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Physical activity in people with mental disorders: Benefits, risks and prescription

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Physical activity in people with mental disorders: Benefits, risks and prescription

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Editorial: Physical activity in people with mental disorders: Benefits, risks and prescription

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Editorial on the Research Topic
Physical activity in people with mental disorders: Benefits, risks and prescription

Physical activity is an essential component of a healthy lifestyle and it has benefits for the prevention and treatment of various physical and mental health conditions (1). However, people with mental disorders often encounter barriers and challenges to participating in regular physical activity. Furthermore, people with the risk of mental disorders are often less properly advised on this matter, together with concerns regarding the potential risks and difficulties of uptake and adherence to physical activity (2). For instance, depressive symptoms have been found to be associated with less participation in physical activity and lower adherence to physical activity regimens recommended by physicians, owing to feelings of insufficient energy and lack of interest and motivation (3). The COVID-19 pandemic has changed the world in many fundamental ways, it has increased stress and uncertainty, and social distancing, quarantine, and lockdown measures have led to reduced physical activity. These factors have also negatively affected mental health outcomes, such as depression, anxiety, and cognitive impairment (4, 5). The relationship between physical activity and mental health during the pandemic era is of great relevance.

In this Research Topic, we investigated the benefits of physical activity for people with mental disorders, and the risks or barriers they encounter when participating in exercises; and exercise or physical activity prescriptions for preventive or therapeutic purposes of mental disorders, especially for people who are restricted in indoor living space (e.g., people in quarantine or telecommuting, people receiving medical treatment or nursery care at home due to limited healthcare resources).

There are three systematic reviews, four intervention studies, and five cross-sectional studies published on this Research Topic (see Table 1).

The systematic reviews and meta-analyses from Tang et al. and Wang et al. indicated that aquatic exercise played a positive role in mental health, and exercise could improve global cognitive function and several specific cognitive functions in patients with amnestic mild cognitive impairment, respectively. Different from their reviews focusing on the benefits of exercises on mental health, Hirschbeck et al. reviewed the effects of psychiatric medications on physical performance and showed that stimulants had consistent performance-enhancing effects on patients with psychiatric disorders and well-trained subjects, while other psychotropic drugs showed different effects in various studies.

Three intervention studies showed the positive effects of exercise prescriptions on mental health. Zhao et al. indicated that personalized exercise prescriptions could improve adherence to interventions and reduce serious adverse events for college students with depressive symptoms. Li R. et al. showed that the 8-week resistance training could increase the heart rate variability in anxious female college students and improve their autonomic nervous disorder, and Lei et al. showed that the 8-week exercise prescription of *Baduanjin* was an effective supportive treatment for lung cancer patients with depression and anxiety. The other intervention study from Robertson et al. aimed to understand the potential mechanism of positive effects of physical activity on depression symptoms, which showed that increased prefrontal cortex gamma during exercises could differentiate between people with and without mental disorders.

Cross-sectional studies in this Research Topic explored the correlation between physical activity or sedentary behavior and mental health outcomes. Liu Y. et al. found that older adults could delay the decline in cognitive reaction time, if they maintained a moderate level of physical activity in both leisure and work time physical activity. Li C. et al. showed that physical activity decreased the severity of depression by improving life satisfaction and making a sense of purpose and meaning in life. Yuan et al. found that children and adolescents with intellectual disabilities spent a long time on after-school sedentary behavior, which is concerning. Liu Z. et al. found that low physical activity levels may be a risk factor for comorbid insomnia and depressive symptoms in patients with chronic schizophrenia. Chen et al. found that the social adaptability of autistic children may be improved by the development of fine motor, which could be an early focus in the interventions for children with autism spectrum disorder.

In summary, studies included in this Research Topic showed a positive association between exercise and mental health outcomes, and the benefits of some exercise prescriptions on patients with mental disorders. Meanwhile, sedentary behavior or lack of physical activity may negatively impact the mental health of some populations. Physical activity is suggested to be added as a routine practice to clinical care or intervention for patients with mental disorders. Given the lack of evidence of some exercise interventions, longitudinal studies are further needed to verify the effects of various exercises. In addition to clinical trials examining the efficacy of exercises, mental health promotion programs including exercise should be conducted, and the effectiveness of exercise prescriptions in the real-world needs to be studied.

TABLE 1 List of articles.

Type	Title
Systematic review	Tang et al. Effects of aquatic exercise on mood and anxiety symptoms: A systematic review and meta-analysis. *Front Psychiatry.* 13:1051551.
	Wang et al. The influence of exercise interventions on cognitive functions in patients with amnestic mild cognitive impairment: A systematic review and meta-analysis. *Front Public Health.* 10:1046841.
	Hirschbeck et al. Psychiatric medication and physical performance parameters—Are there implications for treatment? *Front Psychiatry.* 13:985983.
Intervention study	Zhao et al. Personalized individual-based exercise prescriptions are effective in treating depressive symptoms of college students during the COVID-19: A randomized controlled trial in China. *Front Psychiatry.* 13:1015725.
	Li R. et al. Effect of resistance training on heart rate variability of anxious female college students. *Front Public Health.* 10:1050469.
	Lei et al. An exercise prescription for patients with lung cancer improves the quality of life, depression, and anxiety. *Front Public Health.* 10:1050471.
	Robertson et al. Acute electroencephalography responses during incremental exercise in those with mental illness. *Front Psychiatry.* 13:1049700.
Cross-sectional study	Liu Y. et al. The effect of different types of physical activity on cognitive reaction time in older adults in China. *Front Public Health.* 10:1051308.
	Li C. et al. Health benefits of physical activity for people with mental disorders: From the perspective of multidimensional subjective wellbeing. *Front Psychiatry.* 13:1050208.
	Yuan et al. The after-school sedentary behavior status among children and adolescents with intellectual disabilities. *Front Psychiatry.* 13:1049180.
	Liu Z. et al. Physical activity levels associated with insomnia and depressive symptoms in middle-aged and elderly patients with chronic schizophrenia. *Front Psychiatry.* 13:1045398.
	Chen et al. The relationship between motor development and social adaptability in autism spectrum disorder. *Front Psychiatry.* 13:1044848.

