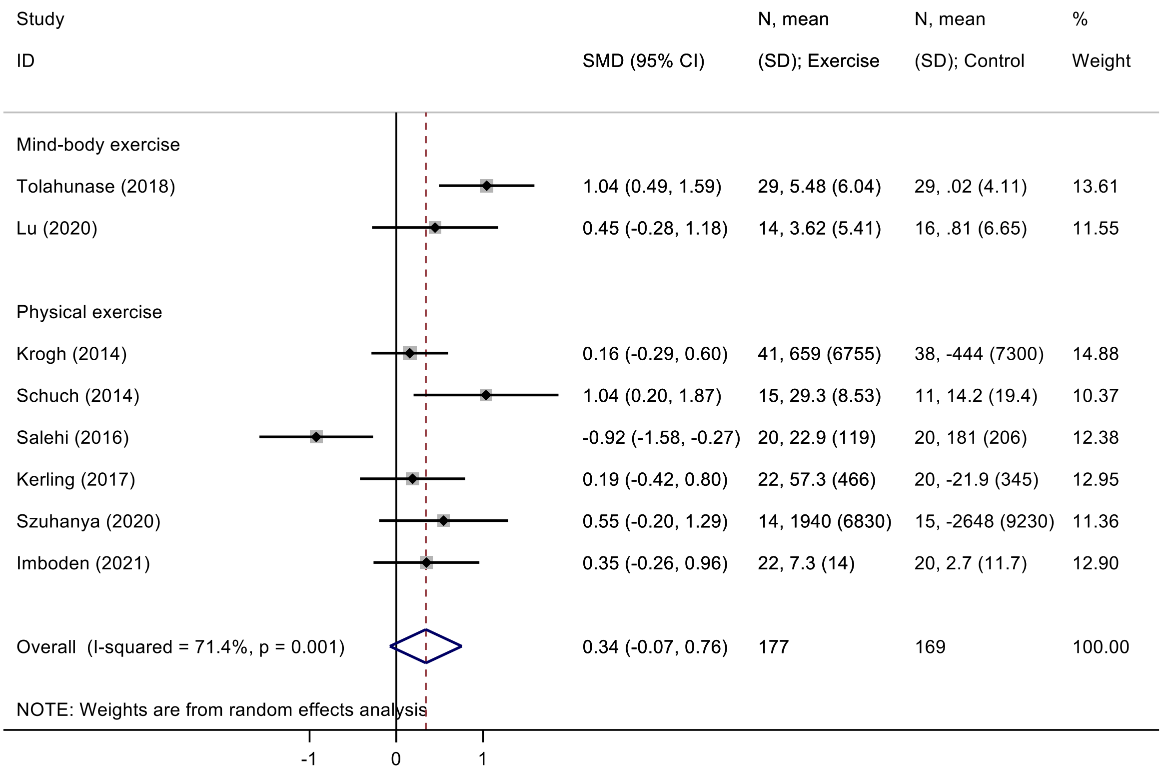


Figure 4. Effect of exercise on BDNF

Data on CRP were reported in two mind-body exercise studies and three physical exercise studies (Euteneuer et al., 2017; Krogh et al., 2012a; Lavretsky et al., 2011b; Nugent et al., 2019; Vučić Lovrenčić et al., 2015). The pooled results suggested that exercise showed no statistically significant effects on CRP levels (SMD=-0.01, p=0.914, I^2=18.5%; **Figure 5**).

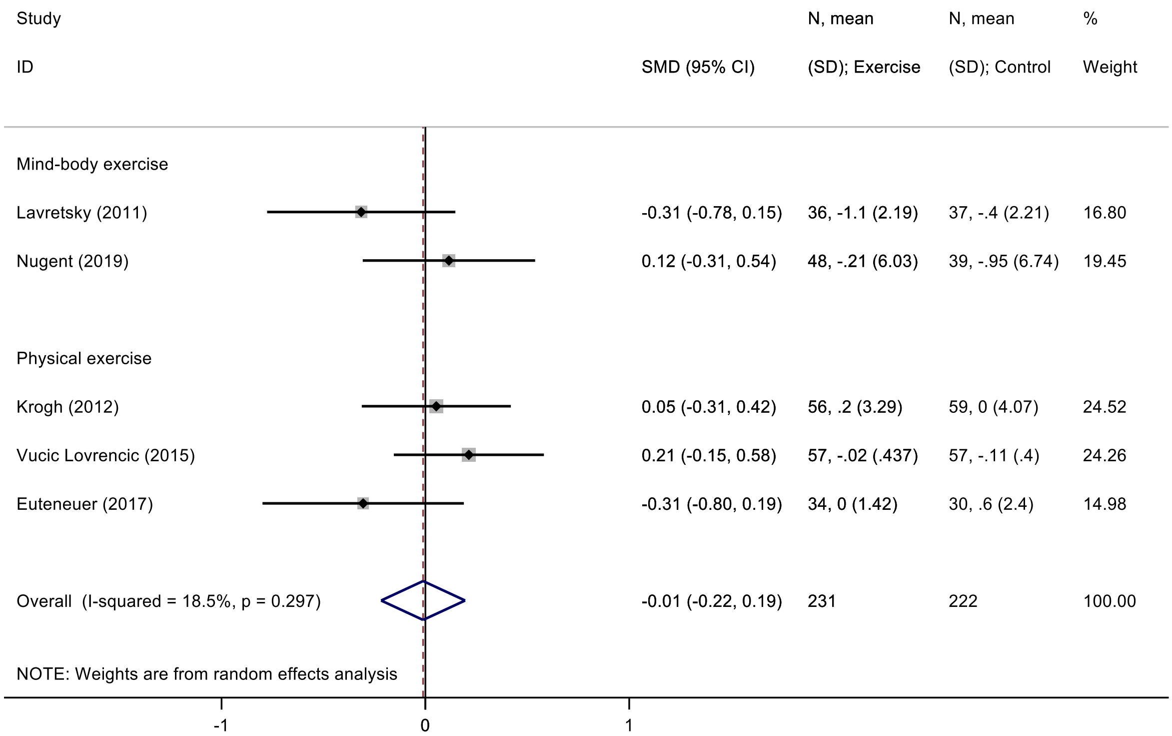


Figure 5. Effect of exercise on CRP

IL-6 data from three mind-body exercise studies and two physical exercise studies (Euteneuer et al., 2017; Ng et al., 2022; Nugent et al., 2019; Tolahunase et al., 2018; Wunram, Oberste, Hamacher, et al., 2021) was pooled, and the result showed a marginally non-significant effect of exercise interventions in reducing IL-6 levels (SMD=-0.51, p=0.077, I^2=86.7%; **Figure 6**).

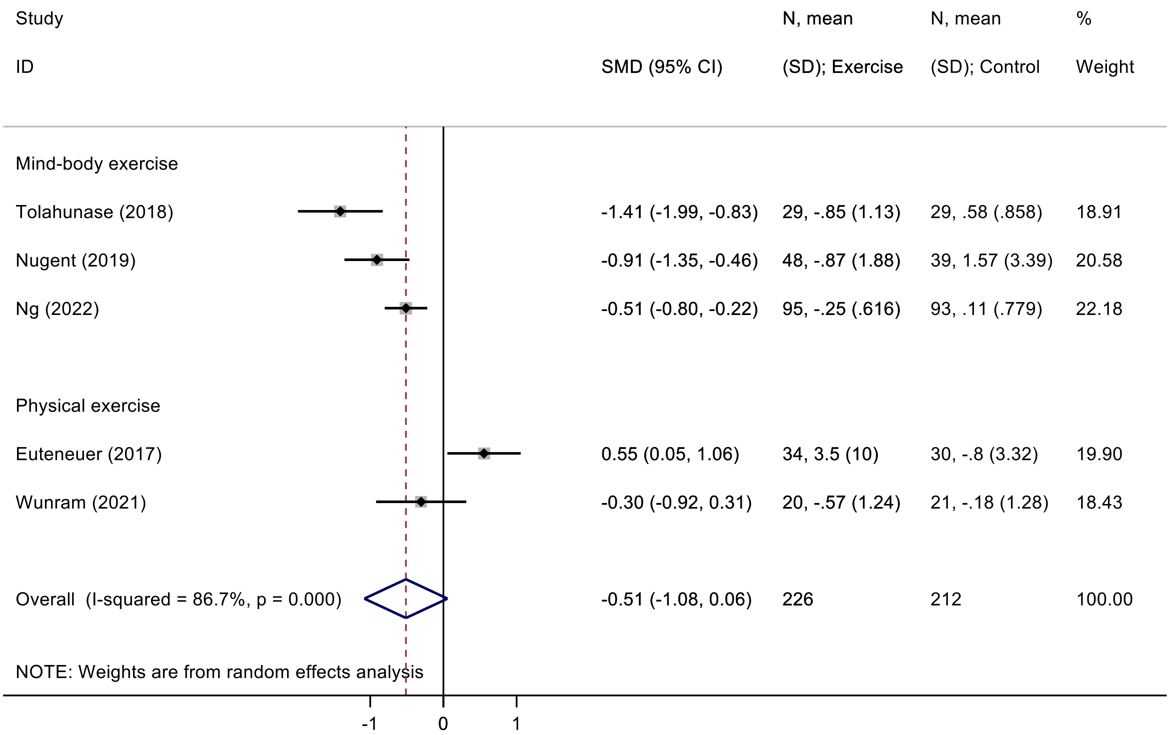


Figure 6. Effect of exercise on IL-6

In addition to the above five outcomes, cardiorespiratory fitness was also evaluated by VO_2max/peak in five physical exercise trials (Kerling et al., 2015; Krogh et al., 2012a; Nabkasorn et al., 2006; Patten et al., 2017; Siqueira et al., 2016) and a significant, large pooled effect of physical exercise on VO_2max/peak was found (SMD=1.20, *p*=0.004, I^2=91.7%; **Figure 7**).

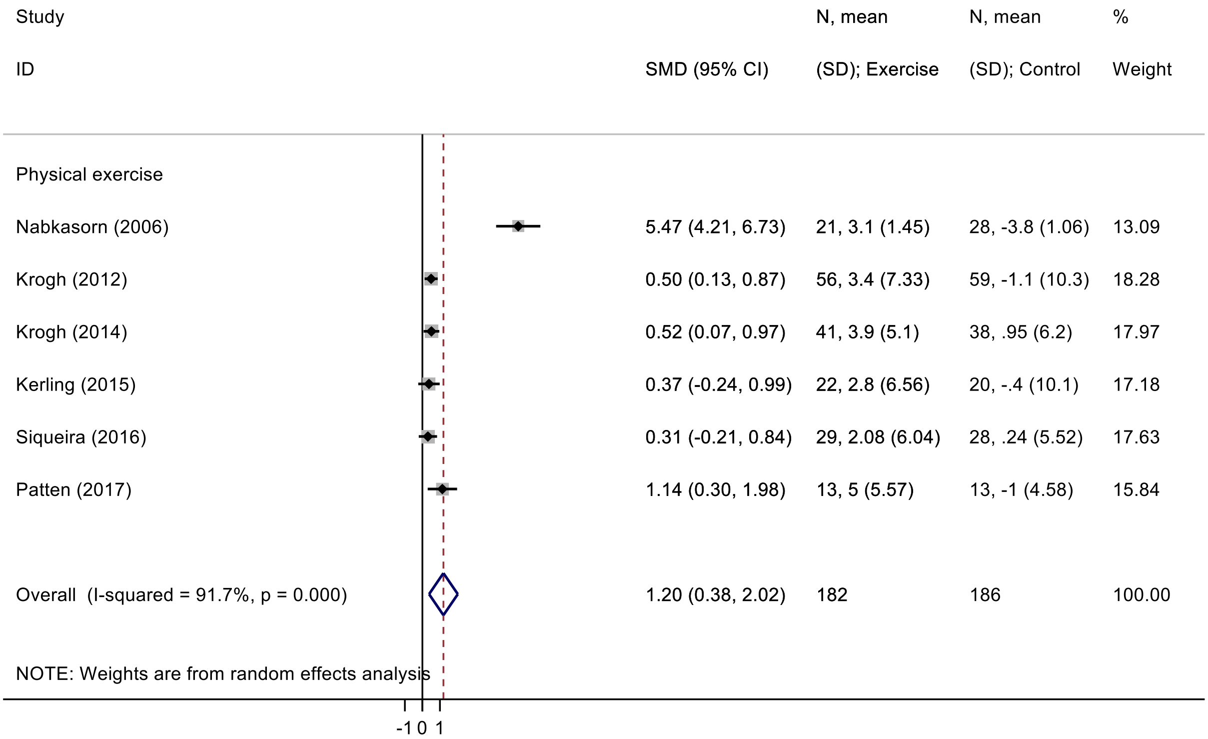


Figure 7. Effect of exercise on VO_2max/peak

One mind-body exercise study had high risk of bias and was excluded in sensitivity analysis to evaluate the impact of the quality of the included studies on the findings (Sarubin et al., 2014). The result showed the overall effect of exercise on cortisol remained significant with a greater effect size (SMD=-1.08, p=0.004, I^2=85.4%; **Figure 8**).

