

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

Wen Sun^a, Erin Yiqing Lu^a, Cong Wang^a, Hector Wing Hong Tsang^{a,b,*}

^a Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China

^b Mental Health Research Centre, The Hong Kong Polytechnic University, Hong Kong SAR, China

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ABSTRACT

Background: Studies have shown that both mind-body and physical exercises are effective in reducing depressive symptoms. However, the pooled evidence on neurobiological mechanisms underlying the antidepressant effect of exercise has 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.

Methods: We followed PRISMA guidelines and searched databases for relevant randomized controlled trials published up to September 12, 2022. Studies that investigated the neurobiological mechanisms of exercise interventions on depressive symptoms were included.

Results: Thirty-two articles were included for review, representing a total sample of 1,820 individuals with depressive symptoms. Our findings demonstrated that cortisol and BDNF were the common potential mediator underlying the antidepressant effects of both mind-body and physical exercises. Additionally, mind-body exercise was shown to decrease IL-6, while physical exercise was found to improve VO₂max/peak, which might also shed light on the linkage between 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. Other neurobiological mechanisms remain inconclusive due to the limited number of studies and research quality.

Conclusions: Exercises were likely to alleviate depressive symptoms through regulation of HPA axis activity, enhancement of neurogenesis, reduction of pro-inflammatory cytokines and improvement of cardiorespiratory fitness. More high-quality studies on the neurobiological responses to mind-body or physical exercises are warranted for a more comprehensive understanding of their antidepressant effects.

1. Introduction

Depression is the most common psychological disorder and a major contributor to the overall global burden of illness (Liu 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, 2021). 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 (WHO) 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, such as yoga, tai chi, and qigong, has received

* Corresponding author. Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, China.

E-mail address: hector.tsang@polyu.edu.hk (H.W.H. Tsang).

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recent attention in the scientific literature and has been shown to be effective in treating depression (Bo et al., 2017; Tsang et al., 2008; Weber et al., 2020; Zou et al., 2018). There is no universal consensus on the definition of mind-body exercise, which has also been grouped under other labels such as mindful exercise (La Forge, 2016), holistic movement practices (Taylor et al., 2021; Vergeer & Biddle, 2021), meditative movement (Larkey et al., 2009), and movement-based embodied contemplation (Schmalzl et al., 2014). However, it can generally be 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 practices that emphasize non-competitive, present-moment, and nonjudgmental introspection (Hempel et al., 2014; Kabat-Zinn, 2003; Khanna & Greeson, 2013; Yeung et al., 2018). 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 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., 2018). This present-focused sensory awareness is consistent with the Buddhist philosophy of mindfulness meditation (Kabat-Zinn, 2003). Meanwhile, in this paper we refer to physical exercise as more conventional body activities without the emphasis on mental engagement, such as aerobic exercise, resistance exercise, and stretching. According to the evidence from recent reviews of randomized controlled trials (RCTs), physical exercise has been shown to be effective in the prevention and treatment of depression (Hu et al., 2020; Smith & Merwin, 2021; Stubbs & Schuch, 2019). Another network meta-analysis compared the effects of aerobic, resistance, and mind-body exercises in elders with clinical depression, with a total of 15 RCTs, and found that all three kinds of exercises had favorable 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 conventional 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 associated 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 antidepressant 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 antidepressant effects 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. 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).

2.1. 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 Table S1. In addition, the reference list of each of the included studies was checked to identify additional relevant studies.

2.2. 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.

2.3. 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.

2.4. 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.