Author contributions

HZ and XT prepared the manuscript. WZ and Y-lT revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Psychiatric medication and physical performance parameters – Are there implications for treatment?

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Introduction: The impact of psychiatric medications and their enhancing or impairing effects on physical performance remains inconclusive. Therefore, with this systematic review we provide a comprehensive overview of frequently used psychotropic drugs and their effects on physical performance for the purpose of providing empirical information and deriving prescription and therapy recommendations for clinical practice.

Methods: We systematically searched PubMed, PsycInfo, and Cochrane databases and extracted human studies investigating the effect of psychotropic drugs on parameters associated with the level of physical performance, such as exercise time, oxygen consumption, heart rate, muscle contraction or blood lactate concentration in physically healthy participants. 36 studies - comprising a broad range of psychotropic agents, such as antidepressants, antipsychotics, sedatives, and stimulants - were selected for final analyses.

Results: Most studies (N = 32) were randomized controlled trials (RCT) with a double-blind crossover design. Antidepressants (N = 21) were the most frequently studied drug class, with contradictory results e.g., performance enhancement in warm environment but not in temperate conditions for bupropion or inconsistent findings between studies for other antidepressants. Antipsychotics (N = 3) mainly showed impairing effects on physical performance, while stimulants (N = 4) were often performance-enhancing. Sedatives (N = 9) may cause a hangover effect.

Conclusion: The examined studies with heterogeneous design showed different effects of psychiatric medications on physical performance. Antipsychotics seemed to be performance impairing, while the findings for antidepressants and sedatives were more inconsistent. Stimulants were the only group with consistent performance-enhancing effects. However, most studies were conducted with a small sample size ($N < 10$), mostly in well-trained subjects rather than in patients with psychiatric disorders, and most studies used single-dose designs. These issues impede the formulation of generalized conclusions for treatment regimes and should therefore be considered in further longitudinal studies for clinically reliable statements. Nevertheless, answering our research question is quite relevant for clinical practice and therapeutic prescription and should be further investigated especially considering the high drop-out rates in drug treatment.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=276103], identifier [CRD42021276103].

KEYWORDS

psychiatric medication, psychotropic drugs, physical performance, athletic performance, sport, exercise, fitness, systematic review

Introduction

Psychopharmacological drugs play a pivotal role in the treatment of severe mental illness. Despite indisputable benefits in treatment regimes, the intake of the medication also bears risks and side-effects. Possible side-effects in terms of exercise performance impairments may include, among others, fatigue, muscle stiffness or weakness and these side-effects can negatively impact physical performance (1, 2).

In the past years, physical exercise has become increasingly important in therapeutic regimes of various psychiatric diseases, e.g., aerobic exercise of moderate-vigorous intensity or in combination with resistance training at a frequency of 2–3 times a week, achieving 150 min of moderate-to-vigorous physical activity (3). Physical exercise in this context is also beneficial for the amount of visceral and epicardial adipose tissue and for factors constituting the metabolic syndrome (4). Therefore, side-effects of psychiatric medications with negative impact on physical performance should be strictly avoided.

Previous scientific background for the effects of psychiatric medication on athletic performance was mainly provided in the population of competitive athletes and healthy people. For example one experimental study with $N = 6$ subjects showed that 70 mg of fluoxetine (selective serotonin reuptake inhibitor = SSRI) reduced the ability to perform prolonged exercise on a bicycle ergometer (5). However, the intake of bupropion (norepinephrine and dopamine reuptake inhibitor = NDRI) increased physical performance in the heat after acute administration (6). Another study examined the intake of tricyclic antidepressants (desipramine 3 mg/kg body weight) in 9 children and 13 adults with no connection to competitive sports. A comparison of treadmill exercise tests before and after a single dose showed no differences in performance, but slight changes in blood pressure and heart rate (7). In summary, the studies were conducted in small sample sizes and results for antidepressive agents were inconclusive. Concerning medication with impact on sleep and anxiety, existing data is also inconsistent. Studies on the so-called Z-substances could not identify impaired athletic performance measured with a 50-m-sprint test after taking two doses of zolpidem 10 mg with $N = 8$ subjects (8), as well as no increased endurance time after a running time test with two doses of zopiclone 7,5 mg in $N = 8$ athletes (9). This is in contrast to buspirone with increased exhaustion after a 45 mg single dose in $N = 13$ athletes after a cycled ergometer test at 80% of maximum oxygen consumption (VO_2max) (10). Other studies found negative effects of melatonin 6 mg in $N = 23$ subjects on psychomotor performance (11).