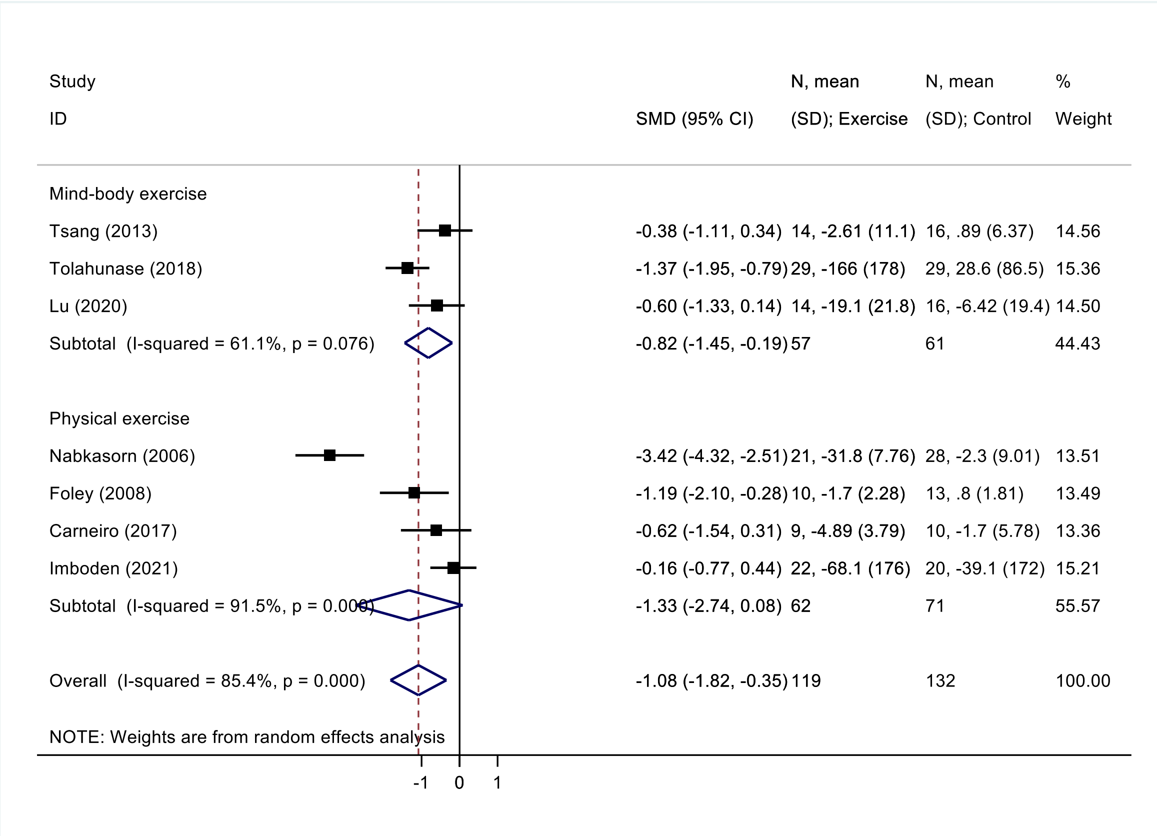


Figure 8. Forest plot of sensitivity analysis on cortisol

The meta-analysis for mechanism outcomes with at least two studies showed that mind-body intervention improved the level of BDNF and reduced the levels of cortisol and IL-6 significantly.

2.5.2.4 Discussion

Main findings

The present systematic review and meta-analysis synthesized the findings from 32 RCTs on the treatment effects of mind-body exercise or physical exercise on different neurobiological outcomes in a total of 1,820 participants with depressive symptoms. With converging evidence from the included studies, we found the potential mediating roles of cortisol, BDNF, and IL-6 underlying the antidepressant effects of mind-body exercises, whereas VO_2max/peak was likely to unpack the linkage between physical exercise and depressive symptoms. In addition, enhanced EEG frontal alpha asymmetry and increased right hippocampal volume may also explain the antidepressant effects of mind-body exercise and physical exercise, respectively. Due to the limited number of included studies on each neurobiological outcome and their associations with depressive symptoms within the subgroups of mind-body exercises and physical exercises, it was infeasible to synthesize the above findings quantitatively. Nonetheless, the present systematic review and meta-analysis provided an updated and in-depth understanding of potential neurobiological mechanisms of mind-body exercise and physical exercise as treatments for depressive symptoms.

Antidepressant mechanisms of exercises

We observed a trend that the effects of physical exercise on neurobiological outcomes were more commonly tested than the effects of mind-body exercise. However, a higher proportion of the included studies on mind-body exercise explored the associations between neurobiological outcomes and depressive symptoms, which suggested the potential mediating roles of different neurobiological pathways. Taking both the treatment-related changes in neurobiological outcomes and their associations with the changes in depressive symptoms into account, we generated theoretical models related to potential neurobiological mechanisms of the antidepressant effects of mind-body exercise and physical exercise as shown in **Figure 9** that reflected the evidence synthesized in the present systematic review and meta-analysis.

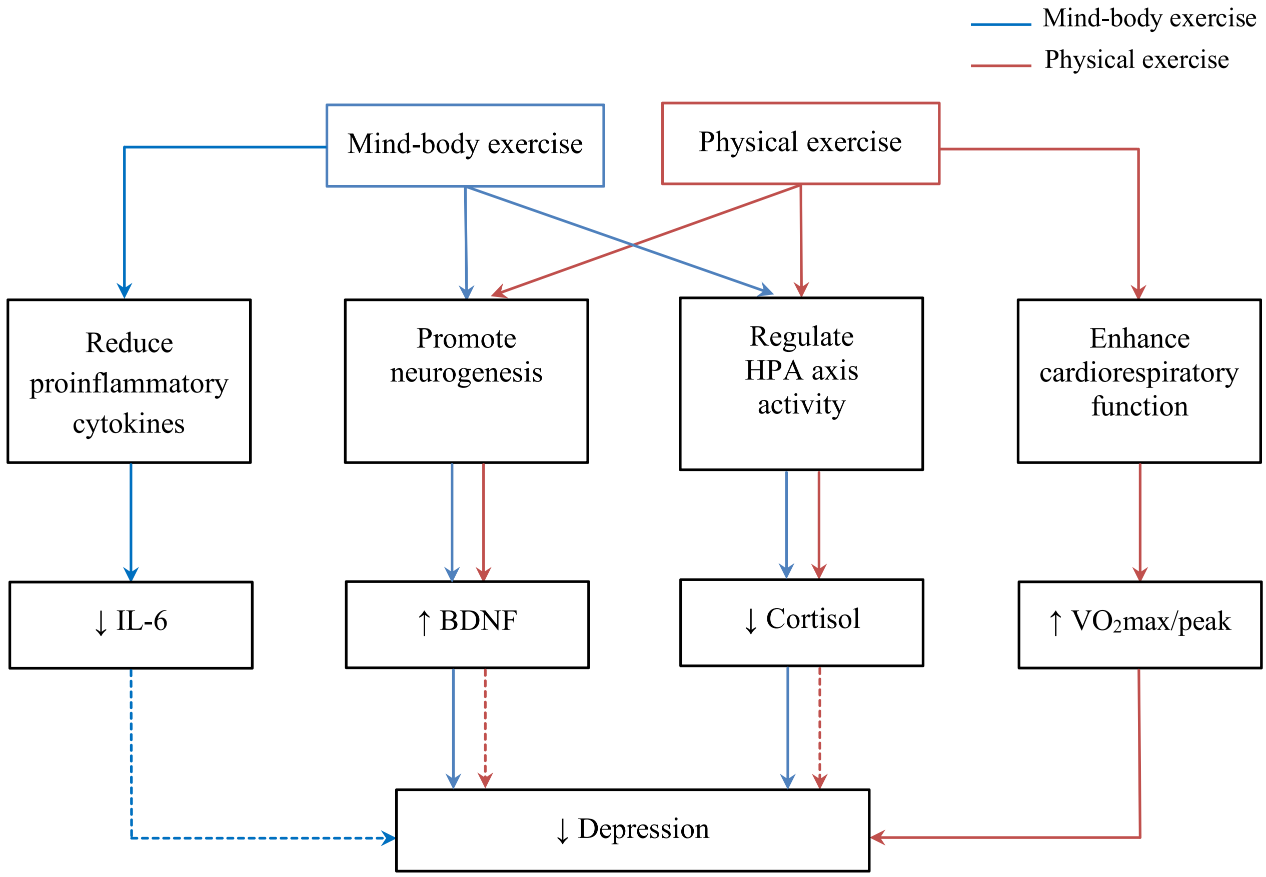


Figure 9. The possible neurobiological pathways of antidepressant effects of exercises

⟶ Reported possible pathway in at least two studies with consistent finding

----➤ Proposed possible pathway

Lowered cortisol and enhanced BDNF as potential mechanism outcomes

We found that both mind-body exercise and physical exercise could potentially regulate the HPA axis activity (manifested as decreased cortisol) and enhance neurogenesis (manifested as increased BDNF). Specifically, significantly more reduction in cortisol levels in intervention group than control group were reported in two studies on mind-body exercise (Lu et al., 2020; Tolahunase et al., 2018) and another two studies on physical exercise (Foley et al., 2008; Nabkasorn et al., 2006), whereas the decreasing trend of cortisol levels were consistently reported in other relevant included studies, except for one study with high risk of bias (Sarubin et al., 2014). Hence, it was reasonable to have significant pooled effects of mind-body exercise and physical exercise on cortisol.

Similarly, significant treatment-related enhancement in BDNF were found in both mind-body exercise studies (Lu et al., 2020; Tolahunase et al., 2018) and physical exercise studies (Kerling et al., 2017; Wunram, Oberste, Ziemendorff, et al., 2021), with promising changing trend reported in other included studies that assessed BDNF. While the pooled effect on BDNF was marginally non-significant, the effect size generated from Salehi and colleagues' (2016) study could be a potential outlier, as it was substantially lower than those of other physical exercise studies. They compared physical exercise to electroconvulsive therapy (ECT), a potent treatment in severe depression(Salehi et al., 2016). Since it was evidenced that BDNF levels increased significantly after ECT (Rocha et al., 2016), the comparison between physical exercise and ECT might underestimate the effect of exercise on BDNF. When this outlier study was removed, a significant pooled effect of mind-body exercise and physical exercise on BDNF was found (**Figure 10**).

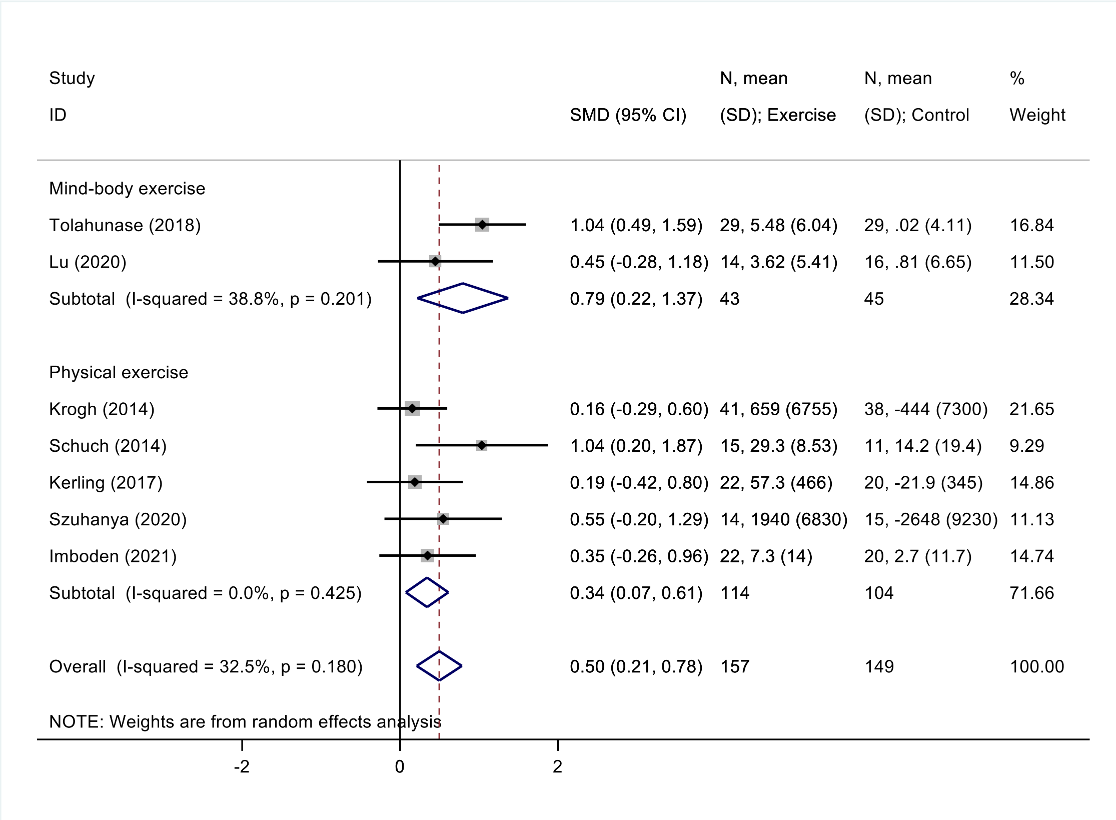


Figure 10. Forest plot of sensitivity analysis on BDNF

Cortisol was found to significantly mediate the effect of qigong on depressive symptoms (Lu et al., 2020), but no significant associations between changes in cortisol and depressive symptoms were reported in physical exercise studies (Foley et al., 2008; Rahman et al., 2019). Similarly, significant correlations between changes in BDNF and depressive symptoms were found after mind-body exercise (Lu et al., 2020; Tolahunase et al., 2018), but not physical exercise (Kerling et al., 2017; Szuhany & Otto, 2020; Wunram, Oberste, Ziemendorff, et al., 2021). It was possible that the associations between alleviations of depressive symptoms, reductions in cortisol, and enhancement of BDNF were stronger after training of mind-body exercise than physical exercise, probably due to the additional mental component in mind-body exercise. The sample sizes of the above studies were generally small, and it may need higher number of participants in RCTs on physical exercise to detect low but significant associations between changes in depressive symptoms and changes in cortisol/BDNF, and even mediation effect elicited from cortisol/BDNF.

Lowered IL-6 as a potential mechanism outcome of mind-body exercise

All the three included studies on mind-body exercise and IL-6 consistently reported significant treatment effects (Ng et al., 2022; Nugent et al., 2019; Tolahunase et al., 2018), and the associations between changes in IL-6 and depressive symptoms were explored and supported in one study (Ng et al., 2022). Hence, it was likely that mind-body exercise can regulate immune system through the reduction of pro-inflammatory cytokines, mainly IL-6. Chronic stress was found to over-activate immune function (Leonard, 2001). Leading to elevated pro-inflammatory cytokines in people with depressive symptoms (Felger & Lotrich, 2013). Through slow movement and diaphragmatic breathing, mind-body exercise promotes physical and psychological relaxation for the management of chronic stress and inflammation (Djalilova et al., 2019). In addition, IL-6 was found to be a salient marker of inflammatory process and response to antidepressant treatment (Hannestad et al., 2011). Hence, the effect of mind-body exercise on IL-6 was more frequently studied, whereas the evidence on other pro-inflammatory cytokines was scarce.

VO_2max/peak as a potential mechanism outcome of physical exercise

According to the six studies on physical exercise and VO_2max/peak, it was consistently reported that depressive participants could have significantly more improvement in VO_2max/peak after physical exercise, compared to those in control groups (Kerling et al., 2015; Krogh et al., 2014; Krogh et al., 2012a; Nabkasorn et al., 2006; Patten et al., 2017; Siqueira et al., 2016). A significant pooled effect of physical exercise on VO_2max/peak was found based on meta-analysis. In addition, the increase in VO_2max/peak was significantly correlated with the decrease in depressive symptoms according to Imboden and colleagues (Imboden et al., 2021). Hence, it was likely that physical exercise alleviates depressive symptoms through the improvement of cardiorespiratory function fitness (CRF), marked by higher VO_2max/peak. A previous study showed that the elderly who completed six months of aerobic exercise had significantly better CRF indicators and ability to complete complex cognitive tests (Kramer et al., 1999) than those in the anaerobic exercise group. The association between CRF and the volume of the prefrontal and anterior cingulate cortex has also been demonstrated (Flöel et al., 2010). Interventional studies have shown that physical exercise might increase the volume of the hippocampus, prefrontal cortex, and anterior cingulate cortex (Colcombe et al., 2006). By improving CRF, physical exercise may counteract the brain atrophy and dysfunction linked to depression, which might be one of the key mechanisms of its antidepressant effect.