2.5. 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. A 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 effects 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 five studies were needed for random-effect meta-analysis with satisfactory statistical power (Jackson & Turner, 2017). Similarly, subgroup analysis on neurobiological outcomes will be performed comparing the effects of mind-body exercise and physical exercise if there were five 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. The statistical analysis was conducted using Stata version 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Study selection and characteristics

Fig. 1 describes in detail the selection process of the systematic review. A total of 3,365 studies were initially identified from the five

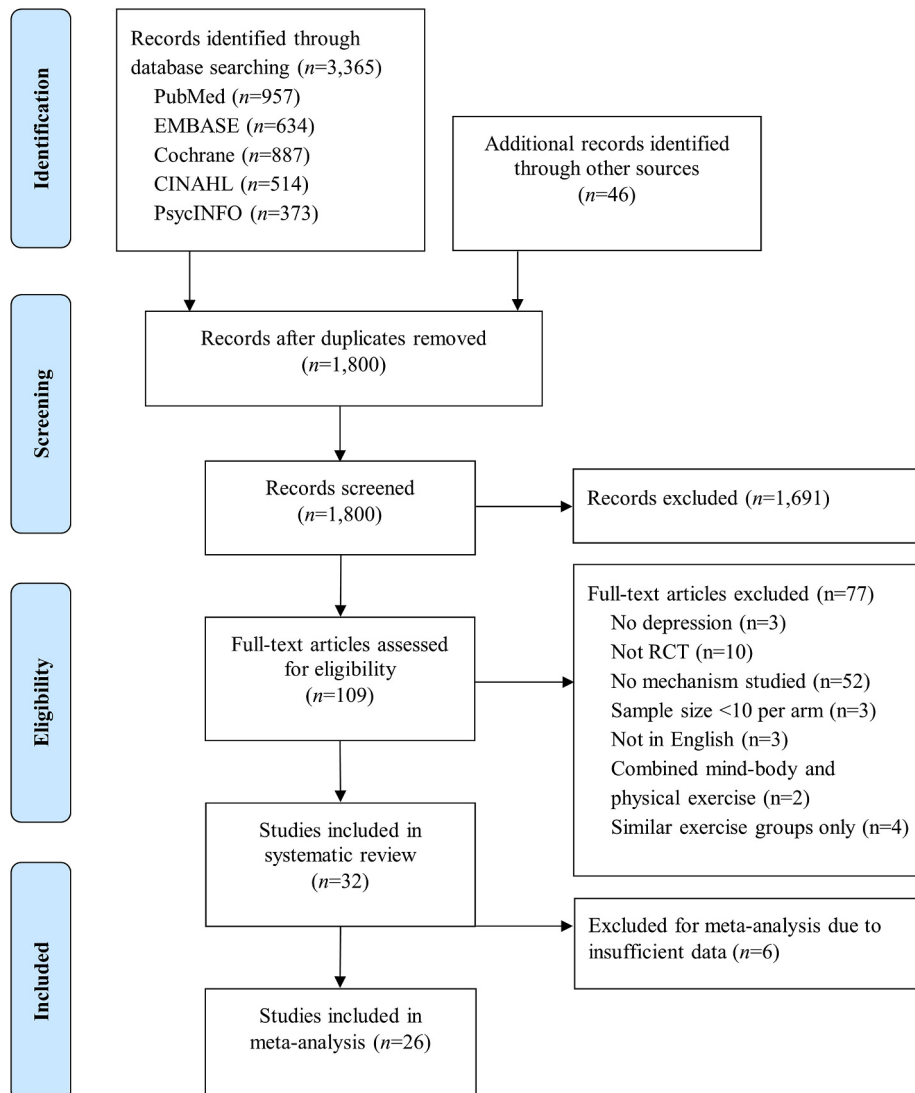


Fig. 1. PRISMA flow chart of the study.

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.

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 physical 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 demographics, intervention, and outcome measurements of the included studies.

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 (Fig. 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 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%).

3.2. 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-1 β , IL-6, IL-10, and TNF- α), metabolism (cholesterol, triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL], insulin, and glucose), the autonomic nervous system (blood pressure [BP] and heart rate [HR]), cardiorespiratory fitness (maximum/peak oxygen uptake [VO₂max/peak]), brain structure, and brain activity responses to exercise.