The described studies mostly referred to healthy adults. Investigations in children/adolescents and elderly people are rare. One study with $N = 45$ showed that the physical activity of adolescents treated with psychotropic medications was significantly impaired compared to adolescents without medication and to healthy controls (12). Similar results were described among elderly people. A 4-year prospective cohort study conducted at the end of the 1980s with $N = 885$ older women (over 70 years) showed that the regular use of benzodiazepines had a negative effect on physical performance, such as walking speed or balance (13).

The occurrence of distressing side-effects often lead to the discontinuation of psychotropic medication and should be considered during treatment (14). The impairments of physical performance displayed above are not restricted to athletes, but might be relevant in a larger context to all treated patients. For patients, it might be difficult to differentiate between subjective side-effects, such as tiredness or fatigue, and objectively measurable impairments in physical performance. Therefore, there is a need to systematically investigate the impact of psychotropic mediation on physical performance as which might have been neglected in the scientific literature despite its relevance.

With this systematic review we want to provide the first comprehensive overview of frequently used psychotropic drugs (antidepressants, antipsychotics, sedatives, and stimulants) and their effects on physical performance in order to provide founded information and derive prescription and therapy recommendations for clinical practice.

Objective

To the best of our knowledge, this is the first systematic review summarizing psychopharmacological effects on physical performance parameters. This overview will help to adequately inform patients and clinicians to avoid wrong conclusions regarding the negative impact of psychotropic agents on physical performance.

Methods

Search strategy

This systematic review was registered on PROSPERO (CRD42021276103). We systematically searched PubMed, PsycInfo and Cochrane databases with all combination of the following search terms: psychotropic drugs OR psychiatric medication OR serotonin reuptake inhibitor OR antidepressant drugs OR antipsychotic drugs OR dopamine reuptake inhibitor OR antidepressants OR antipsychotics OR sedatives OR anxiolytics OR hypnotics OR mood stabilizer AND athletic performance OR exercise performance OR physical performance OR physical fitness OR exercise testing OR aerobic capacity OR elite athletes.

The database search was last updated on August 05, 2022. All citations were screened for relevance by title in a first step, by abstract in a second step and by full-text in a last step. In all included records, the citations were screened manually for further relevant studies that may have not been detected by the systematic search. The systematic literature search and selection was performed by AH, the selection was afterward reviewed independently by DS. Both AH and DS retrieved the relevant information, and the results were compared. In case of disagreement, a third author (AR) was consulted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were considered.

Eligibility criteria

We included studies that contain an evaluation of psychotropic drugs on physical performance, such as exercise time, oxygen consumption, heart rate, muscle contraction or blood lactate concentration in physically healthy adult human participants. No limitations were defined for the type of psychiatric disorder and the type of studies. All studies that were published until December 31, 2021, in English language were considered. We excluded studies without specific data about physical fitness, animal, preclinical and molecular studies as well as expert opinions and position statements.

Quality assessment

Each publication was reviewed using the Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist which assess the internal validity as well as the external validity of our included studies (15). The more the required criteria (e.g., appropriate and clearly focused question, randomization, adequate concealment method, blinding, or percentage of dropout) can be agreed to, the higher the quality is rated. A distinction is made between high quality, acceptable, low quality and unacceptable. We further used the simple Jadad Scale quickly assessing the methodological quality of a clinical trial that included three items (randomization, blinding, and withdrawals/dropouts) and is evaluated with a point system via yes-and-no questions (16).

Results

We were able to include 36 studies in the final analysis (see **Figure 1**). A detailed description of included publications and study types as well as the reviewed quality scores are shown in **Table 1**.

Study selection

The initial search without further restrictions resulted in 20,590 citations. After elimination of duplicates, 8,890 citations were included for further analysis. The screening on title/abstract level eliminated 8,766 citations (124 remaining). After full-text screening, 36 citations were considered for final analysis. **Figure 1** presents the PRISMA chart.

Study characteristics

For a better overview, we divided the included studies into four groups: antidepressants ($N = 21$), antipsychotics ($N = 3$), sedatives ($N = 9$), and stimulants ($N = 4$). The experimental testing consisted of isokinetic measurements of individual muscle (groups) and bicycle cycling at the individual percentage of VO_{2max} or maximum wattage (W_{max}) and physical fitness tests (e.g., vertical jumps, standing jumps, and sprints). Across all RCTs, the mean sample size was $N < 10$ with a minimum of 5 (17) and a maximum of 27 (18). The drugs were mostly administered as a single dose and taken the night before or in the morning of the experiment. Continuous administration was only given in two studies (19, 20).