Potential mechanisms in brain structure and activity

We obtained one study supporting the enhanced EEG frontal alpha asymmetry after a mind-body exercise (Chan et al., 2013) and another study demonstrating the increased right hippocampal volume after aerobic exercise (Krogh et al., 2014), and changes in both outcomes were significantly related to treatment-related reductions in depressive symptoms. Since both outcomes closely reflect emotional dysregulation in depression, the treatment effects of mind-body exercise and physical exercise on brain structure and activity are important in understanding their antidepressant effects. However, since each of the findings was derived from a single study, we did not mention the mechanisms of brain structure and activity in Figure 9. Nonetheless, it is warranted to further exploration in the potential mediating roles of EEG frontal alpha asymmetry and hippocampal volume underlying the antidepressant effects of mind-body exercise and physical exercise.

4.3 Limitations and future directions

Several limitations of the present systematic review and meta-analysis should be noted. First, although RCTs provide the highest level of evidence, only a limited number of RCTs were included in the review. The current findings should be interpreted with caution. Considering the variations in participant characteristics, intervention specifics, and assessment tools across the included studies, it was infeasible conduct subgroup analyses or meta-regression that may explain such heterogeneity. Looking forward, more RCTs with powered sample size and high quality are needed to unravel the underlying mechanisms of antidepressant effects of mind-body exercise and physical exercise, respectively. Second, many of the subjects of the studies included in this review were concurrently taking anti-depressants. As a result, it is difficult to make a strong conclusion on whether the effect and mechanism are related to exercise or medication. There is a possibility that the changes in depressive symptoms and mechanism outcomes could be attributed to both an independent effect of exercise and a synergistic effect with the medication used. Furthermore, we found that correlations between changes in neurobiological outcomes and depressive symptoms were not reported in three mind-body exercise and twelve physical exercise studies, future studies might consider the investigation of the correlations such that the clinical relevance of exercise intervention could be further understood, which could in turn benefit the application and promotion of exercise for patients with depression. Fourth, some biomarkers of other pathways which haven’t been studied in human RCTs were not included in this review. Last but not least, among the studies included in the current meta-analysis, half of those on mindful exercise used qigong in Hong Kong, whereas all the non-mindful exercise studies were from western countries. As qigong originated in China, its effectiveness may also be enhanced as a result of cultural compatibility and should be further validated (So et al., 2020). As depression involves complex interactions of numerous pathways, the understanding of anti-depressive mechanisms needs to be further analyzed using the bio-psycho-social model in the future.

2.5.2.5 Conclusion

Mind-body exercise was likely to alleviate depressive symptoms through the regulation of HPA axis activity, the enhancement of neurogenesis, whereas physical exercise was consistently shown to improve CRF, which could in turn, reduce depressive symptoms. The understanding of these potential neurobiological mechanism can inform the choice and design of exercise protocol as complementary treatment for people suffering from depressive symptoms. It was noteworthy that mind-body exercise was found to treat depressive symptoms through the enhanced EEG frontal alpha asymmetry, and enhanced hippocampal volume was associated with the reduced depressive symptoms after physical exercise. Given the limited number of included studies and high heterogeneity in participants, interventions, and neurobiological outcomes, the potential mechanisms identified in the present systematic review and meta-analysis should be further tested, and they were far from being exhaustive. More high-quality RCTs are warranted for better understanding of how mind-body exercise and physical exercise treat depressive symptoms.

2.6 Rationale of the main study

In recent years, mind-body exercises have gained increasing popularity. More and more research studies have been conducted to evaluate their impact on health outcomes. Many clinical trials have supported the efficacy of mind-body exercises for alleviating depressive symptoms in older adults with depression. The findings of our two systematic reviews provide evidence that mind-body exercise can improve mental health and cognitive function effectively. Practicing qigong may help to enhance cognitive function in older adults with depression. However, few research has investigated cognitive effects of qigong exercise and changes in brain functioning underlying the therapeutic effects of qigong in depression. In late life, depression and cognitive impairment are two conditions that highly comorbid, therefore qigong could be a promising treatment option for older adults with depressive symptoms.

In order to bridge these literatures, the current pilot study examined the cognitive and neurophysiological effects of Baduanjin qigong in older adults with depressive symptoms. Baduanjin qigong practice was selected as intervention in the current study for the following reasons. First, Baduanjin is a safe and inexpensive intervention with advantages in both physical and psychological well-beings, and this form of qigong was easy to learn and easily accessible for elderly population. According to the review of Baduanjin for health benefits, three to four months duration was recommended for producing psychological benefits while maximizing intervention acceptability (Wang et al., 2013). Baduanjin qigong was delivered every week for a duration of 12 weeks in the main study. Second, based on the literature review, the evidence regarding the effects of Baduanjin on cognitive symptoms was inconclusive. Although there are studies showed Baduanjin practice has beneficial effects on cognitive function in older adults, no research examined cognitive effects of Baduanjin in depressed population. In addition, reviews and meta-analyses provide inconsistent results regarding the effects of Baduanjin on specific domains of cognition. Furthermore, the possible mechanisms underlying the effects of qigong remain unknown. Therefore, more trials are needed to reach more definitive conclusions and to provide more evidence for clinical practice.

It is therefore hypothesized in this study that Baduanjin qigong would significantly outperform waitlist control in enhancing global cognitive function in older adults with depressive symptoms. The proposed theoretical framework for the associated changes in brain activities that result in improvement in global and specific cognitive functions, as depicted in Figure 1. While current findings from meditation, physical exercise, combined intervention, and other types of mind-body exercise suggested these possible pathways, studies are needed to advance the understanding of these mechanisms driving the effects of qigong on cognition. The SR1 found that mind-body exercise could significantly improve cognitive domains that are related to core depressive symptoms, such as attention and executive functions. However, direct investigations of qigong's influence upon cognition in depression have been limited. In addition, whether qigong is related to the changes in brain activity in older adults with depressive symptoms needs to be explored by more research. Due to the limited resources for research, the qigong-related benefits in specific cognitive functions, including attention and executive functions (inhibitory control and working memory), and enhancement in brain activation (N2 and P3 amplitude) were studied as secondary objectives. Moreover, we explored the correlations between changes in brain activity and changes in cognitive function and potential mediating roles of changes in brain activity that unpack the qigong-related cognitive benefits as another set of secondary analyses.

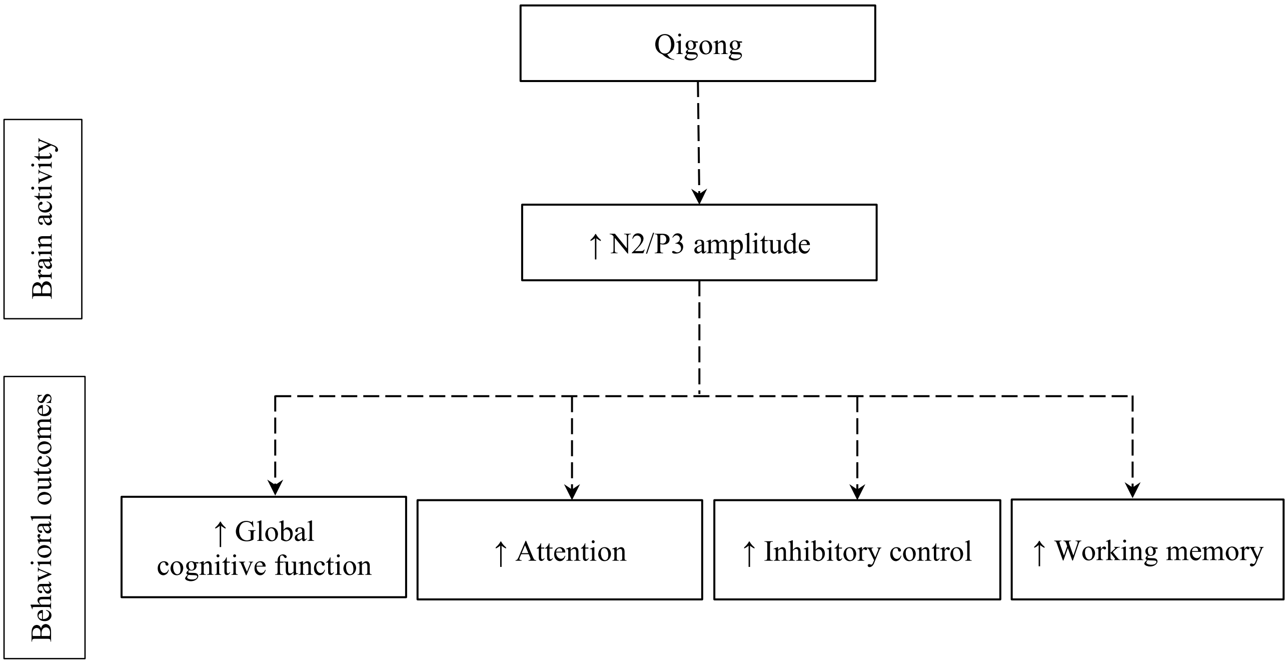


Figure 1. Potential neural pathways of the cognitive effects of qigong intervention. Dotted lines indicate linkages between possible neuroelectrophysiological correlates and changes in cognitive states.

Based on the rationale mentioned above, we proposed a two-arm, randomized, single-blinded controlled trial. This pilot study randomly assigned older adults with depressive symptoms to either the Baduanjin intervention group or the waitlist control group.

Chapter 3: Research Methodology

3.1 Research design

This study was a pilot randomized controlled trial comparing cognitive function of a 12-week Baduanjin qigong group a waitlist control group. The primary outcome variable was global cognitive function, and the secondary outcomes were attention, working memory, and inhibitory control of the older adults. EEG data were also obtained to explore the neurophysiology mechanism of qigong intervention. This study was approved by the Human Subjects Ethics Committee from The Hong Kong Polytechnic University (HSEARS20210125009).

3.2 Setting and participants

Older adults from community were approached and recruited through health talks (online and face-to-face ones) and posters at the campus of The Hong Kong Polytechnic University (PolyU) and on social media. Both recruitment, assessment, and intervention were conducted at PolyU in Hong Kong.

Older adults were eligible for inclusion if they:
(i) were 60 years or older;
(iii) had mild or severer levels of depressive symptoms as indicated by the Geriatric Depression Scale (GDS-8) scores of 5 or above (Sheikh & Yesavage, 1986), or Depression Anxiety and Stress Scale-21 (DASS-21) depression subscale scores of 4 or above (Henry & Crawford, 2005); and
(iv) were self-identified as physically stable and without life-threatening diseases.

The broad inclusion criteria were intentionally designed to enhance the generalizability of the study results. By including a wide demographic and diverse individual profile, the study sample could be representative of target population that older adults usually present with mixed health conditions.

Exclusion criteria for participants were:

(i) having a history of practicing or receiving training of any form of mind-body or regular exercises (including tai chi, yoga, and qigong, or regular physical activity > 3 times/week) during the month prior to study enrollment;

(ii) having changed medications or the dose of medications prescribed for their health condition in the month prior to study enrollment;

(iii) evidencing severe cognitive or language impairment as defined as a score of less than 21 on Montreal Cognitive Assessment (MoCA-5min) (Wong et al., 2015) (Feng et al., 2021);

(iv) undergoing electroconvulsive therapy, psychotherapy, or psychoeducation for a psychological or psychiatric condition; and

(v) being unable to demonstrate satisfactory standing balance.

3.3 Sample size

We hypothesized that Baduanjin qigong training could improve cognitive function effectively compared with controls in older adults. For this hypothesis, the required sample size was calculated based on the results of a meta-analysis of qigong on global cognitive function in older adults, which indicated a medium (Cohen's *f*) of 0.2 (Wang et al., 2022). Power calculations using G*Power 3.1 software showed that a sample size of 52 would provide a power of 0.8 with an $\alpha = 0.05$ to detect a significant group difference. Hence, considering a 20% attrition rate, a total of 66 (33 subjects per group) older adults with depressive mood needed to be included for the study.

3.4 Randomization

An independent researcher assigned the participants to the intervention and waitlist control groups using computer-generated simple random allocation sequencing. The allocation was kept concealed and it was revealed when participants completed assessments at baseline. The research personnels performing the assessments and data analysis were blinded to the group assignment.

3.5 Intervention

The Baduanjin intervention was offered to the participants in qigong group.

According to the review of Baduanjin for health benefits, three to four months duration was recommended for producing psychological benefits while maximizing intervention acceptability (Wang et al., 2013). Therefore, the Baduanjin qigong was delivered every week for a duration of 12 weeks, with two sessions per week and 60 minutes of exercise a day. Baduanjin involves eight consecutive and simple body movements, and it took about 10 to 15 minutes for a complete cycle of the Baduanjin . Each cycle of the eight movements was performed two to three times during the training session. Each session begins with a guided breathing and mindfulness practice, and the warm-up and cool down were done before and after qigong practice. Qigong exercises was practiced in a group format by qualified instructors with bachelor's degree or above in Psychology and/or Rehabilitation Sciences. Before delivering health qigong intervention, all the instructors were trained by a professor in practice with over 30 years of clinical experience and expertise in health qigong. To ensure the instructors' competence in intervention delivery, they have passed the examination administered by the professor in practice.

3.6 Outcome measures

3.6.1 Primary outcome

Global cognitive function. The Montreal Cognitive Assessment (MoCA) was used to evaluate global cognitive function. It is a widely used concise test that designed and validated for detection of cognitive impairment (Nasreddine et al., 2005). MoCA is a brief assessment that measures visuospatial skill, executive function, naming, attention and concentration, language, calculation, memory, and orientation. The total score of MoCA is ranging from 0 to 30 with a higher score indicates better overall cognitive function. It is suggested that MoCA can be considered the most suitable tool for quantifying cognitive impairment (Bernstein et al., 2011). The *Hong Kong version MoCA (HK-MoCA)* was revised by Wong et al. (Wong et al., 2009). Previous studies have shown good sensitivity, reliability and validity of HK-MoCA in Chinese older adults with all educational levels (Yeung et al., 2014).