3.2.1. Mind-body exercise

The levels of cortisol, serotonin, BDNF, CRP, IL-1 β , 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 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 non-significant effect compared to the control group (Lu et al., 2020), while no significant result was found in the other RCT (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 non-significant reduction within mind-body exercise intervention, and such decrease was not found to be significantly more than control groups (Lavretsky et al., 2011; Nugent et al., 2019). IL-1 β 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 a non-significant effect was exhibited (Nugent et al., 2019). Chan et al. found that after ten sessions of the mind-body intervention, subjects exhibited significantly increased electroencephalogram (EEG) alpha asymmetry, which is an indication of left-side anterior activation (Chan et al., 2013).

3.2.2. Physical exercise

Cortisol was studied in six trials. Two found that physical exercise led to a 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). One study found that group jogging reduced epinephrine levels significantly more than the control group (Nabkasorn et al., 2006). Carneiro et al. provided data on dopamine and showed that intervention group exhibited a significantly higher dopamine level after physical exercise compared with 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 VEGF (Krogh et al., 2014).

CRP was studied in four trials, and no significant changes were registered in participants practicing exercise compared to controls (Euteneuer et al., 2017; Krogh et al., 2012; Patten et al., 2017; Vučić Lovrenčić et al., 2015). Three studies observed non-significant effects 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., 2012). Krogh et al. (Krogh et al., 2012) 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 differences (Kerling et al., 2015; Krogh et al., 2012). Heart rate was studied in two trials and was found to show significantly more decreases in the aerobic exercise groups than in 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., 2012, 2014; 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

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 min/session, 2 sessions/week, 5 weeks	Wait-list control	↓ BDI**	↓ Cortisol	Not reported
Lavretsky et al. (2011)	United States	Older adults with MDD	70.6	E: 36 C: 37	Tai Chi Chih	120 min/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 min/session, 1 session/week, 10 weeks	Wait-list control	↓ BDI-II*	↑ EEG alpha asymmetry and theta coherence in alpha asymmetry in the fronto-posterior region	Participants with improvement in depression were significantly more likely to exhibit increased alpha asymmetry in the intervention group only ($\phi = 0.70, p = 0.009$).
Tsang et al. (2013)	Hong Kong SAR	Depressed elders with chronic illness	80.1	E: 21 C: 17	Qigong (Eight-Section Brocades)	45 min/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 min/week, 5 weeks	Pharmacological treatment only	↓ HAMD-21	↑ Cortisol	Not evaluated directly.
Tolahunase et al. (2018)	India	Adults with MDD	38.0	E: 29 C: 29	Yoga- and meditation-based lifestyle intervention	120 min/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 ($p < 0.001$, inferential statistics not reported).
Nugent et al. (2019)	United States	Adults with MDD	45.2	E: 48 C: 39	Hatha Yoga	80 min/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 min/session, 2 sessions/week, 12 weeks	Cognitive training	↓ PHQ-9***	↓ Cortisol* ↑ Serotonin [^] ↑ BDNF*	Cortisol: $r = 0.83, p < 0.0001$ Serotonin: $r = -0.37, p = 0.047$ BDNF: $r = -0.35, p = 0.058$ Indirect effect of mediation model based on bootstrapping (cortisol): 95%CI ($-0.87, -0.33$), $p = 0.002$
Ng et al. (2022)	Hong Kong SAR	Adults with depressive symptoms	55.3	E: 95 C: 93	Qigong	180 min/week, 8 weeks	Wait-list control	↓ CES-D***	↓ IL-6*** ↓ IL-1 β ***	Changes in depressive symptoms were significantly correlated with changes in IL-6 ($r = 0.17, p < 0.01$) and IL-1 β ($r = 0.15, p < 0.05$).
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 min/session, 5 days/week, 8 weeks	Usual daily activity	↓ CES-D**	↓ Cortisol** ↓ Epinephrine* ↓ HR** ↑ VO ₂ peak**	Not reported
Foley et al. (2008)	New Zealand	Depressed adults	/	E: 10 C: 13	Moderate intensity aerobic exercise	30–40 min/session, 3 sessions/week, 12 weeks	Mild intensity stretching	↓ BDI-II ↓ MADRS	↓ Cortisol*	Depression severity was not correlated with cortisol at baseline or post-intervention (inferential statistics not reported).
Krogh et al. (2010)	Denmark	Adults with depression	38.9	E: 47 C: 48	Aerobic training at 70–90% maximal HR	40–60 min/session, 2 sessions/week, 16 weeks	Relaxation exercise	↓ HAMD-17	→ Cortisol → Growth hormone → Prolactin	Not reported