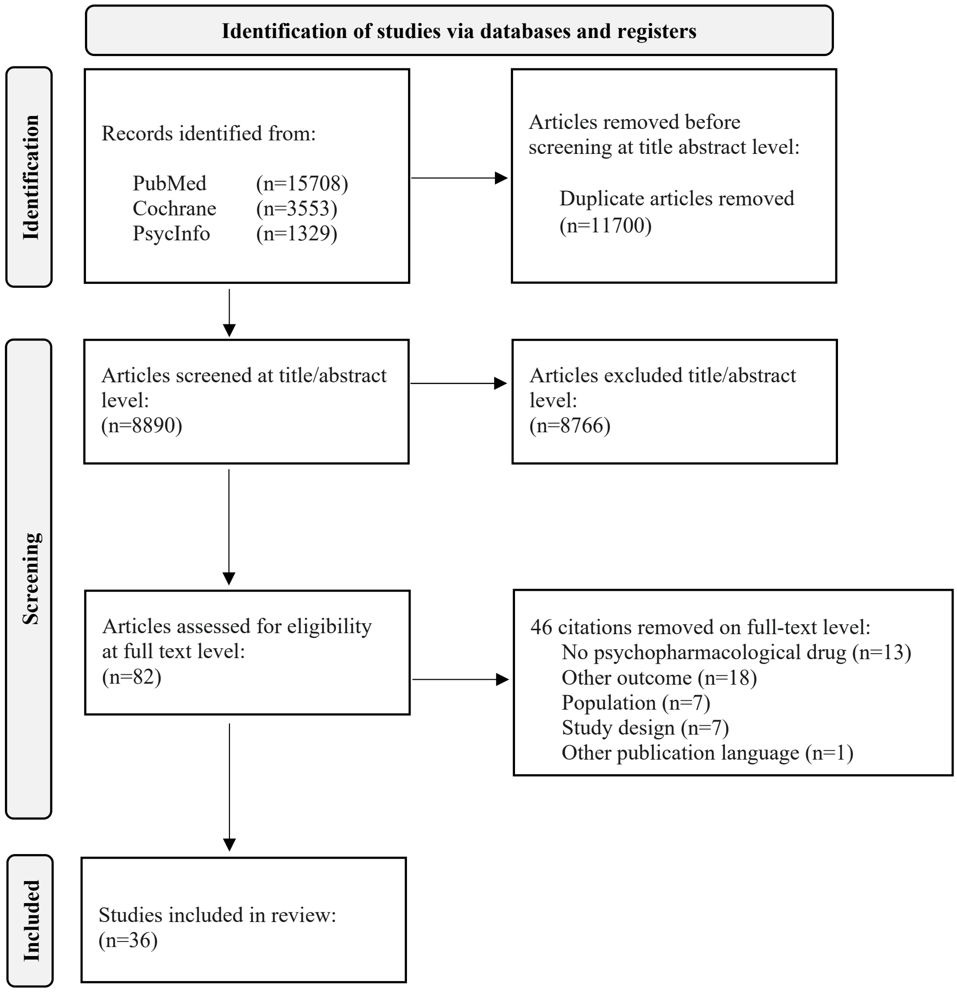

FIGURE 1
PRISMA flow diagram of included studies.

Results of individual studies

A detailed summary of all publications including study population, experimental testing design, drug, time of drug intake and relevant physical performance outcomes is provided for antidepressants in Table 2, for antipsychotics in Table 3, for sedatives in Table 4, and for stimulants in Table 5. The statistical data are shown in the Supplementary material.

Antidepressants

Our search resulted in 21 studies that met our inclusion criteria. The majority examined the effects of antidepressants (fluoxetine, paroxetine, bupropion, and reboxetine) on physical/athletic performance, which were measured through ergometric cycling or isokinetic muscle measurements. There were 17/21 studies for antidepressants, that only recruited male participants with similar age (approximately between 19 and 27 years old). There is only one study with female and just 2/21 studies with mixed participants.

Effects of paroxetine

Our search resulted in six publications examining paroxetine (21–26). All drug administration of paroxetine were given as a single-dose of 20 mg in physically active men (21–26) and women (21, 25). In addition, one study further compared 10 and 40 mg of paroxetine but they did not affect physical performance (24). Another study showed that paroxetine did not influence exercise duration of cycling as well (22). Three other studies found that paroxetine decreased physical performance in cycling (23, 24, 26). Paroxetine increased activation of unfatigued muscle but exacerbated central fatigue during prolonged sustained contractions (21). During a sustained submaximal contraction, paroxetine had no influence on motor performance or on the development of central

TABLE 1 List of evaluated psychiatric drugs.