3.6.2 Secondary outcomes

Attention Network Test (ANT) is the computer-based test that combined the Posner's cueing task and the Flanker task (Fan et al., 2002). It was adopted in different populations for evaluating efficiency of attention networks, including older adults and individuals with depression (Sinha et al., 2022; Williams et al., 2016). The ANT paradigm began with a practice block of 24 trials, followed by 2 experimental blocks, each involving 96 trials. The participants were required to determine the central arrow's direction by avoiding false interference stimuli. On each trial, a row arrows to the left or right was displayed either in the center, at the top or bottom of the screen as stimulus. Cues were presented before the stimuli to provide information about the location of the stimulus. The central arrow was flanked by congruent (same direction) or incongruent (opposite direction) conditions. The neutral condition consists of a central arrow and non-arrow flankers (**Figure 3.1**). Cognitive function was reflected by the behavioral performance (i.e., reaction time).

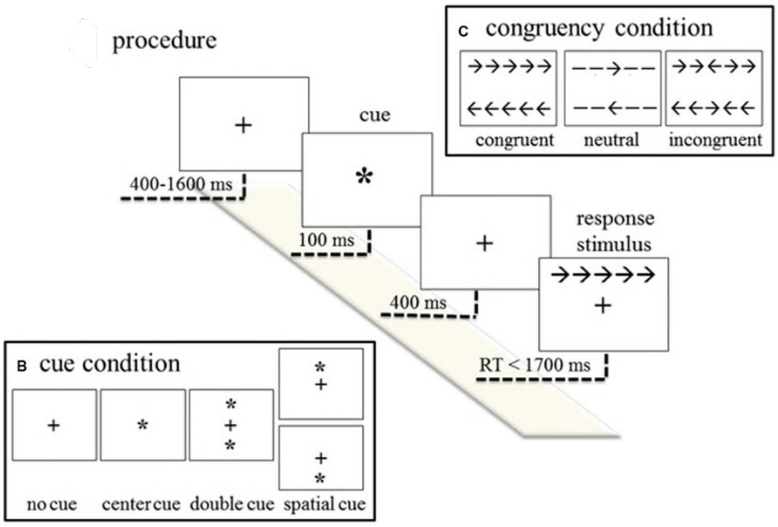


Figure 3.1 Attention Network Task experimental protocol

N-back task is one of the most commonly used measurement for working memory in depression (Nikolin et al., 2021). The n-back paradigm included 0-back and 2-back conditions, which represented low and high working memory load, respectively. Both conditions were assessed by 3 times (blocks) alternately, with a 30-second rest block between two experiment blocks. Each block was preceded by a 5-second cue to inform the following task condition, followed by 40 pseudo-randomized trials (10 targets and 30 non-targets). In 0-back condition, subjects were asked to click the left button once “0” appeared and click the right button for other digits. In 2-back condition, subjects were asked to click the left button when the current number was the same as the number that appeared two trials before; otherwise, they are instructed to click the right button. Each number stimulus presentation time was 500 milliseconds, following an interdigit interval of 1500 milliseconds (**Figure 3.2**). The behavioural performance (i.e., reaction time) was used to reflect cognitive functions measured by the n-back task (Rubien-Thomas et al., 2024).

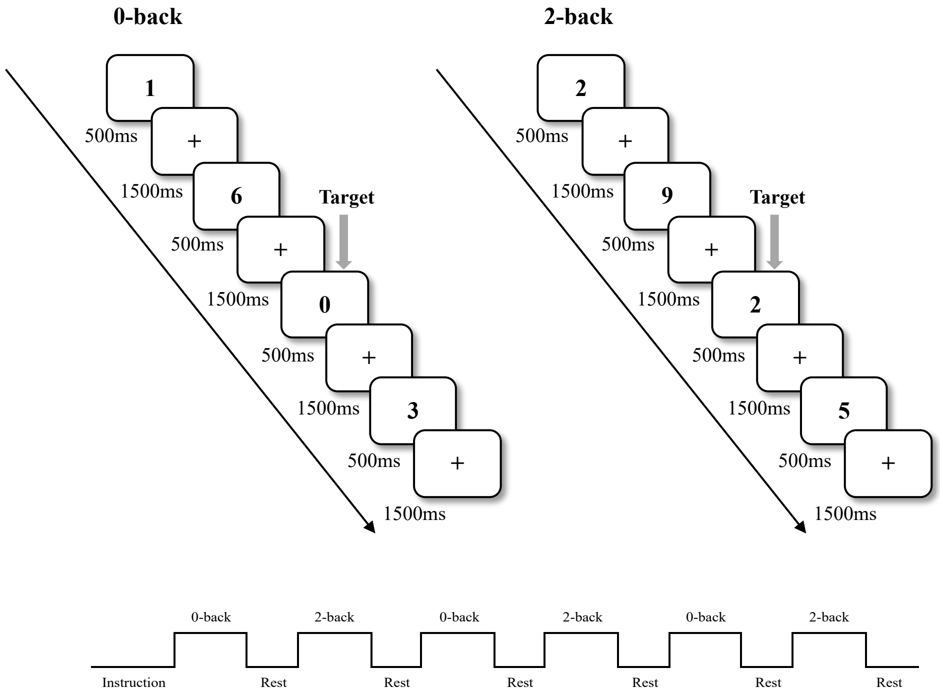
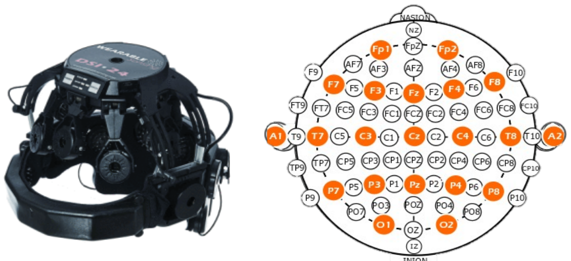


Figure 3.2 N-back task experiment

The attention ability of the participants was measured by the neutral and congruent conditions of the ANT task, and the 0-back condition of the n-back task. Inhibition of the individual was assessed by the incongruent condition of the ANT task. Working memory capacity was measured by the 2-back condition of the n-back task.

Several strategies were adopted to minimize the learning effects of the assessments. For MoCA, the alternate forms were used when necessary to mitigate the learning effects by varying the test materials between assessments. For computer cognitive tests, a familiarization session was conducted before the assessment to allow participants to become familiar with the test procedures, thereby reducing the impact of novelty and learning effects on subsequent measurements. In addition, participants had no access to practise the tasks during the intervention period and a 12-week interval was shown to be sufficient to decay the learning effect (Nishiguchi, Yamada, Tanigawa, Sekiyama, Kawagoe, Suzuki, Yoshikawa, Abe, Otsuka, Nakai, et al., 2015).

EEG data collection was conducted using the DSI-24 with 21 electrodes and the placement in accordance with the International 10/20 System (**Figure 3.3**) before and after intervention. The impedances were maintained below 10 kΩ. Participants underwent the EEG measurement during performing the ANT and n-back tasks.



(a) DSI-24

(b) 21 sensors positioned according to the 10-20 International System

Figure 3.3 (a) DSI-24 headset and (b) the placement of electrodes

EEG data preprocessing was performed by EEGLAB Toolbox in MATLAB® R2023b (Delorme & Makeig, 2004) (The MathWorks Inc., Natick, MA, USA). EEG signals were re-referenced to the earlobe electrodes (A1, A2). Data were finite impulse response (FIR) filtered with the frequency pass band of 0.1-30 Hz. In addition, artefacts from body movements were removed according to the examiner's records during the EEG experiments. Stimulus-locked epochs were extracted from 200ms prestimulus through 1000ms poststimulus. For each epoch, a baseline correction for the prestimulus 200ms was performed. Independent Component Analysis (ICA) was then performed for epoched data to remove the remaining artifacts. Components were rejected if the probability as an artifact was greater than 0.9 detected by ICA. Epochs exceeding ± 100μV were also rejected as artifacts. The EEG preprocessing methods were adopted according to previous ERP studies (Michaelides et al., 2022; Riek et al., 2023).

3.7 Procedure

Older adults who were interested in and signed up for this study were screened according to the criteria mentioned in Section 3.2. An information sheet outlining the study information was first distributed and explained to eligible subjects, and written informed consent was then obtained from all participants. The participants were assigned a subject code each and allocated to either qigong intervention or waitlist control by the random-number generator. Basic demographics were collected at baseline, including age, sex, education, marital status, diagnosis of chronic diseases. Participants of the qigong group received a 12-week Baduanjin training programme. All participants underwent assessment at baseline and 12 weeks after baseline (post intervention). After the completion of all assessments, the Baduanjin intervention was delivered to the waitlist control groups. Adverse events were assessed during each session of Baduanjin training and at the post assessment: the participants were asked to report any adverse events during and after Baduanjin practice; the instructor was asked to monitor each training session and record any observed adverse events. To compensate for the time spent in the project, each participant received incentives in cash. Over the course of 18 months, recruitment, intervention, and assessment were carried out in five batches. All collected data are saved in a cabinet and only the research team for this study has the access to the data.

3.8 Data analysis

Data analysis was conducted according to intention-to-treat principle, and missing values were imputed using last observation carried forward method. Group differences in demographic and baseline levels of cognitive performance were evaluated using t-test and chi-square test. The level of significance throughout data analysis was set at $p < 0.05$. To test the Primary Hypothesis for the Main Study (as stated in Section 1.4), a repeated-measures analyses of variance (RM ANOVA) was conducted, with MoCA as the dependent variable, group (qigong and waitlist) and time (baseline, post-treatment) as the independent variables. A significant treatment effect of Baduanjin will be indicated if a significant Group*Time effect emerges, with the participants in the Baduanjin condition evidencing larger improvements in global cognitive function than those in the control condition, as shown by post-hoc comparisons of changes in MoCA scores between groups. The post-hoc comparison was performed by Bonferroni test and Greenhouse-Geisser correction was applied for non-sphericity data (Jennings & Wood, 1976). Effect size of qigong on global cognitive function in comparison to waitlist was presented as η_p^2 for ANOVA.

Secondary outcomes of attention, inhibitory control, and working memory were obtained by participants' performance of the ANT and n-back task. Mean reaction time (RT) for correct trials were analysed by trial type for each group. RT was calculated as the mean RT for correct responses in each task condition. To explore the effects of qigong on the secondary outcomes, the same RM ANOVA and post-hoc analysis were conducted with effect size presented by η_p^2.

ERP data were analysed with RM ANOVA for N2 and P3 amplitudes separately, following the same statistical procedures as those for global and specific cognitive functions. The ERP components were calculated by averaging the amplitudes recorded at the selected electrodes and time windows (210-350ms for N2, 350-550ms for P3) (Alderman et al., 2016; Chang et al., 2017) for correct responses by trial type. The anterior N2 was found frequently examined at frontal electrode sites (Folstein & Van Petten, 2008; Gehring et al., 1992), while posterior P3 component was most robust at parietal electrode sites (Aly & Kojima, 2020; Johnson Jr, 1993). N2 and P3 components were analyzed for Fz and Pz electrode sites, respectively. Additionally, correlation analyses were used to explore the association between the pre-post changes in cognitive performance and ERP amplitudes (Alderman et al., 2016; Niu et al., 2016). Mediation analysis were performed with PROCESS macro (Hayes, 2017) if the following condition were fulfilled: 1) significant Group*Time effects in N2 or P3 amplitudes emerged from RM ANOVA, and 2) significant correlation was found between changes in N2 or P3 amplitudes and any cognitive outcome. Statistical analysis of this study was conducted by SPSS 27.0 software (SPSS, Inc., Chicago, IL, USA).

Chapter 4: Results

4.1 Study flow and participant characteristics

In total, 65 older adults with depressive symptoms were enrolled in this pilot study. Thirty-four were allocated into the qigong intervention and 31 were randomized into the control group. The dropout rate for this study was 7.7% which was fairly balanced between groups (intervention group: 8.8%; control group: 6.5%). No adverse events occurred during the 12-week intervention period. Detailed information on the study flow is presented in **Figure 4.1**.

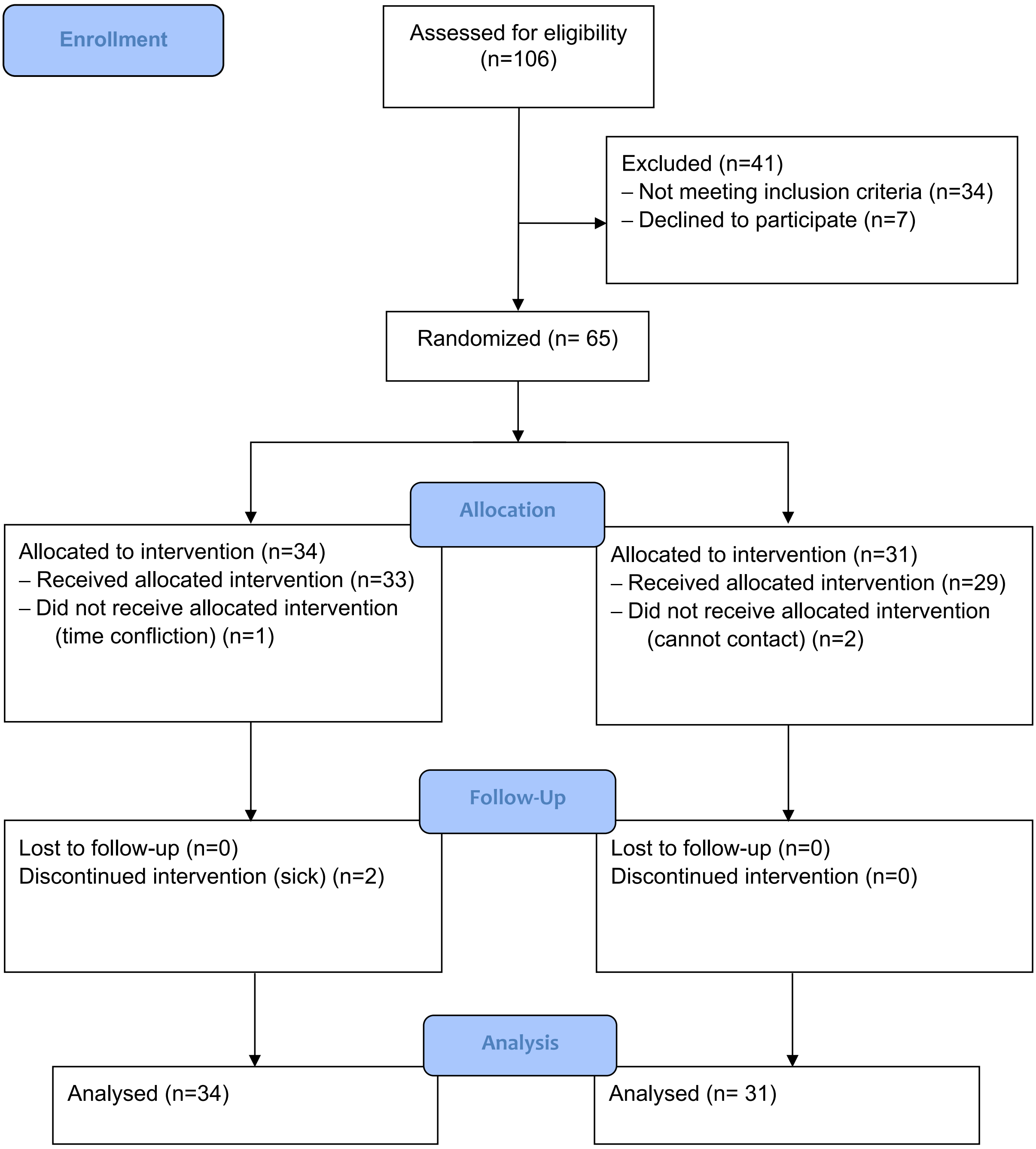


Figure 4.1 Flow diagram of the study

The descriptive statistics of the demographics data and the comparisons between qigong and control groups are shown in **Table 4.1**. No significant differences were observed for characteristics (i.e. age, sex, level of education, marital status, any chronic disease and regular medication, having at least mild depressive symptoms) between the two groups (*p*s > 0.15).