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Table 1 (continued)

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
Hemat-Far et al. (2012)	Iran	Depressed female students	/	E: 10 C: 10	Moderate intensity aerobic exercises	40–60 min/session, 3 sessions/week, 8 weeks	Normal life without physical activity	↓ BDI-21*	↑ Serotonin	Not reported
Krogh et al. (2013)	Denmark	Adults with MDD	41.9	E: 53 C: 58	Aerobic exercise at 80% maximal HR	45 min/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 min/session, 3 sessions/week, 12 weeks	Attention control group	HAMD-17	↑ BDNF ↓ VEGF ↓ IGF-1 ↑ VO ₂ max* → fMRI hippocampal volume	The decrease in depression was significantly correlated with the increase in right hippocampal volume ($\rho = 0.30, p = 0.03$).
Krogh et al. (2012)	Denmark	Outpatients with MDD	41.6	E: 56 C: 59	Aerobic training at 65–80% VO ₂ max	45 min/session, 3 sessions/week, 12 weeks	Attention control group (stretching exercise: bike, stretching, low intensity throwing and catching balls)	↓ BDI-II ↓ HAMD-17	↑ CRP ↓ BP ↓ Cholesterol ↓ HDL ↓ Triglycerides ^c ↓ Glucose* ↑ Insulin ↑ VO ₂ max*** ↑ BDNF	Not reported
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 min/session, 3 sessions/week, 6 weeks	Treatment as usual	↓ BDI-II ↓ MADRS	↑ HDL*** ↓ Triglycerides ↓ Glucose ↓ BP ↓ HR* ↑ VO ₂ peak** ↓ Adiponectin ↓ CRP	Not reported
Vučić Lovrenčić et al. (2015)	Croatia	Type 2 diabetic patients with subsyndromal depression	58.1	E: 66 C: 69	Light-to-medium intensity flexibility, stretching, and strengthening exercises	90 min/session, 1 session/week, 6 weeks	Treatment as usual	↓ CES-D	↓ Serotonin***	Not reported
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 min/session, 3 sessions/week, 24 weeks	Phoenix (three dates daily)	↓ GDS	↓ Serotonin***	Not reported
Siqueira et al. (2016)	Brazil	Adults with symptomatic MDD	38.8	E: 29 C: 28	Aerobic exercise at 60–85% VO ₂ max	4 times/week, 4 weeks	Anti-depressant only	↓ BDI ↓ HAMD	↑ VO ₂ max*	The changes in depressive symptoms were not correlated with the changes in VO ₂ max: BDI: $r = 0.95, p = 0.19$ HAMD: $r = -0.58, p = 0.35$ Depression symptoms were not significantly associated with BDNF levels pre- or post-intervention (inferential statistics not reported).
Salehi et al. (2016)	Iran	Adults with MDD	29.7	E: 20 C: 20	Aerobic exercise training at 60–75% VO ₂ max	40–45 min/session, 3 times/week, 4 weeks	Electroconvulsive therapy (ECT)	↓ BDI-21 ↓ HAMD-21	↑ BDNF	Not reported
Carneiro et al. (2017)	Portugal	Moderately clinical depressed patients	50.2	E: 13 C: 13	Aerobic exercise at 72% maximum HR	45–50 min/session, 3 sessions/week, 16 weeks	Pharmacotherapy only	↓ BDI-II*	↓ Cortisol ↓ Serotonin ↓ Dopamine*	Not reported

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Table 1 (continued)