Psychiatric drug		References	Study design	*N*	SIGN	Jadad Scale
Antidepressants	Paroxetine	Kavanagh et al. (21)	Randomized, double-blind, placebo controlled, and crossover design	15	+	3
		Strachan et al. (22)	Randomized, double-blind, placebo controlled, and crossover design	8	++	4
		Strüder et al. (23)	Randomized, double-blind, placebo controlled, and crossover design	10	++	3
		Teixeira-Coelho et al. (24)	Randomized, double-blind, placebo controlled, and crossover design	16	++	4
		Thorstensen et al. (25)	Randomized, double-blind, placebo controlled, and crossover design	15	+	3
		Wilson et al. (26)	Randomized, double-blind, placebo controlled, and crossover design	7	++	5
	Fluoxetine	Meeusen et al. (27)	Randomized, double-blind, placebo controlled, and crossover design	8	++	4
		Parise et al. (19)	Randomized, double-blind, placebo controlled, and crossover design	11+12	++	5
	Sertraline	Bilici et al. (28)	Case control study	38	+	/
	Fluvoxamine					
	Citalopram					
	Bupropion	Cordery et al. (29)	Randomized, double-blind, placebo controlled, and crossover design	9	++	4
		Onus et al. (30)	Randomized single-blind design	8	+	3
		Piacentini et al. (31)	Randomized, double-blind, placebo controlled, and crossover design	8	++	4
		Roelands et al. (20)	Randomized, double-blind, placebo controlled, and crossover design	8	++	4
		Roelands et al. (32)	Randomized, double-blind, placebo controlled, and crossover design	10	++	4
		Watson et al. (6)	Randomized, double-blind, placebo controlled, and crossover design	9	++	4
	Reboxetine	Goekint et al. (33)	Randomized, double-blind, placebo controlled, and crossover design	11	++	4
		Klass et al. (34)	Randomized, double-blind, placebo controlled, and crossover design	10	++	4
		Klass et al. (35)	Randomized, double-blind, placebo controlled, and crossover design	9	+	4
		Piacentini et al. (36)	Randomized, double-blind, placebo controlled, and crossover design	7	++	4
		Roelands et al. (37)	Randomized, double-blind, placebo controlled, and crossover design	9	++	4
	Ritanserin	Meeusen et al. (38)	Randomized, double-blind, placebo controlled, and crossover design	7	++	4
Antipsychotics	Oxypertine	Adamson and Finlay (17)	Randomized, double-blind, and crossover design	5	−	3
	Clozapine	Kim et al. (39)	Cross-sectional study	30 + 15	+	/
	Olanzapine	Perez-Cruzado et al. (40)	Cross-sectional study	62	+	/
	Risperidone					
Sedatives	Benzodiazepine	Charles et al. (18)	Randomized, double-blind, placebo controlled, and crossover design	8 + 27	+	4
		Collomp et al. (41)	Randomized, double-blind, placebo controlled, and crossover design	7	++	4
		Collomp et al. (42)	Randomized, double-blind, placebo controlled, and crossover design	7	++	4
		Ergen et al. (43)	Randomized, double-blind, placebo controlled, and crossover design	24	++	4
		Grobler et al. (44)	Randomized, double-blind, placebo controlled, and crossover design	12	++	4
	Z-drugs	Grobler et al. (44)	Randomized, double-blind, placebo controlled, and crossover design	12	++	4
		Suda et al. (45)	Randomized, double-blind, placebo controlled, and crossover design	12	++	3
		Ito et al. (8)	Randomized, double-blind, placebo controlled, and crossover design	8	++	3
		Ito et al. (46)	Randomized, double-blind, placebo controlled, and crossover design	21	++	3
		Tafti et al. (9)	Randomized, double-blind, placebo controlled, and crossover design	8	++	2
Stimulants	Methylphenidate	King et al. (47)	Randomized, double-blind, placebo controlled, and crossover design	15	−	3
		Klass et al. (34)	Randomized, double-blind, placebo controlled, and crossover design	10	++	4
		Roelands et al. (48)	Randomized, double-blind, placebo controlled, and crossover design	8	++	4
	Others	Westover et al. (49)	Cross-sectional study	245	+	/

N, total sample size; SIGN, ++, high quality; +, acceptable, −, low quality; Jadad Scale, 0–5 (with 5 as the maximum; /, not applicable).

fatigue (25). Heart rate and lactate blood concentration increased during exercise but did not differ between trials (22–24, 26).

Effects of fluoxetine

Exercise performance during cycling was not affected by fluoxetine (20 mg) in well-trained young men (27). Another RCT examined that there were no significant effects of fluoxetine on strength or high-intensity exercise performance in young male athletes and no parallel change in muscle strength of knee extensors was measured after acute fluoxetine administration (40 mg, 6 h before testing) (19). There was no suppression of maximal voluntary contraction strength with continuous fluoxetine administration (40 mg, every day for 2 weeks) (19).

TABLE 2 Antidepressants: experimental testing, drug and measured performance parameters.

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
Kavanagh et al. (21)	Study 1: $N = 14$ Study 2: $N = 11$ Study 3: $N = 8$	Isometric elbow flexion torque, biceps brachii EMG and triceps brachii EMG was recorded from the dominant limb and were measured during a series of maximal contraction tasks. Study 1: 8 maximal elbow flexions, each maintained until torque declined to less than 60% MVC ≥ 3 s (s). Time-to-task failure was calculated from the onset of elbow flexion torque to the time that torque declined to 60% MVC ≥ 3. Study 2: Voluntary activation was examined for the non-fatigued and fatigued biceps muscle via electrical stimulation of intramuscular fibers (motor nerve). Electrically evoked increases in torque were quantified during maximal contractions (superimposed twitch) and for the relaxed muscle (resting twitches). Study 3: F-waves were obtained from the abductor digiti minimi before and after a series of maximal fifth digit abduction contractions.	Paroxetine 20 mg	4 h before exercise testing	**Primary:** MVC. **Secondary:** Alertness. RPE. Max. torque. Voluntary activation. F-waves.	**Study 1:** MVC: ↑ (4%). Max. torque: 11 N ↑, 3 N ↓. Alertness: ↓. RPE: ↑. **Study 2:** Max. torque: ↑. Voluntary activation, unfatigued muscle: ↑. Voluntary activation, fatigued muscle: ↓. **Study 3:** **2-s MVC.** F-waves: ↓. F-waves area: ↓. F-waves persistence: ↓. **60-s MVC** F-waves: ↓. F-waves area: ↓. F-waves persistence: ↓.
Strachan et al. (22)	$N = 8$	Cycling tests at 60% of VO_2max until exhaustion in a warm (32°) condition.	Paroxetine 20 mg.	5 h before exercise trials	**Primary:** Time to exhaustion. **Secondary:** Heart rate. Blood lactate. RPE.	Time to exhaustion: →. Heart rate: →. Blood lactate: →. RPE: →.
Strüder et al. (23)	$N = 10$	Cycling with workload (256.0 ± 19.5 W) corresponded to a blood lactate level of 2.0 mmol/l in an incrementally graded exercise test until exhaustion.	Paroxetine 20 mg.	Approx. 5 h before exercise trials.	**Secondary:** Time to exhaustion. Heart rate. Blood lactate.	Time to exhaustion: ↓. Heart rate: →. Blood lactate: →.
Teixeira-Coelho et al. (24)	$N = 16$	Cycling at 50 rpm until voluntary termination of the exercise at an intensity corresponding to 60% Wmax (fatigue protocol).	Paroxetine 10 mg/20 mg/40 mg.	One capsule at 12:00 pm on the experimental testing day.	**Primary:** Exercise time. **Secondary:** Heart rate. Blood lactate. RPE.	Exercise time: ↓ 15% in 20 mg. Heart rate: →. Blood lactate: →. RPE: →.