Table 4.1 Demographic information and baseline characteristics of participants

Characteristics	**Qigong** (n=34)	**Control** (n=31)	**Total** (n=65)	t-test or Chi square	*p-value*
Age (y)	69.9±4.5	69.5±3.8	69.7±4.2	0.172	0.679
Sex (male/female)	11/23	12/19	23/42	0.287	0.592
Level of education					
Primary	4 (11.8%)	5 (16.1%)	9 (13.8%)		
Secondary	18 (52.9%)	19 (61.3%)	37 (56.9%)	1.318	0.517
Above secondary	12 (35.3%)	7 (22.6%)	19 (29.2%)		
Marital status					
Married	23 (67.6%)	21 (67.7%)	44 (67.7%)	2.825	0.588
Single/divorced/widowed	11 (32.4%)	10 (32.3%)	21 (32.3%)		
Chronic disease					
Yes	27 (79.4%)	27 (87.1%)	54 (83.1%)	0.681	0.409
No	7 (20.6%)	4 (12.9%)	11 (16.9%)		
Regular medication					
Yes	19 (55.9%)	21 (67.7%)	40 (61.5%)	0.964	0.326
No	15 (44.1%)	10 (32.3%)	25 (38.5%)		
GDS	7.8±3.5	6.6±3.3	7.3±3.4	2.129	0.150
DASS-D	13.8±9.1	13.1±7.7	13.5±8.4	0.141	0.709

Descriptive statistics are presented as mean±SD and number (%).
GDS = Geriatric Depression Scale.
DASS-D = Depression Anxiety Stress Scales 21 - Depression subscale.

As listed in **Table 4.2**, the behavioural and neurophysiological measures, including MoCA score, accuracy and reaction time of ANT and n-back tasks, and mean amplitudes of N2 and P3 components, were not significantly different between the qigong intervention and control group at baseline (*p*s > 0.10).

Table 4.2 Comparisons of outcome measures at baseline

	Qigong	**Control**	t-test	*p-value*
MoCA	27.9±1.9	27.3±2.1	1.289	0.261
Attention network task				
Neutral RT	666.2±121.6	663.2±104.8	0.011	0.917
Congruent RT	657.4±122.5	659.7±119.9	0.006	0.939
Incongruent RT	802.5±132.0	798.0±132.2	0.019	0.892
N-back task				
0-back RT	521.4±75.4	539.9±74.2	0.995	0.322
2-back RT	699.4±118.2	705.0±167.4	0.025	0.876
N2 amplitude				
ANT-neutral	-0.90±0.26	-0.89±0.32	0.005	0.959
ANT-congruent	-0.41±0.34	-0.78±0.34	0.610	0.438
ANT-incongruent	-0.40±0.34	-0.60±0.36	0.136	0.713
0-back	-1.32±0.36	-1.20±0.51	0.040	0.843
2-back	-1.02±0.40	-1.05±0.38	0.003	0.955
P3 amplitude				
ANT-neutral	7.65±0.37	7.78±0.58	0.038	0.846
ANT-congruent	7.15±0.32	7.53±0.38	0.608	0.439
ANT-incongruent	5.98±0.41	6.18±0.49	0.101	0.752
0-back	4.42±0.47	4.85±0.52	0.376	0.542
2-back	4.03±0.50	4.10±0.53	0.012	0.914

Descriptive statistics are presented as mean±SD.
MoCA = Montreal Cognitive Assessment.
RT = reaction time (ms).

4.2 Cognitive and electrophysiological outcomes

Both within-group comparison of baseline and posttest in each group and between-group comparisons were conducted for the primary outcome, MoCA score, and secondary outcomes, including cognitive performance of ANT task and n-back task, N2 and P3 mean amplitudes. The summary statistics for the behavioral and electrophysiological measures are presented in **Table 4.3.**

4.2.1 Global cognitive function

Hypothesis 1 of the study was supported; for MoCA score, RM ANOVA found significant main effects of time (F = 10.014, p = 0.002, η_p^2 = 0.137) and group (F = 5.186, p = 0.026, η_p^2 = 0.076), and a significant time*group interaction (F = 4.313, p = **0.042**, η_p^2 = 0.064). There was a significant pre-to-post increase in MoCA score for the qigong group (p < 0.001), while no significant pre-post difference was found in the control group (p = 0.455). At post assessment, qigong intervention group also displayed significant better global cognitive function compared to the waitlist control group (p = 0.004).

Table 4.3 Outcome measures in the two groups

	Qigong	Control	Group effect			Time effect			Group*Time effect		
Measures	Mean±SD	Mean±SD	*F*	*p-value*	η_p^2	*F*	*p-value*	η_p^2	*F*	*p-value*	η_p^2
MoCA											
Post-assessment	29.0±1.3 [a]	27.5±2.4	5.186	0.026	0.076	10.014	0.002	0.137	4.313	**0.042**	0.064
Post-Pre difference	1.1±1.9 [b]	0.2±1.5									
Attention											
ANT-Neutral RT											
Post-assessment	600.9±104.3 [a]	652.5±79.2	1.101	0.298	0.017	10.923	0.002	0.148	5.609	**0.021**	0.082
Post-Pre difference	-65.3±109.0 [b]	-10.8±75.8									
ANT-Congruent RT											
Post-assessment	598.7±114.6 [a]	649.2±84.5	1.156	0.286	0.018	7.221	0.009	0.103	3.511	0.066	0.053
Post-Pre difference	-58.7±116.4 [b]	-10.5±94.7									
0-back RT											
Post-assessment	481.8±69.9 [a]	528.2±65.7	5.665	0.020	0.083	5.114	0.027	0.075	1.515	0.223	0.023
Post-Pre difference	-39.6±107.6 [b]	-11.7±84.2									
Inhibitory control											
ANT-Incongruent RT											
Post-assessment	716.0±124.7 [a]	777.9±108.4	1.096	0.299	0.017	13.545	<0.001	0.177	5.260	**0.025**	0.077
Post-Pre difference	-86.5±127.5 [b]	-20.1±114.5									

Working memory											
2-back RT											
Post-assessment	653.7±90.8	671.4±149.9	0.201	0.655	0.003	3.736	0.058	0.056	0.088	0.768	0.001
Post-Pre difference	-45.7±135.6	-33.6±199.9									
N2 amplitude											
ANT-Neutral											
Post-assessment	-1.82±0.45	-0.93±0.42	1.565	0.216	0.025	1.512	0.224	0.024	1.311	0.257	0.021
Post-Pre difference	-0.92±0.53	-0.33±0.57									
ANT-Congruent											
Post-assessment	-1.43±0.36 [a]	-0.95±0.38	0.020	0.888	0.001	2.951	0.091	0.046	1.517	0.223	0.024
Post-Pre difference	-1.03±0.47	-0.17±0.51									
ANT-Incongruent											
Post-assessment	-1.37±0.35	-0.44±0.45	0.979	0.326	0.016	1.157	0.286	0.019	2.256	0.138	0.036
Post-Pre difference	-0.96±0.51	-0.16±0.55									
0-back											
Post-assessment	-2.43±0.39	-1.43±0.55	1.513	0.223	0.024	2.291	0.135	0.036	0.983	0.325	0.016
Post-Pre difference	-1.12±0.06	-0.23±0.65									
2-back											
Post-assessment	-1.61±0.54	-0.84±0.45	0.666	0.418	0.011	0.171	0.680	0.003	0.775	0.382	0.013
Post-Pre difference	-0.59±0.62	0.21±0.67									

P3 amplitude											
ANT-neutral											
Post-assessment	9.64±0.44 [a]	8.16±0.41	2.131	0.150	0.034	7.151	0.010	0.105	3.293	0.075	0.051
Post-Pre difference	1.99±0.60 [b]	0.38±0.65									
ANT-congruent											
Post-assessment	9.19±0.38 [a]	7.89±0.50	1.207	0.276	0.019	10.483	0.002	0.147	5.105	**0.027**	0.077
Post-Pre difference	2.04±0.50 [b]	0.36±0.55									
ANT-incongruent											
Post-assessment	7.91±0.57 [a]	6.34±0.51	1.391	0.243	0.022	6.677	0.012	0.099	4.844	**0.032**	0.074
Post-Pre difference	1.93±0.55 [b]	0.16±0.59									
0-back											
Post-assessment	6.31±0.41	5.12±0.46	0.536	0.467	0.009	7.346	0.009	0.107	4.100	**0.047**	0.063
Post-Pre difference	1.89±0.54 [b]	0.27±0.59									
2-back											
Post-assessment	5.20±0.45	4.30±0.42	0.543	0.464	0.009	3.153	0.081	0.049	7.740	0.211	0.026
Post-Pre difference	1.17±0.52 [b]	0.20±0.57									

[a] Significant difference between groups at post-test, $p < 0.05$.
[b] Significant difference between post-test and pre-test, $p < 0.05$.
RT = reaction time (ms).

4.2.2 Cognitive performance

Attention.

Hypothesis 2a was partially supported by the results of reaction time in neutral condition. It was showed a significant main effect of time (F = 10.923, p = 0.002, η_p^2 = 0.148), with post-assessment revealing faster reaction time than baseline; while no effect of group (F = 1.101, p = 0.298, η_p^2 = 0.017) was found; importantly, a significant interaction (F = 5.609, p = **0.021**, η_p^2 = 0.082) was observed, with a drop in reaction time from baseline to post-assessment in the qigong intervention group (p < 0.001), while no changes in the control group (p = 0.520). Qigong intervention group also presented significant shorter reaction time compared to the waitlist control group at post-assessment (p = 0.030). For another two measures of attention, the results showed no significant interaction effect of group and time for the congruent condition (p = 0.066) and 0-back condition (p = 0.223).

Inhibitory control.

Hypothesis 2b was supported. For reaction time of incongruent condition, there was a significant effect of time (F = 13.545, p < 0.001, η_p^2 = 0.177), with post-assessment revealing faster reaction time than baseline; while no effect of group (F = 1.096, p = 0.299, η_p^2 = 0.017) was found; importantly, a significant interaction (F = 5.260, p = **0.025**, η_p^2 = 0.077) was observed, with a shorter reaction time from baseline to post-assessment in the qigong intervention group (p < 0.001), while no changes in the control group (p = 0.341). Qigong intervention group also presented significant shorter reaction time compared to the waitlist control group at post-assessment (p = 0.037).

Working memory.

Hypothesis 2c was not supported by the main analysis. For reaction time of 2-back condition, there was no significant interaction effect of group and time (p = 0.768).

4.2.3 Electrophysiological data

N2 mean amplitudes.

In the ANT task, the RM ANOVA for N2 amplitudes at Fz found no significant main effects of time, group, and time*group interaction for neutral (ps > 0.21), congruent (ps > 0.09) and incongruent (ps > 0.13) task conditions.

In the n-back task, the RM ANOVA for N2 at Fz found no significant main effects of time, group, and time*group interaction for 0-back (ps > 0.13) and 2-back (ps > 0.38) conditions.

P3 mean amplitudes.

For P3 amplitudes of neutral condition, a significant main effect of time (F = 7.151, p = 0.010, η_p^2 = 0.105) was presented, with significantly larger P3 amplitudes at post-test relative to pre-test; but no significant effect of group (p = 0.150) and interaction (p = 0.075) were found.

For P3 amplitudes of congruent condition, the RM ANOVA revealed a significant main effect of time (F = 10.483, p = 0.002, η_p^2 = 0.147), with significantly larger P3 amplitudes at post-assessment relative to baseline; while no significant effect of group (F = 1.207, p = 0.276, η_p^2 = 0.019) was found. Importantly, a significant interaction between time and group (F = 5.105, p = **0.027**, η_p^2 = 0.077) was observed, with increased amplitudes from baseline to post-assessment in the qigong group ($p < 0.001$), but no changes was found in the waitlist control (p = 0.508). The analysis also demonstrated greater P3 amplitudes in the qigong group than the control group at post-assessment (p = 0.040), but no between-group difference was observed at baseline (p =0.439).

For P3 amplitudes of incongruent condition, the RM ANOVA analysis showed a significant main effect of time (F = 6.677, p = 0.012, η_p^2 = 0.099), with significantly larger P3 amplitudes at post-assessment relative to baseline; no significant effect of group (F = 1.391, p = 0.243, η_p^2 = 0.022) was found. A significant time*group interaction (F = 4.844, p = **0.032**, η_p^2 = 0.074) were observed, with increased amplitudes from baseline to post-assessment in the qigong group (p = 0.001), but no difference was found in waitlist control (p = 0.795). Larger P3 amplitudes were observed in the qigong group than the control group at post-assessment (p = 0.048), while no between-group difference was found at baseline (p =0.752).

For P3 amplitudes of 0-back condition, analysis showed a significant main effect of time (F = 7.346, p = 0.009, η_p^2 = 0.107), with significantly larger P3 amplitudes at post-assessment relative to amplitudes at baseline; no significant effect of group (F = 0.536, p = 0.467, η_p^2 = 0.009) was found; and a significant interaction (F = 4.100, p = **0.047**, η_p^2 = 0.063) was observed, with increased pre- to post- amplitudes in the qigong group (p = 0.002), while no changes in the control group (p = 0.626).