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
Euteneuer et al. (2017)	Germany	Adults with MDD	37.3	E: 36 C: 30	CBT emphasizing exercise (walking, jogging, swimming, gyms)	40 min/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 min/session, 3 sessions/week, 6 weeks	Treatment as usual	↓ BDI-II ↓ MADRS	↑ BDNF*	The changes in depressive symptoms and BDNF were not significantly correlated (inferential statistics not reported).
Olson et al. (2017)	United States	Adults with MDD	21.1	E: 15 C: 15	Moderate intensity aerobic exercise	3 sessions/week, 8 weeks	Light intensity stretching	↓ BDI-II*	↑ EEG N2 amplitude*	The changes in depressive symptoms were significantly correlated with the changes in N2 amplitude ($r = 0.51, p < 0.01$). Indirect effect of mediation model based on bootstrapping: $-5.21 (-13.69, 3.26), p > 0.05$
Patten et al. (2017)	United States	Female with moderate-to-severe depression	37.5	E: 15 C: 15	Vigorous intensity aerobic exercise	30–40 min/session, 3 sessions/week, 12 weeks	Health education	↓ PHQ-9	→ CRP → IL-6 → TNF- α ↑ VO ₂ max**	Not reported
Rahman et al. (2019)	Sweden	Adults with mild to moderate depression	/	E: 38 C: 27	Physical exercise	60 min/session, 3 sessions/week, 12 weeks	Treatment as usual	↓ MADRS*	↓ Cortisol	The changes in depression severity were not associated with cortisol levels ($p > 0.57$, inferential statistics not reported).
Szuhan and 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 min/session, 9 sessions in total, 12 weeks	Stretching plus behavioral activation	↓ BDI-II ↓ MADRS	↑ BDNF	The changes in depression were not significantly correlated with the changes in BDNF: BDI-II ($r = -0.26, p = 0.35$) MADRS ($r = 0.35, p = 0.21$)
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 min/session, 3 sessions/week, 6 weeks	Active control activities	↓ HAMD-17 ↓ BDI-21	↓ Cortisol ↑ BDNF ↑ TNF- α	The changes in depressive symptoms were significantly correlated with VO ₂ max ($r = -0.322, p = 0.049$).
Wunram, Oberste, Hamacher, et al. (2021)	Germany	Depressed Adolescents	16.0	E: 20 C: 21	Vigorous aerobic activity treatment	30 min/session, 3–5 days/week, 6 weeks	Treatment as usual	↓ DIKJ	↓ IL-6 ↓ TNF- α	The associations between IL-6 and TNF- α on depression scores were not significant 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 min/session, 3–5 days/week, 6 weeks	Treatment as usual	↓ DIKJ	↑ BDNF** ↑ IGF-1	The depression-scores changes were not significantly correlated with changes in BDNF and IGF-1.

E: exercise intervention; C: control; CBT: cognitive-behavioral therapy; BDI: Beck Depression Inventory; CES-D, Center for Epidemiologic Studies 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; VO₂max/peak: maximum/peak oxygen uptake.

r, rho or phi: correlation coefficient.

↑ Increased in exercise group.

↓ Decreased in exercise group.

→ No change in exercise group.

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

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.

3.2.3. Associations between neurobiological outcomes and depressive symptoms

3.2.3.1. 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 significantly 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 levels 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-1 β 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).

3.2.3.2. Physical exercise. For physical exercise, twelve of the 23 included studies investigated the associations between 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 changes in depressive symptoms 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 et al., 2021a, 2021b). Two studies investigated the correlation between changes in depressive symptoms with VO₂max, and one found a significant correlation (Imboden et al., 2021) while the other showed a 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 that the increase in right hippocampal volume was associated with the decrease in depressive symptoms (Krogh et al., 2014).

3.3. Quantitative synthesis of effects on neurobiological outcomes

Data were 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., 2010, 2013; Rahman et al., 2019; Woolery et al., 2004; Wunram et al., 2021a, 2021b). Due to the limited number of included studies, we could not identify five or more studies for each neurobiological outcome within either mind-body 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).