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TABLE 2 (Continued)

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
Thorstensen et al. (25)	*N* = 15	Low-intensity isometric measurement of elbow flexor (unfatigued, fatigued for 30 min at 15% of MVC and recovery).	Paroxetine 20 mg.	One capsule 4 h prior to the commencement of experiments.	**Primary:** Peak torque. **Secondary:** Voluntary activation. Perceived fatigue. Biceps silent period.	Peak torque: →. Voluntary activation: →. Perceived fatigue: ↑. Biceps silent period: ↓.
Wilson et al. (26)	*N* = 7	Cycling at 70% of VO_2max until exhaustion.	Paroxetine 20 mg.	6 h before each test.	**Primary:** Endurance time. **Secondary:** Relative work load (%VO_2max). Heart rate. Blood lactate peak. RPE.	Endurance time: ↓. %VO_2max: →. Heart rate: →. Blood lactate peak: ↓ after 15 min. RPE: →.
Bilici et al. (28)	*N* = 38	Isokinetic measurements of quadriceps and hamstring muscles: 6 maximal repetitions of knee extension and flexion at velocities of 60°/s and 180°/s before and after subchronic antidepressant treatment.	3 months drug therapy of Fluoxetine (20 mg), Sertraline (50 mg), Fluvoxamine (100 mg), and Citalopram (20 mg).	Daily dose.	**Primary:** Isokinetic muscle performance (IMP): Peak torque (PT). Total work (TW). Acceleration time (AT).	PT: ↑. TW: ↑. AT: ↓.
Meeusen et al. (27)	*N* = 8	90-min cycling at 65% Wmax.	Fluoxetine-HCl 20 mg.	Two capsules the night before and the morning of the experiment.	**Primary:** Exercise time. **Secondary:** Blood lactate. RPE.	Exercise time: →. Blood lactate: ↑ in resting. RPE: →.

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TABLE 2 (Continued)

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters (primary/secondary)	Statistical outcome *(data compared to placebo/all trials)*
Parise et al. (19)	Acute study: $N = 11$ Chronic study: $N = 12$	Acute study: repeated 30-s maximal cycling tests (2 tests) (Wingate); Cycling to exhaustion at 80% VO_2max; Isokinetic measurements of right knee extensor. Chronic study: single 30-s maximal cycling test (Wingate); cycling to exhaustion at 90% VO_2max; Isokinetic measurements of dorsiflexors.	Acute study: fluoxetine 40 mg. Chronic study: fluoxetine 40 mg.	Acute study: 6 h before testing. Chronic study: daily for 2 weeks.	**Acute study:** **Primary:** MVC. **Secondary:** Peak power. Mean power. Fatigue index. Blood lactate. Time to exhaustion. **Chronic study:** **Primary:** MVC. **Secondary:** Peak power. Mean power. Blood lactate. VO_2max. Ventilation. Heart rate.	**Acute study:** MVC: ↓. Peak power: →. Mean power: →. Fatigue index: →. Blood lactate: →. Time to exhaustion: →. **Chronic study:** MVC: →. Peak power: →. Mean power: →. Blood lactate: →. VO_2max: →. Ventilation: ↓. Heart rate: →.
Cordery et al. (29)	$N = 9$	60-min cycling at 60% VO_2 peak followed by a 30-min performance test, in which participants were asked to complete as much work as possible in a warm (30°C) environment.	Bupropion 600 mg (2 × 2 doses 150 mg).	In two doses the night before and the morning of experiment.	**Primary:** Watts. **Secondary:** Total work. Heart rate.	Watts: ↑. Total work done: ↑. Heart rate: →.
Onus et al. (30)	$N = 8$	30-min-intensity cycling at 50% Wmax in either warm (32°C) or moderate (20°C) ambient conditions followed by a self-paced time trial with each section interspersed with a 30 s maximal sprint at 9, 19 and 29 min. Isokinetic measurements of forearm flexors and knee extensors (rectus femoris, vastus medialis, vastus lateralis, biceps femoris).	Bupropion 600 mg (2 × 300 mg).	One dose the night before and the second dose 3 h prior to each testing session.	**Primary:** Total distance. **Secondary:** Mean power output. Peak power output. Mean speed. Max speed. Heart rate. RPE.	**Fixed intensity:** Total distance: →. Mean power output: →. Peak power output: →. Mean speed: →. Max speed sprints: ↓ in 20°C, ↓ in 32°C. Heart rate: →. RPE: →, ↑in 32°C. **Self-paced:** Total distance: →. Mean power output: →. Peak power output: →. Mean speed: →. Max speed: →. Heart rate: →. RPE: ↑ in 32°C.