For P3 amplitudes of 2-back condition, there was no significant effect of time, group and interaction between time and group (ps > 0.08) were observed.

To conclude, Hypothesis 3a was not supported, while Hypothesis 3b was partially supported by the results of congruent, incongruent, and 0-back task conditions (**Table 4.3**). Figure 4.2 depicts stimulus-locked grand average ERP waveforms at Fz and Pz for the ANT task and n-back task.

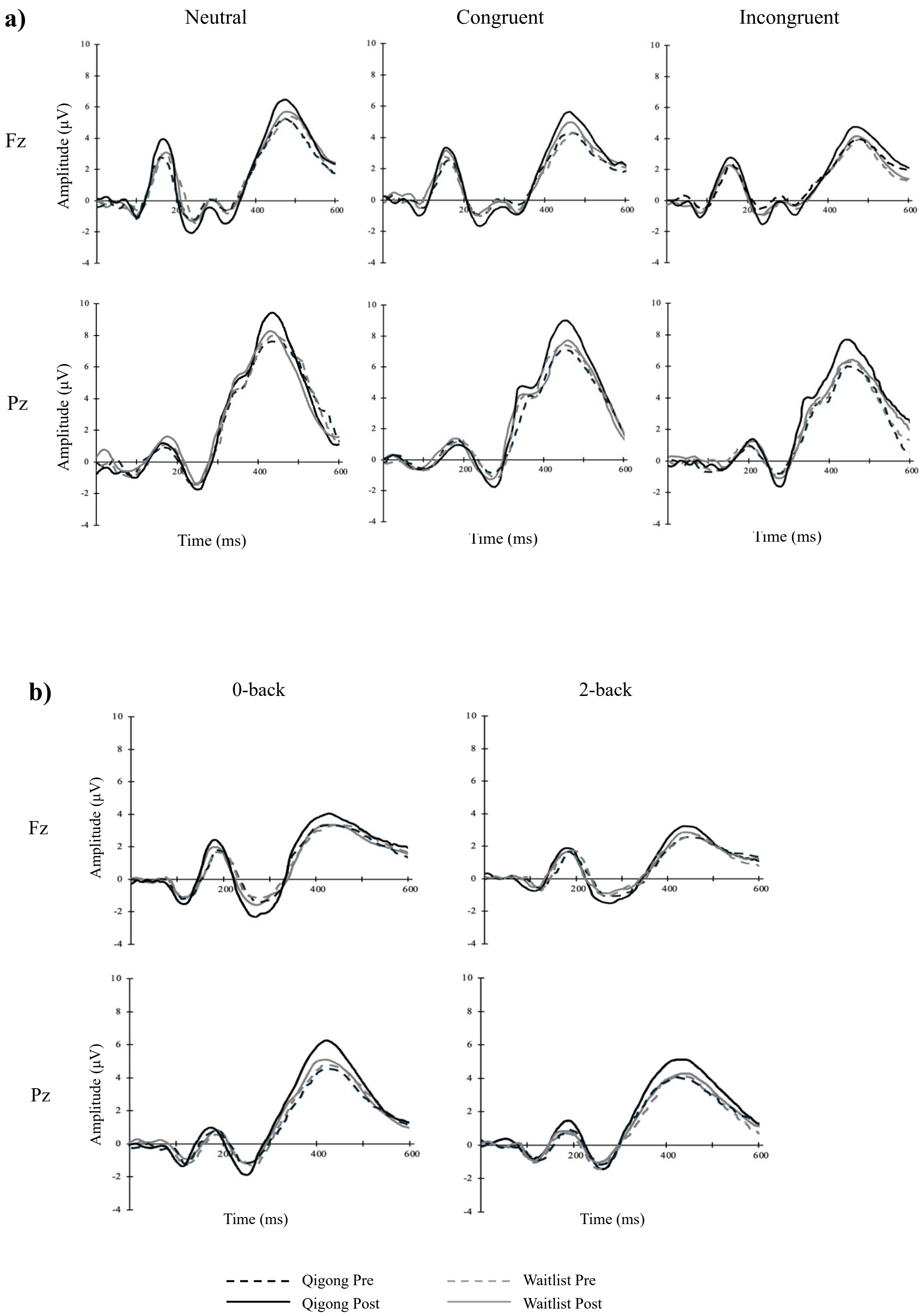


Figure 4.2 Grand average ERP waveforms of ANT task and n-back task

4.3 Cognitive performance and ERP amplitudes

Bivariate correlations were calculated to examine whether changes in cognitive performance were associated with enhanced neural responses. Hypothesis 4 was supported by the results. **Table 4.4** shows that changes in N2 amplitude was correlated with improvements in neutral, incongruent, and 2-back task conditions. The correlation between the changes in P3 amplitude and neutral, incongruent, 0-back, and 2-back task conditions were also significant. Thus, better cognitive performance was associated with larger N2 and P3 mean amplitudes, indicating a possible neurophysiological mechanism of improvement in specific cognitive domains, including attention, inhibitory control and working memory.

Table 4.4 Correlation between changes of cognitive performance and ERP amplitudes

	N2 amplitude	P3 amplitude
Neutral	-0.329*	0.387*
Congruent	-0.243	0.225
Incongruent	-0.303*	0.470*
0-back	-0.206	0.396*
2-back	-0.262*	0.297*

* $p < 0.05$

Exploratory mediation analysis was performed to explore the mediating effect of changes in P3 amplitude in the relationship between qigong intervention and cognitive improvement. Hypothesis 5 was supported as the results found that the indirect effect reached significance for cognitive performance of inhibitory control (**Figure 4.3**). In addition, when the mediating variable was controlled for, intervention showed no significant direct effect on cognitive performance, suggesting that enhanced P3 amplitudes could significantly mediate the relationship between qigong training and improved cognitive function at post-intervention.

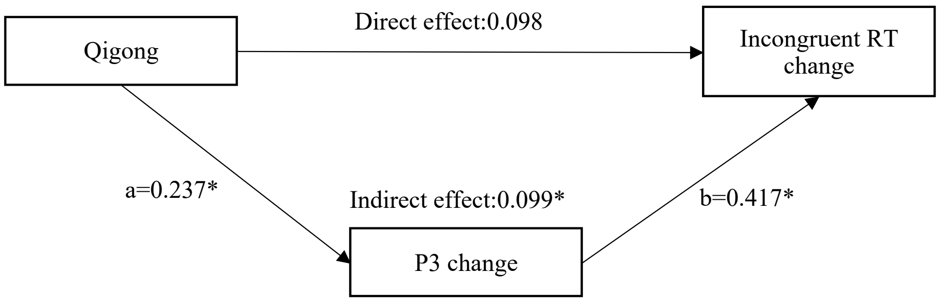


Figure 4.3 Mediation analysis diagram with standardized regression coefficients, * p<0.05

5.1 DISCUSSION

Qigong is a form of mind-body exercise involves interconnected physical movements, breathing techniques, and attention. Previous studies have documented beneficial effects of qigong on mental health and cognitive functions (Chan & Tsang, 2019; Wang et al., 2022). Nevertheless, further studies are needed to investigate the cognitive effects of qigong in older adults with depressive symptoms, where empirical evidence is scarce. In this pilot study, preliminary and pioneering results showed an improvement in global cognitive function observed at post-intervention following qigong intervention, which supported the primary hypothesis of the study. The secondary hypotheses are also partially supported. The study found enhanced attention, inhibitory control, and increased P3 amplitudes after qigong intervention. The results indicate that qigong may improve cognitive function through the enhanced neural responses. To our knowledge, this is also the first attempt to investigate changes in brain functioning by ERP components following Baduanjin practice and explore whether qigong improves cognitive function through mediating effect of brain functioning. The results have contributed to better understanding of qigong on cognitive functions of older adults with depressive symptoms in both the clinical effects and the underlying brain function.

5.1.1 Global cognitive function

The current results supported Hypothesis 1 that qigong training provided a significant positive effect on global cognitive function in older adults with depressive symptoms, in comparison with waitlist controls. It is important to note that further analysis showed that qigong might have provided positive impact in global cognitive function following 12 weeks of Baduanjin qigong intervention, while controls presented no difference from baseline to post-assessment.

As mentioned in the literature review chapter, there has been a lack of previous studies evaluating the cognitive effects of qigong in depressed individuals. We have performed a systematic review on non-pharmacological interventions for cognitive outcomes in depression (SR1). Although the meta-analytic results showed that mind-body exercise could benefit global cognitive function, the included studies in older adults with depression were only conducted with tai chi exercise. To date, no previous study has ever applied qigong as an intervention for their cognitive function. Our preliminary results have filled the research gap in this aspect. Baduanjin practice is composed of eight specific movements and is less complex than tai chi. As it engages the entire body, this exercise modality can be of low-to-moderate intensity. The simplicity of Baduanjin makes it more accessible and less challenging to older adults, which has the potential to lead to greater cognitive benefits as a result of more frequent and sustained participation (Song et al., 2022). For older adults with depressive symptoms, the simplicity of Baduanjin during the learning and practicing process might also contribute to maintaining and improving their self-efficacy (Tsang et al., 2006; Xiao et al., 2018), thereby further positively affects depressive and cognitive symptoms. Individuals with higher self-efficacy may engage in challenging tasks and persist longer, leading to better performance on cognitive assessments. Self-efficacy also contributes to better emotion regulation that helps mitigate the negative effects of stress on cognitive performance (Aggarwal et al., 2014).

Mind-body exercise has presented significant effects on global cognitive function among older adults with dementia (Yorozuya et al., 2019) and mild cognitive impairment (Xu et al., 2021), whereas non-significant changes were found in those with healthy cognition (Jin et al., 2020; Wu et al., 2019). Our results regarding global cognitive function are consistent with and have extended these findings to older adults with depressive symptoms, as they also often experience cognitive decline or at high risk of cognitive impairment. More important, the prevalence rates for older adults to have mild to moderate depressive symptoms have been remarkable. It was estimated that approximately 50% of older adults in Hong Kong presented depressive symptoms (Jin et al., 2022). Baseline cognitive function was found to moderate the effect of Baduanjin intervention on global cognitive function in this study, while education level showed no moderating effect.[^] Global cognitive function improved more for individuals with lower baseline cognitive function, whereas minimal improvement was found for those with better baseline cognitive function. It is possible to assume that mind-body exercise, such as qigong, has a greater sensitivity to benefit global cognitive function among cognitively impaired individuals than those with intact cognition. As a result, Baduanjin might be an ideal option for older adults suffering from depression to practice mind-body exercises for cognitive health.

It should be noted that the underlying mechanisms of qigong on cognitive functioning in older adults with depression are still under investigation. From a neurobiological perspective, the findings of our systematic review (SR2) suggested that mind-body exercise was likely to provide therapeutic effects through the regulation of the hypothalamic-pituitary-adrenal (HPA) axis activity, the enhancement of

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[^] Moderation analysis: baseline cognitive function (p<0.001); level of education (p=0.760) neurogenesis, modulation of immune system, and enhancement of brain activity. First, hyperactivity of the HPA axis is often observed in individuals with depression and leads to elevated cortisol levels, which can be neurotoxic and related to reduced neuroplasticity, leading to worse activity and structural changes in brain (Ouanes & Popp, 2019). There is evidence showing that qigong practice could decrease level of cortisol (Lu et al., 2020; Ponzio et al., 2015), which may be considered a possible mechanism for its cognitive benefits in depression. Second, increased level of brain-derived neurotrophic factor (BDNF) was found after mind-body practice in individuals with depressive symptoms (Lu et al., 2020; Tolahunase et al., 2018). As a neurotrophin, BDNF plays an important role for the health and function of neurons in the brain. It is involved in upregulation of neurogenesis, promotion of synapses in neurons, and improvement of neural structure, which are the basis of cognitive function and brain health (Gourgouvelis et al., 2017; Kellner et al., 2014; Knaepen et al., 2010). Therefore, it may be postulated as an important mechanism for the effects of qigong training. Third, mind-body exercise is likely to regulate immune system through the reduction of pro-inflammatory cytokines, such as the interleukin-6 (IL-6) (Ng et al., 2022; Nugent et al., 2019; Tolahunase et al., 2018). Elevated pro-inflammatory cytokines were found in depressed individuals and the overexpression of IL-6 was shown to be related to altered function of neurotransmitters, impaired synaptic plasticity and neurogenesis (Felger & Lotrich, 2013; McAfoose & Baune, 2009; Trapero & Cauli, 2014) that may impair cognitive function. Qigong exercise can help regulate inflammation through both physical and mental relaxation (Djalilova et al., 2019), thereby lead to improvements in cognitive health. Last but not least, depressed patients had abnormal activity in frontal and parietal brain regions which regulate cognition (Fitzgerald et al., 2008; Lin et al., 2021). It is worthwhile to test these pathways in future studies. However, more well-designed large-scale studies should be conducted to further evaluate the validity of the above neurophysiological mechanisms which provide scientific evidence for the therapeutic effects of qigong.

In summary, our systematic reviews (SR1 and SR2) demonstrated the promising, yet untested cognitive benefits of qigong for depressed older adults; our pilot RCT showed that qigong has a significant effect on global cognitive function in older adults with depressive symptoms, where significant improvement was observed after qigong training while no difference in the waitlist control group. This is the first study to investigate the effect of qigong on global cognitive functions in older adults with depressive symptoms, to our best knowledge. It significantly extended the knowledge and scientific evidence of the cognitive benefits of qigong in depressed older adults, and it supported qigong as a treatment option. The neurobiological mechanisms of such cognitive benefits may be multi-facet, and these are warranted to be examined in future studies for in-depth understanding.

5.1.2 Attention, inhibitory control, and working memory

Attention is a cognitive domain which compromised in depression and deteriorates prior to other functions (Braver & Barch, 2002; Saunders & Summers, 2011). This pilot study explored changes in attention of a 12-week Baduanjin qigong intervention compared to waitlist control in older adults with depressive symptoms. Hypothesis 2a was partially supported. It is showed that the qigong training significantly decreased response time of correct neutral trials which measures attention, compared to the controls. Further post-hoc analysis revealed that only those in the qigong intervention group displayed a significant faster response time at post-intervention than baseline. However, for another two measures of attention, congruent condition and 0-back condition, no significant changes were detected after the qigong intervention. The discrepancy in the results regarding attention might be due to the differences in difficulty of the tasks. Since the cognitive demands in the congruent and 0-back conditions are generally lower than neutral trials, the non-significant results may be attribute to the ceiling effect, where the baseline performance leaving little room for further notable improvement. Baduanjin mind-body training involves the awareness of and focus on breathing and movements, these practices can contribute to improved attention and concentration (Kozasa et al., 2012; Tang et al., 2007). It is possible that participants of qigong mind-body intervention attained a higher level of meta-awareness, which enabled them to release cognitive appraisals of irrelevant information thus enhance their attentional sustainability (Gothe et al., 2017). From a cognitive perspective, in addition to following the instruction to mirror the postures, this guided intervention requires participants to maintain an inner focus and proprioception during the qigong training, which might also explain its beneficial effects on attention in older adults with depressive symptoms.