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 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%; Table 2 and Fig. S1a). One mind-body exercise study had high risk of bias and was

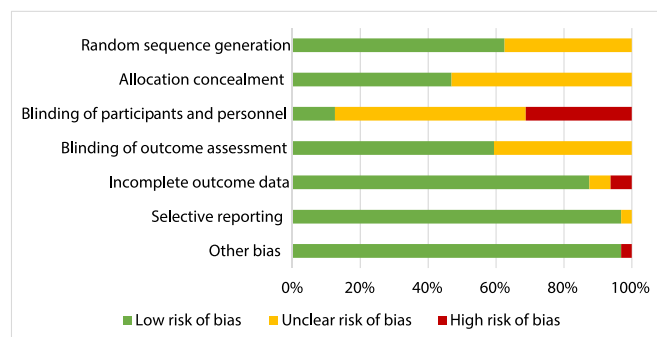


Fig. 2. Risk of bias summary.

excluded from sensitivity analysis to evaluate the impact of the quality of the included studies on the findings (Sarubin et al., 2014). The result showed that the overall effect of exercise on cortisol remained significant with a greater effect size (SMD = -1.08, p = 0.004, I^2 = 85.4%; Fig. S2a).

Two mind-body exercise and three physical exercise studies presented the data on serotonin (Abdelhamid et al., 2016; Carneiro et al., 2017; Hemat-Far et al., 2012; Lu et al., 2020; Tsang et al., 2013). The pooled result showed that exercise intervention produced a non-significant reduction of serotonin levels (SMD = -2.48, p = 0.086, I^2 = 97.8%; Table 2 and Fig. S1b).

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 a non-significant improvement in BDNF following exercise (SMD = 0.34, p = 0.107, I^2 = 71.4%; Table 2 and Fig. S1c).

Data on CRP were reported in two mind-body exercise studies and three physical exercise studies (Euteneuer et al., 2017; Krogh et al., 2012; Lavretsky et al., 2011; 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%; Table 2 and Fig. S1d).

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 non-significant effect of exercise interventions in reducing IL-6 levels (SMD = -0.51, p = 0.077, I^2 = 86.7%; Table 2 and Fig. S1e).

In addition to the above five outcomes, cardiorespiratory fitness was also evaluated by VO₂max/peak in five physical exercise trials (Kerling et al., 2015; Krogh et al., 2012; Nabkasorn et al., 2006; Patten et al., 2017; Siqueira et al., 2016) and a significant, large pooled effect of physical exercise on VO₂max/peak was found (SMD = 1.20, p = 0.004, I^2 = 91.7%; Table 2 and Fig. S1f).

4. Discussion

4.1. 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 VO₂max/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.

4.2. Antidepressant mechanisms of exercises

We observed that there were more studies evaluated the effects of physical exercise on neurobiological outcomes 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 Fig. 3 that reflected the evidence synthesized in the present systematic review and meta-analysis.

4.2.1. 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 reductions 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 non-significant decrease 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 was 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 changes reported in other included studies that assessed BDNF. The effect size generated from Salehi and colleagues' study could be a potential outlier to the pooled result of BDNF, as it was substantially lower than those of other physical exercise studies. They compared physical exercise to electroconvulsive therapy (ECT), a potent treatment for 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 (SMD = 0.50, $p = 0.001$, $I^2 = 32.5\%$; Fig. S2b).

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 only observed after training of mind-body exercise, probably due to its additional mental component. The sample sizes of the above studies were generally small, and it may need a larger number of participants in RCTs on physical exercise to detect low but significant associations between changes in depressive symptoms and changes in cortisol and BDNF, and even mediation effect elicited from cortisol and BDNF.

4.2.2. 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) and lead 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 the 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.

4.2.3. VO₂max/peak as a potential mechanism outcome of physical exercise

According to the six studies on physical exercise and VO₂max/peak, it was consistently reported that depressive participants could have significantly more improvement in VO₂max/peak after physical exercise, compared to those in control groups (Kerling et al., 2015; Krogh et al., 2012, 2014; Nabkasorn et al., 2006; Patten et al., 2017; Siqueira et al., 2016). A significant pooled effect of physical exercise on VO₂max/peak was found based on meta-analysis. In addition, the increase in VO₂max/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 VO₂max/peak. A previous study showed that the elderly who completed six months of aerobic

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 ₂ max/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; VO₂max/peak: maximum/peak oxygen uptake.