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TABLE 2 (Continued)

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
Piacentini et al. (31)	*N* = 8	Cycling tests (time trial) starting at 65% Wmax until the participants completed a predetermined amount of work (equal to about 90 min cycling at 65% Wmax as fast as possible).	Bupropion 600 mg (2 × 300 mg).	The night before and the morning of the experiment.	**Secondary:** Exercise time. Heart rate. Blood lactate. RPE.	Exercise time: →. Heart rate: →. Blood lactate: →. RPE: →.
Roelands et al. (20)	*N* = 8	60-min cycling at 55% of Wmax followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible) in warm (30°C) condition.	Bupropion 3 × 150 mg; Bupropion 7 × 300 mg (2 × 150 mg).	One pill (150 mg) for each of the first 3 days and two capsules for the remaining 7 days (one pill in the morning, the second in the afternoon).	**Primary:** Exercise time. **Secondary:** Mean power output (W). Heart rate. RPE.	Exercise time: →. Mean power output: →. Heart rate: →. RPE: →.
Roelands et al. (32)	*N* = 10	60-min cycling at 55% of Wmax followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible) in warm (30°C) condition.	Bupropion (2× à 150 mg/225 mg/300 mg).	The night before and the morning of the experiment.	**Primary:** Exercise time. **Secondary:** Heart rate. RPE.	Exercise time: ↓ in 300 mg (faster). Heart rate: ↑ in 300 mg. RPE: →.
Watson et al. (6)	*N* = 9	60-min cycling at 55% of Wmax followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible) in temperate (18°C) or warm (30°C) conditions.	Bupropion 600 mg (2 × 300 mg).	The night before and the morning of the experiment.	**Primary:** Exercise time. **Secondary:** Power output (W). Heart rate. RPE.	**18°C:** Exercise time: →. Power output: →. Heart rate: →. RPE: →. **30°C:** Exercise time: ↓ (9% faster). Power output: ↑. Heart rate: ↑. RPE: →.
Goekint et al. (33)	*N* = 11	60-min cycling at 55% of the maximal power output (Wmax) followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible).	Reboxetine 16 mg (2 × 8 mg).	The night before and the morning of experiment.	**Secondary:** Exercise time. Heart rate. RPE.	Exercise time: ↑ (14.6 ± 15.5% slower). Heart rate: ↑ during 60 min cycling; → during time trial. RPE: →.

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TABLE 2 (Continued)

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters (primary/secondary)	Statistical outcome *(data compared to placebo/all trials)*
Klass et al. (34)	*N* = 10	60-min cycling at 55% of (Wmax) followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible). Neuromuscular measurements of knee extensors (rectus femoris, vastus medialis, and biceps femoris).	Reboxetine 16 mg (2 × 8 mg).	The night before and on arrival in the lab on experiment day.	**Primary:** Exercise time. **Secondary:** Heart rate. RPE. Mean power output. MVC torque.	Exercise time: ↑ (9.4% slower). Heart rate: →. RPE: →. Mean power output: ↓. MVC torque: →.
Klass et al. (35)	*N* = 9	Repeated 3-s submaximal isometric contractions of the knee extensors (rectus femoris, vastus medialis, vastus lateralis, and biceps femoris) with a 2-s rest between each contraction and performed until task failure.	Reboxetine 16 mg (2 × 8 mg).	The night before and on the arrival in the lab on experiment day.	**Primary:** Endurance time. **Secondary:** Heart rate. RPE. MVC torque.	Endurance time: ↓ (15.6% shorter). Heart rate: ↑. RPE: ↑. MVC torque: ↓ (41.1%).
Piacentini et al. (36)	*N* = 7	Cycling tests (time trial) starting at 65% Wmax until the participants completed a predetermined amount of work (equal to about 90 min cycling at 65% Wmax).	Reboxetine 8 mg (2 × 4 mg).	The night before and the morning of the experiment.	**Primary:** Exercise time. **Secondary:** Heart rate. Blood lactate. RPE.	Exercise time: →. Heart rate: →. Blood lactate: →. RPE: →.
Roelands et al. (37)	*N* = 9	60-min cycling at 55% of (Wmax) followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible) in temperate (18°C) or warm (30°C) conditions.	Reboxetine 16 mg (2 × 8 mg).	The night before and the morning of the experiment.	**Primary:** Exercise time. **Secondary:** Power output. Heart rate. Blood lactate. RPE.	**18°C/30°C:** Exercise time: ↓. Power output: ↓. Heart rate: ↑. in 18°C; → in 32°C. Blood lactate: ↓ in 18°C. RPE: →.
Meeusen et al. (38)	*N* = 7	Cycling to exhaustion at 65% Wmax.	Ritanserin (0,3 mg/kg).	Two capsules 24 h the day before and immediately before the experiments.	**Primary:** Time to exhaustion. **Secondary:** Heart rate. Blood lactate. Respiratory quotient (RQ).	Time to exhaustion: →. Heart rate: →. Blood lactate: →. RQ: ↑.

N, total sample size; MVC, maximal voluntary contraction; RPE, rating of perceived exertion; →, no changes; ↑, increase/longer time; ↓, decrease/shorter time.

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TABLE 3 Antipsychotics: experimental testing, drug and measured performance parameters.