Inhibitory control involves suppressing irrelevant information and inappropriate responses. This is a process of successfully guiding and managing basic cognitive functions and emotions (Gotlib & Joormann, 2010; Krompinger & Simons, 2011). Incongruent condition that requires upregulation of inhibitory control was used to evaluate individual's cognitive inhibition. This pilot study supported Hypothesis 2b that the 12-week qigong training significantly improved inhibitory control compared to the control group. Further post-hoc results showed that only the qigong group presented a significant faster reaction time of incongruent condition than baseline performance. Although a recent review revealed significant positive effects of Baduanjin on general executive functions (Lin et al., 2022), no research has further explored the possible benefits of Baduanjin in inhibitory control, a sublevel of executive function that may result in difficulties in filtering negative distractions and suppressing inappropriate emotional responses in depression. The positive effects of qigong intervention of our study have underscored the importance of beneficial effects of mind-body exercise on inhibitory control for older adults with depressive symptoms. The association between qigong practice with improvements in inhibitory control may be explained by several ways. Firstly, Baduanjin has been reported to enhance cardiopulmonary function through active and conscious regulation of breath frequency and depth (Panza et al., 2018). It was shown that the improvement of cardiopulmonary function was positively related to inhibitory control (Chang et al., 2015). Secondly, for accurate movements during practicing Baduanjin, it is essential for participants to maintain a calm state of mind and avoid distractions. This state might effectively mitigates anxiety, stress and depression, thus enhance inhibitory control performance in the frontal lobe (Wang & Lyu, 2024). In addition, it was proposed that physical exercise induces a highly neuroplastic environment that can amplify the impact of cognitive training on inhibitory control (Fabel et al., 2009; Raichlen & Alexander, 2017). Their findings suggest that intervention protocols that include both physical and cognitive components are highly effective in improving inhibitory control.

The results of the pilot study suggest that qigong did not produce direct beneficial effects on working memory, where Hypothesis 2c was not supported. There has been very limited research effort to examine whether mind-body exercise can improve working memory in depressed populations (Yeung et al., 2018a); and the existing evidence is still limited and insufficient to draw any conclusions on this. The non-significant findings in terms of working memory might have explained by the characteristics of participants and nature of the intervention. Importantly, the Baduanjin intervention of this study might not involve sufficient working memory training for generating significant effects. The participants were instructed to learn and practice qigong through a slow progression which only required them to follow the verbal instructions and visual demonstrations with low demand for working memory. For self-practice after intervention sessions, they were encouraged to select and perform any movements based on self-preference for promoting more practice. Therefore, the intervention might not challenge the brain to engage and enhance working memory. Moreover, as a secondary outcome, this pilot study might have limited power to detect changes in working memory. The findings suggest that future Baduanjin studies should consider involving an intervention protocol with more processes to train working memory, such as performing movements selectively rather than following the standard sequence and comparing different movements. This more demanding practice protocol may make a difference to the effect on working memory of the participants. Further studies along this line are needed.

From a neurophysiological perspective, qigong might be associated with brain changes that related to attention and executive functions. According to fMRI studies, although the evidence is limited, mind-body exercise was suggested to regulate activation patterns in various brain regions, including frontal and parietal areas, enhance frontoparietal functional connections, and increase cortical thickness and gray matter volume of brain, which play a critical role in cognitive functions (Han et al., 2023; Henz & Schöllhorn, 2017; Pan et al., 2018). The findings indicated that qigong mind-body practice has the potential to improve cognitive function through changes of brain activities; however, according to our systematic review (SR2), no previous study has investigated effects of qigong on cognitive and brain functioning in depressed population. Hence, to provide a better understanding of the therapeutic effects of qigong, this study has further explored changes in brain activity by ERPs and possible relationship between improvements in cognition and brain function after the Baduanjin training (Section 5.1.3).

In summary, the current pilot study showed that the Baduanjin qigong exercise had beneficial effects on global cognitive function and cognitive subdomains, including attention and inhibitory control. Qigong exercise may induce positive impacts on these behavioural performances through incorporating physical movements with breathing control and mindfulness techniques. The benefits of qigong mind-body exercise on cognitive function might be attributed to adaptive behavioral activation, acquisition of psychological techniques, such as relaxation, perseverance, and mindfulness. However, current empirical evidence of neurobiological changes in individuals with depressive symptoms after qigong exercise is still limited and more studies are warranted.

5.1.3 ERPs and the relationship with cognitive function

The present study has broadened the behavioral findings by exploring the possible cognitive processes affected by qigong practice via the investigation of brain activities using ERP. The current pilot study explored the effect of qigong on N2 component since it was yet to be examined previously. The results of our study indicate that qigong exercise might have little influence on N2 component, where Hypothesis 3a was not supported. The first explanation of this results might be the improved efficiency to use neural resources when performing cognitive tasks. The findings of better cognitive performance but less changes in N2 amplitude may imply a training-induced improvement in neural efficiency for different task demands in participants after the intervention. As supported by pervious fMRI and ERP studies, it is possible that participants were able to perform better (shorter reaction time) in cognitive tasks without involving more energy (brain activity) after the learning effects resulting from the intervention (Nishiguchi, Yamada, Tanigawa, Sekiyama, Kawagoe, Suzuki, Yoshikawa, Abe, Otsuka, & Nakai, 2015; Zhang et al., 2024). Furthermore, as N2 amplitude is suggested to reflect the detection of response conflict or the upregulation of cognitive control during early stages of response inhibition, it is possible that qigong exercise likely affects attention at later stages of the cognitive processing that are represented by changes in P3 instead of N2 (Tillman & Wiens, 2011; Van Veen & Carter, 2002). It should be noted that only limited research of physical exercise has investigated changes in N2 component, and current evidence is mixed (Chang et al., 2017; Drollette et al., 2014; Themanson & Hillman, 2006). Various factors might contribute to the ambiguous findings, including participant characteristics, task designs, and exercise protocols among different studies. As it is the first study to explore the cognitive dynamics using ERP components in qigong mind-body exercise, more research is required to further test our findings.

The P3 component has been proposed as a neural index to reflect the allocation of attentional resources and processing capacity (Gao et al., 2013). When stronger attentional focus on a particular stimulus, amplitudes in P3 increased. In spite of the fact that we are still unable to precisely determine the meaning and source location of P3, it provides an indication of the response speed and accuracy of a given task regardless of behavioral action (Polich, 2007; Verleger, 1997). Along with positive changes in cognitive performance, we found that qigong group revealed significant larger P3 amplitudes after intervention than at baseline, regardless of the task condition, thereby Hypothesis 3b was supported. Our results suggests that qigong can improve behavioral performance on different cognitive demanding tasks (i.e. flanker neutral and incongruent conditions) by increasing more attentional and neural resource allocation.

It has been shown that older adults practicing tai chi had a larger P3 amplitudes in a task-switching task measuring executive functions (Fong et al., 2014). Similarly, our study observed enhancement in P3 amplitudes for the flanker congruent and incongruent conditions, and 0-back condition, indicating that qigong exercise may help engage more attentional resource allocation processes and information categorization in tasks related to both basic information processing and response inhibition. Collectively, qigong exercise appears to be associated with general cognitive enhancement based on both neuroelectric and behavioral evidence. The effects might be explained by physical exercise and mindfulness elements of mind-body exercise. First, the successive body movements can enhance respiratory activity of the participants (Kim et al., 2015), and derive improvement of cardiovascular function and increase blood flow in the brain leading to improvement in cognitive function or prevention in cognitive decline (Hall et al., 2001). Second, during practicing qigong, mindfulness involves maintaining focus on a selected object (i.e. breathing and movements) and disengaging from distractions (Lutz et al., 2009). There has been evidence suggesting that mindfulness induces significant changes in autonomic nervous system regulation, including respiration and heart rate (Iversen et al., 2000), along with alterations of the central autonomic network (EE, 1997). Moreover, mindfulness practice was found to increase the volume of the hippocampus (Hölzel et al., 2011) and modulate parietal and prefrontal structures (Dickenson et al., 2013). Therefore, it is helpful for older adults with depressive symptoms to practice qigong regularly for improving physical, mental and cognitive health and leading a better overall quality of life.

Furthermore, the findings from the exploratory correlation and mediation analysis suggest that changes in P3 amplitude may be a mediating variable of the association between qigong training with improved cognitive performance related to inhibitory control at post-intervention. The results indicate qigong is possible to improve cognitive function through enhancing brain functioning. Hypotheses 4-5 were partially supported by the results. Nevertheless, the definitive conclusion on the mediated effect cannot be drawn due to the relatively small sample size. As suggested by Fritz and MacKinnon, a minimum sample size of 179 is required for 0.8 power to detect an effect in the current mediation model (Fritz & Mackinnon, 2007). Thus, the findings regarding mediation analysis should be interpreted with caution and future fully powered studies with adequate sample size are needed to test the possible neurophysiological mechanisms of qigong exercise. Furthermore, in this study, no significant mediating effect was found for MoCA score, the measurement of global cognitive function. As MoCA also assesses other cognitive domains, such as memory, language, visuospatial and orientation, qigong may have effects on these domains and lead to improvement in overall cognitive function. However, the neurophysiological changes related to other cognitive domains were not measured directly in this study, thus the improvements in other cognitive domains were not reflected in our ERP data. In addition, other mechanisms have been proposed for the therapeutic effects of qigong, including changes in neuroendocrine, neurotransmission, neurogenesis, inflammation, and brain structure. It is possible that qigong provides cognitive effects through these pathways which were not able to be fully explained by neurophysiological results of the current study.

5.2 Implications and recommendations

5.2.1 Research

Cognitive dysfunction is frequently complicated in depression and usually persists during the course of antidepressant treatment of depression (Bhalla et al., 2006) (Gallagher et al., 2013). Cognitive impairment is closely related to long-term functional outcomes and resistance to antidepressant therapy (McIntyre et al., 2013; Pimontel et al., 2012). Depressive symptoms are linked to increased risk of cognitive decline (Köhler et al. 2010). It was estimated that late-life depression increases approximately two-fold the risk of developing dementia (Diniz et al., 2013). Cognitive impairment may reduce the ability of daily functioning, which in turn increases stress and helplessness feeling, potentially worsening depressive symptoms and leading to dementia (Aziz & Steffens, 2017). Therefore, it is informed that more integrated treatment strategies are needed to address both mental health and cognitive function simultaneously. Research has documented that mind-body exercise could benefit global cognition, cognitive flexibility, working memory, verbal fluency and learning in cognitively impaired older adults (Wu et al., 2019). Our systematic review and meta-analysis (SR1) of existing RCTs found that in addition to improving global cognitive function, mind-body exercise also produced positive effects on attention and executive functions in older adults with depressive symptoms. However, most of the mind-body exercise studies conducted among the depressed population mainly focused on the anti-depressive effects, while cognitive function was typically considered as a secondary outcome or neglected. Research in this aspect remains therefore at an early stage. To our knowledge, our main study is a pioneering attempt to examine the effects of qigong in improving cognitive functions in older adults with depressive symptoms, who are often complicated by or vulnerable to cognitive impairment. The results of the current pilot study have supported the effects of qigong mind-body exercise in improving global cognitive function and some specific cognitive domains, including attention and inhibitory control in older adults with depressive symptoms. Given the limited studies and insufficient data published so far, conclusions on the effect of mind-body exercise on cognitive function in depression cannot be validly confirmed. However, our pioneering results have provided the foundation for further studies to explore this in the future.

It has been reported that cognitive impairment is associated with structural and neuroelectric abnormalities of the brain (Driscoll et al., 2003; Sun et al., 2014). Research has suggested that mind-body exercise might benefit cognition for older adults by the enhancement of functional connectivity among various brain areas, regulation of the activation in prefrontal cortex and hippocampus, and alternation of brain ERPs (Wang et al., 2023). This pilot study adds to the existing evidence that qigong mind-body practice might enhance the brain activity related to cognitive process. This is demonstrated by the increased P3 amplitudes in the qigong intervention group. The effects of mind-body exercise on brain function were mostly studied in older adults with MCI or dementia and using tai chi as intervention. Our study expands the existing literature by using qigong, a more suitable mind-body exercise for vulnerable older adults, as intervention, and older adults with depressive symptoms as the study population. This study supported that qigong is promising in improving brain activity and therefore benefits cognitive function. Future research should be conducted to examine long-term effect of qigong on cognitive function in depressed population.

From a neurobiological perspective, several plausible molecular and cellular pathways have been proposed to provide explanations on how mind-body exercise influences the changes in brain structure and activity. Researchers have suggested that alterations in neuroendocrine (cortisol), neurotransmitters including norepinephrine, serotonin and dopamine, proinflammatory cytokines, and molecular systems including brain-derived neurotrophic (BDNF) and insulin-like growth factors (IGF-1), might be the neurobiological mechanisms underlying the exercise-induced cognitive effects (Erickson & Liu-Ambrose, 2016). The SR2 revealed that mind-body exercise might reduce levels of cortisol and IL-6 and increase level of BDNF, which may be potential mechanisms of therapeutic effects of qigong. Lowered cortisol level was linked to alleviated stress-induced neuron damage and enhanced prefrontal cortex activity (Abdanipour et al., 2015; Knezevic et al., 2023; Wheelock et al., 2016). IL-6 and CRP were found to mitigate neuroinflammation and enhance neuronal plasticity (Levin & Godukhin, 2017; Yirmiya & Goshen, 2011). Studies showed that BDNF could enhance the survival and integration of new neurons (Cunha et al., 2010; Pisani et al., 2023). Nevertheless, the current evidence regarding the possible mechanisms of the beneficial antidepressant and cognitive effects of qigong is still lacking. It is therefore recommended that future research investigate how qigong impacts neurotrophic factors, neuroendocrine and inflammation markers in order to determine the connection between these changes and cognitive enhancements. Moreover, a further exploration of qigong-related brain changes using more advanced neuroimaging techniques such as fMRI and fNIRS is warranted, given the strength of associations observed within the expected direction, and more work of mechanisms is necessary to further our understanding of the therapeutic application of qigong as an intervention in depressed population.