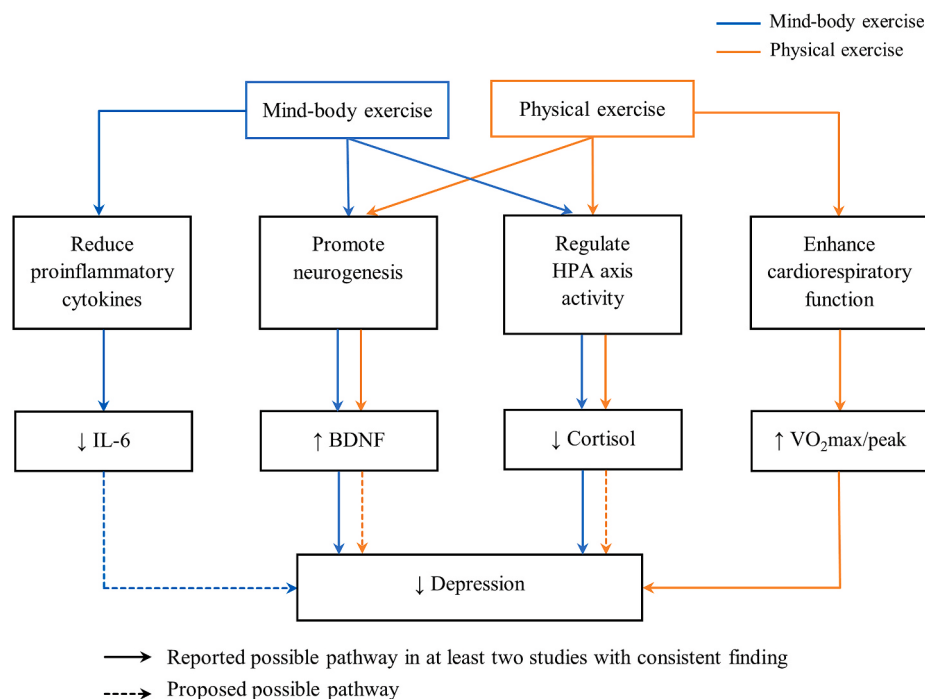


Fig. 3. The possible neurobiological pathways of antidepressant effects of exercises.

exercise had significantly better CRF indicators and the 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.

4.2.4. 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 Fig. 3. 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 to 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. Third, 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. And the mediating effects of the neurobiological outcomes were only tested in one study on mind-body exercise (Lu et al., 2020) and one study on physical exercise (Olson et al., 2017). Future studies might consider the investigation of the correlations and mediations 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 have not been studied in human RCTs were not included in this review. In addition, the extent of mindfulness involved in the mind-body exercise studies was not evaluated in the current review, future research should consider and report this important component in mind-body exercise studies. Last but not least, among the studies included in the current meta-analysis, half of those on mind-body exercise used qigong in Hong Kong, whereas all the physical 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 antidepressant mechanisms needs to be further analyzed using the bio-psycho-social model in the future.

5. Conclusion

It seems common for both mind-body and physical exercises to alleviate depressive symptoms through the regulation of HPA axis activity and the enhancement of neurogenesis. Only mind-body exercise was found to decrease pro-inflammatory cytokines, whereas physical exercise was consistently shown to improve CRF, which might in turn,

reduce depressive symptoms. The understanding of these potential neurobiological mechanisms can inform the choice and design of exercise protocol as a 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 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 a better understanding of how mind-body exercise and physical exercise treat depressive symptoms.

CRediT authorship contribution statement

Wen Sun: Data Curation, Formal analysis, Writing - Original Draft, Review & Editing. Erin Yiqing Lu: Methodology, Writing - Review & Editing, Supervision. Cong Wang: Writing - Review & Editing. Hector Wing Hong Tsang: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mhpa.2023.100538>.

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