5.2.2 Clinical practice

The current study provides further evidence that qigong exercise is a promising option to benefit both mental health and cognitive health for older adults. It has become increasingly evident that cognitive decline exacerbates psychosocial deficits, occupational function, interpersonal relationships and daily activity, resulting in a reduction in overall quality of life and increase in burden of illness (Cambridge et al., 2018; Evans et al., 2014). It is therefore possible that improvement of the underlying cognitive function may alter the course of depression and contribute to improved functional outcomes. Since older adults with depressive symptoms usually experience or are at risk of cognitive dysfunction, it is meaningful to identify and elucidate that qigong exercise is effective in both depressive symptoms and cognitive function. From our results, health professionals can recommend older adults with depressive symptoms to practice qigong as an evidence-based option in order to prevent cognitive impairment or improve cognitive performance of global cognition, attention, and inhibitory control. By developing a regular practice habit, they may benefit mentally and cognitively in the long run.

Among all the major types of exercise, Baduanjin qigong is likely to be more suitable overall for promoting health in older adults, particularly for those with depressive symptoms. In addition to its beneficial effects demonstrated in this study, there were no adverse event reported which supports that Baduanjin is safe for older adults to practice regularly. Further, it was observed that subjects participated qigong training were able to practice and memorize all the movements of Baduanjin accurately, which suggests that older adults can perform and learn Baduanjin. By practicing the simple movements of Baduanjin, it is possible that participants may be more confident in making greater efforts, which will result in improvements of health-related outcomes.

Moreover, it has been reported that the dropout rate for physical activity intervention in patients with depression is approximately 30% (Mura et al., 2014), and older adults usually have chronic diseases and therefore typically show a lower tolerance to high-intensity exercise. However, in our study, the dropout rate was 8.8% in the qigong group which indicating a great acceptability of the intervention in the study population. Collectively, our study showed that Baduanjin qigong may be a generally well-tolerated exercise modality for assisting health professionals to treat disease-related symptoms in older adults. In community settings such as the Old Age Homes and District Health Centres, more regular qigong programs can be developed and offered to older adults to promote benefits of qigong for health. Note again that this is safe, cost-effective, and can be practiced with minimal support from health professionals. Similarly, it is also suggested that health professionals such as occupational therapists and nurses should be trained in qigong, so that they can incorporate qigong practices into existing therapeutic regimens for older adults with depression in hospital settings where the patients may have more medical complications, offering a holistic approach to patient care.

5.3 Limitations of the study

First, the sample size of the current pilot study was modest. Meanwhile, it brings an advantage that enabled a more supportive and focused intervention process for the participants, which might strengthen the effects on cognitive and neurobiological outcomes. However, since the sample size of current study may not be sufficient, fully powered future studies are needed to confirm our findings on secondary outcomes and mediating effects.

Second, the participants were recruited from community settings, and their depressive and/or cognitive symptoms were generally mild. It is therefore reasonable that cognitive improvement was small in this study as the participants were slightly impaired in their cognitive ability. Besides, it should also be noted that the self-rating of depression adopted in this study lacks diagnostic precision. Future research should combine self-reports with clinician-rated tools to achieve more reliable assessment. In addition, it is uncertain whether our findings can be generalized to other older adults with moderate to severe depressive symptoms and cognitive issues. Further studies may consider including a sample with diagnosed depression and cognitive impairment to further test and extend the current findings.

Third, this study aimed to examine the cognitive effects of qigong specifically compared to a waitlist control with no intervention. The non-active control may induce potential bias: 1) As the waitlist group did not account for other effects such as social interaction or attention from researchers, and observed benefits might partially from these factors; 2) The results only reflect intervention efficacy compared with no treatment instead of other interventions, thus limiting the generalizability of the findings. Therefore, the effectiveness of qigong could be further examined in future studies in comparison with other interventions, such as physical exercise and mindfulness.

Forth, the missing data were handled by last observation carried forward method, which might underestimate the variability of the data and lead to potential bias. Future research should consider more advanced statistical techniques, such as multiple imputation and mixed models, for managing missing data to provide more reliable and less biased results.

Last but not least, as no comprehensive neurocognitive test was included in this study, it is unable to confirm that qigong is beneficial to all the cognitive domains. Nonetheless, the cognitive domains that we measured, namely attention, working memory, and inhibitory control, were considered closely related to and the fundamentals of other cognitive functions and particularly important in depression. In future research, a full set of cognitive tests may be included with a longer follow-up period to corroborate and extend the findings of qigong on cognitive function.

Chapter 6: Conclusion

Depression is the most prevalent mental health problem that significantly affects approximately 30% of older population. These older adults often experience or are at high risk of cognitive impairment which may further worse daily functioning. Qigong, a Chinese traditional mind-body exercise, is commonly accepted and practiced among older adults. As a simple form of qigong that integrates both physical and mental elements, Baduanjin has been hypothesized to be a potentially promising intervention for alleviating depressive and cognitive symptoms in depression. Yet, the current evidence regarding its cognitive benefits in older adults with depressive symptoms is still limited and mixed. Moreover, the neuropsychological effects of Baduanjin practice remain unclear.

The results of our study support the main hypothesis that the 12-week Baduanjin qigong intervention is effective in improving global cognitive function in older adults with depressive symptoms compared to waitlist control. The results also partially support the secondary hypotheses. In particular, this pilot study suggests better cognitive performance in attention and inhibitory control after Baduanjin training. Nevertheless, no significant changes in working memory were observed among older adults of the Baduanjin training group. Furthermore, this study shows increased P3 amplitudes for multiple cognitive function domains at post-intervention than baseline. Finally, the results indicate that P3 amplitudes might mediate the relationship between Baduanjin practice and improvement in cognitive function. This pilot study provides feasible and efficacious data for the cognitive effects of qigong exercise. Our findings suggest that qigong is a safe and suitable intervention for older adults with depressive symptoms to helps in mood regulation, cognitive and brain function improvement.

Since the findings regarding secondary outcomes are exploratory and suggestive, further investigation is required in future studies.

Overarching conclusions from the thesis highlight the widespread utility of qigong training for benefiting cognitive function in depression. Therefore, in response to the growing demand for non-pharmacological treatments, we recommend qigong as an intervention or adjunctive therapy to help older adults with depressive symptoms achieve psychological and cognitive well-being. Besides, the beneficial effects of qigong in depression may involve multiple pathways. Further research efforts using more sophisticated research designs and more advanced neuroimaging techniques with larger sample size are warranted to determine the therapeutic effects and underlying neurophysiological mechanisms of qigong in reducing depressive symptoms and enhancing cognitive function.

Appendix A: Geriatric Depression Scale (GDS)

老人抑鬱評估表 (GDS)

請回想在**過去一星期內**，曾否有以下感受，若有請選是，沒有則選否。

項目	**是**	**否**
1.你基本上對自己的生活感到滿意嗎?	☐	○
2.你是否己放棄了很多以往的活動和嗜好?	○	☐
3.你是否覺得生活空虛?	○	☐
4.你是否常常感到煩悶?	○	☐
5.你是否常常感到心情愉快呢?	☐	○
6.你是否害怕將會有不好的事情發生在你身上呢?	○	☐
7.你是否大部份時間感到快樂呢?	☐	○
8.你是否常常感到無助? (即是沒有人能幫自己)	○	☐
9.你是否寧願晚上留在家，而不愛出外做些有新意的事情? (譬如:去海洋公園或大會堂看表演)	○	☐
10.你是否覺得你比大多數人有多些記憶的問題呢?	○	☐
11.你認為現在活著是一件好事嗎?	☐	○
12.你是否覺得自己現在是一無是處呢?	○	☐
13.你是否感到精力充足?	☐	○
14.你是否覺得自己的處境無望?	○	☐
15.你覺得大部份人的境況比自己好嗎?	○	☐

Appendix B: Depression, Anxiety and Stress Scale (DASS-21)

Chinese DASS21 情緒自評量表（一）

DASS21

姓名：

日期：

填表說明：

請小心閱讀以下每一個句子，並在其右方圈上一數字，表示「過往一個星期」如何適用於你。答案並無對錯之分。請不要花太多時間在某一句子上。

評估量表：

0＝不適用
1＝頗適用，或間中適用
2＝很適用，或經常適用
3＝最適用，或常常適用

1	我覺得很難讓自己安靜下來	0	1	2	3
2	我感到口乾	0	1	2	3
3	我好像不能再有任何愉快、舒暢的感覺	0	1	2	3
4	我感到呼吸困難（例如不是做運動時也感到氣促或透不過氣來）	0	1	2	3
5	我感到很難自動去開始工作	0	1	2	3
6	我對事情往往作出過敏反應	0	1	2	3
7	我感到顫抖（例如手震）	0	1	2	3
8	我覺得自己消耗很多精神	0	1	2	3
9	我憂慮一些令自己恐慌或出醜的場合	0	1	2	3
10	我覺得自己對將來沒有甚麼可盼望	0	1	2	3
11	我感到忐忑不安	0	1	2	3
12	我感到很難放鬆自己	0	1	2	3
13	我感到憂鬱沮喪	0	1	2	3
14	我無法容忍任何阻礙我繼續工作的事情	0	1	2	3
15	我感到快要恐慌了	0	1	2	3
16	我對任何事也不能熱衷	0	1	2	3
17	我覺得自己不怎麼配做人	0	1	2	3
18	我發覺自己很容易被觸怒	0	1	2	3
19	我察覺自己在沒有明顯的體力勞動時，也感到心律不正常	0	1	2	3
20	我無緣無故地感到害怕	0	1	2	3
21	我感到生命毫無意義	0	1	2	3

Appendix C: Physical Activity Readiness Questionnaire (PAR-Q)

體能活動適應
能力問卷 —PAR-Q
(修訂版—2017 年 9 月)

體能活動適應能力問卷與你
(一份適用於 15 至 69 歲人士的問卷)

經常進行體能活動不但有益身心，而且樂趣無窮，因此，愈來愈多人開始每天多做運動。對大部分人來說，多做運動是很安全的。不過，有些人則應在增加運動量前，先行徵詢醫生的意見。

如果你計劃增加運動量，請先回答下列 7 條問題。如果你介乎 15 至 69 歲之間，這份體能活動適應能力問卷會告訴你應否在開始前諮詢醫生。如果你超過 69 歲及沒有經常運動，請徵詢醫生的意見。

普通常識是回答這些問題的最佳指引。請仔細閱讀下列問題，然後誠實回答：

請答「是」或「否」

是	否	
☐	☐	1. 醫生曾否說過你的心臟有問題，以及只可進行醫生建議的體能活動？
☐	☐	2. 你進行體能活動時會否感到胸口痛？
☐	☐	3. 過去一個月內，你曾否在沒有進行體能活動時也感到胸口痛？
☐	☐	4. 你曾否因感到暈眩而失去平衡，或曾否失去知覺？
☐	☐	5. 你的骨骼或關節(例如脊骨、膝蓋或髖關節)是否有毛病，且會因改變體能活動而惡化？
☐	☐	6. 醫生現時是否有開血壓或心臟藥物（例如 water pills）給你服用？
☐	☐	7. 是否有其他理由令你不應進行體能活動？

如果你的答案是：

一條或以上答「是」

在開始增加運動量或進行體能評估前，請先致電或親身與醫生商談，告知醫生這份問卷，以及你回答「是」的問題。

- 你可以進行任何活動，但須在開始時慢慢進行，然後逐漸增加活動量；又或你只可進行一些安全的活動。告訴醫生你希望參加的活動及聽從他的意見。
- 找出一些安全及有益健康的社區活動。

全部答「否」

如果你對這份問卷的全部問題誠實地答「否」，你有理由確信你可以：

- 開始增加運動量——開始時慢慢進行，然後逐漸增加，這是最安全和最容易的方法。
- 參加體能評估——這是一種確定你基本體能的好方法，以便你擬定最佳的運動計劃。此外，亦主張你量度血壓；如果讀數超過 144/94，請先徵詢醫生的意見，然後才逐漸增加運動量。

→ **延遲增加運動量：**

- 如果你因傷風或發燒等暫時性疾病而感到不適——請在康復後才增加運動量；或
- 如果你懷孕或可能懷孕——請先徵詢醫生的意見，然後才決定是否增加運動量。

請注意：如因健康狀況轉變，致使你隨後須回答「是」的話，便應告知醫生或健身教練，看看應否更改你的體能活動計劃。

不得更改問卷內容。歡迎複印整份問卷(必須整份填寫)

體能活動適應能力問卷來源：The Canadian Society for Exercise Physiology

本人已閱悉、明白並填妥本問卷。本人的問題亦已得到圓滿解答。

姓名:______________________ 身分證明文件號碼:______________________
簽署:______________________ 日期:______________________
家長或監護人簽署:______________________ 見證人:______________________
（適用於 18 歲以下的參加者）

備註：1. 你提供的資料，只作處理租訂康樂及文化事務署健身室設施或康體活動報名事宜之用，本署授權人員基於上述目的方可查閱。遞交問卷後，如欲更正或查詢個人資料，請與接受報名的分區櫃檯職員聯絡。

2. 如果在上述問卷中有一個或以上「是」的答案，即表示你的身體狀況可能不適合參與有關活動。故為安全起見，請你先行諮詢醫生的意見；並須在報名或租訂健身室設施時出示醫生紙，證明你的身體狀況適宜參與有關活動。如未能出示醫生紙，則須填妥「申請人聲明」，並於報名或租訂健身室設施時連同報名表一併遞交。

3. 如你拒絕填寫此問卷，有關的健體活動報名或租訂健身室設施申請將不獲受理。此問卷由填寫當日起計一年內有效；如在一年有效期後，健身室使用者須再次填寫此問卷。

如因健康狀況轉變，致使你隨後對上述的任何問題的回答轉為「是」的話，則本問卷即告無效。

Appendix D: Health declaration form for participants aged 70 or above

<u>年滿 70 歲或以上的申請人須填寫以下聲明</u>

聲明（請在下列其中一個方格內加上「✓」號）

本人謹此聲明：

☐ 1. 本人經常參加體能活動，並且有能力參加這項活動，因此無須出示醫生證明書證明本人有能力參加這項活動。本人明白如對本身能力有任何懷疑，應在參加活動前，徵詢醫生的意見。

☐ 2. 本人並非經常參加體能活動，但經醫生檢查後，證明健康良好，適宜參加這項活動。現附上醫生證明書，以供參考。

申請人簽署 : ______________________

申請人姓名(正楷) : ______________________

日期 : ______________________

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