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
Adamson et al. (17)	*N* = 5	Visual stimulus test. Grip strength test. Lumbar pull. Chinnings (pull-ups).	Oxypertine 0 mg/5 mg/ 10 mg/20 mg/ 40 mg.	Each dose repeated twice 2 h before starting the tests.	**Secondary:** Reaction time. Grip strength. Lumbar pull. Chinning number.	Reaction time: →. Grip strength: ↓. Lumbar pull: ↓. Chinning number: →.
Kim et al. (39)	*N* = 30 HC = 15	Incremental cycling (start at 30 W with an increase of 10 W per minute) until exhaustion.	Clozapine: participants treated were divided into groups based on their antipsychotic medication status: those treated mainly with clozapine (i.e., in an amount greater than 50% of total CPZE) comprised the clozapine group, those treated mainly with other antipsychotics (i.e., in an amount greater than 50% of total CPZE) comprised the non-clozapine group.		**Primary:** Resting heart rate. Peak heart rate. Heart rate reserve. **Secondary:** VO_2 peak. Oxygen pulse. Ventilation. Respiratory exchange ratio. RPE.	Resting heart rate: ↑. Peak heart rate: ↑. Heart rate reserve: ↓. VO_2 peak: ↓. Oxygen pulse: →. Respiratory exchange ratio: →. RPE: → *(compared to the non-clozapine group).*
Perez-Cruzado et al. (40)	*N* = 62	Physical fitness test battery: – Passive knee extension test. – Calf muscle flexibility test. – Anterior hip flexibility test. – Functional shoulder rotation test. – Timed-stand test. – Partial sit-up test. – Seated push-up test. – Grip test. – Single leg stance (open and closed eyes). – Functional reach test. – 2-min step test.	Risperidone consumer. Olanzapine consumer.		**Secondary:** Physical fitness: Aerobic condition. Flexibility. Balance. Strength.	**Risperidone:** Flexibility: →. Balance: →. Strength: →. Aerobic condition: ↓ *(compared to the non-risperidone-group).* **Olanzapine:** Flexibility: →. Balance: ↓. Strength: ↓. Aerobic condition: ↓ *(compared to the non-olanzapine-group).*

N, total sample size; RPE, rating of perceived exertion; →, no changes; ↑, increase/longer time; ↓, decrease/shorter time; HC, healthy control.

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TABLE 4 Sedatives: experimental testing, drug and measured performance parameters.

References	Sample size	Exercise testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
Charles et al. (18)	*N* = 8 + 27	Study 1: cycling 10 min at 120 Watts, than until to exhaustion with the work load being increased by 20 watts each minute. Study 2: cycling for 4 min at 50, 100, and 150 watts, respectively, and then until exhaustion.	Nitrazepam 10 mg. Temazepam 30 mg.	Double-Dummy protocol for 9 nights: Period 1: Temazepam (3 × 10 mg). Period 2: Nitrazepam (2 × 5 mg). Period 3: placebo 2 weeks interval between each period. Medication was taken 0.5 h before retiring.	**Secondary:** Peak level of exercise. Heart rate. Mean oxygen (O_2) consumption.	**Study 1:** **Nitrazepam** Peak level of exercise: ↓. Heart rate: →. Mean O_2 consumption from 140 W: ↑. **Temazepam:** Peak level of exercise: ↓. Heart rate: →. Mean O_2 consumption: →. **Study 2:** **Nitrazepam:** Peak level of exercise: ↓. Heart rate: ↑. Mean O_2 consumption: →. **Temazepam:** Peak level of exercise: ↓. Heart rate: ↑. Mean O_2 consumption: →.
Collomp et al. (41)	*N* = 7	Wingate Test on a cycle ergometer	Lorazepam 1 mg	4 h before exercise testing	**Primary:** Peak power (PP) **Secondary:** Mean power (MP). Percentage of power decrease (% PD). Blood lactate.	Peak power: ↓. Mean power: →. % PD: →. Blood lactate: ↓.
Collomp et al. (42)	*N* = 7	Cycling at 85% VO2max until exhaustion.	Lorazepam 1.5 mg.	3 h before exercise testing.	**Primary:** Exercise time. **Secondary**: Blood lactate.	Exercise time: →. Blood lactate: ↓.
Ergen et al. (43)	*N* = 24	6× distance shooting (each round 3 arrows in 8 series, means in summary 24 shots).	Diazepam 5 mg.	Not provided.	**Primary:** Shooting scores. **Secondary:** Heart rate. Clicker reaction time. Aiming behavior. Center of pressure.	Shooting scores: →. Resting heart rate: →. Shooting heart rate: →. Clicker reaction time: →. Aiming behavior: →. Center of pressure: →.

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TABLE 4 (Continued)

References	Sample size	Exercise testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
Grobler et al. (44)	*N* = 12	30-m sprint test. Agility test. Graded treadmill running test to exhaustion.	Loprazolam 2 mg. Zopiclone 7.5 mg.	10 pm the night before exercise testing.	**Secondary:** Sprint time. Total time agility test. Time to exhaustion. Oxygen uptake. Max. ventilation rate. Max. heart rate. RPE.	**Both drugs:** Sprint time: →. Total time agility test: →. Time to exhaustion: →. Oxygen uptake: →. Max. ventilation rate: →. Max. heart rate: →. RPE: →.
Ito et al. (8)	*N* = 8	Vertical jumps. 50-m sprint.	Zolpidem 10 mg	11 pm the night before exercise testing.	**Secondary:** Vertical jumps (cm). 50-m sprint (s).	Vertical jumps: →. 50-m sprint: →.
Ito et al. (46)	*N* = 21	Forward bending. Right grip strength. Right quadriceps muscle strength. Repeated side jumps.	Zaleplon 10 mg.	Immediately before going to bed.	**Secondary:** Forward bending (cm). Grip strength (kg). Quadriceps strength (kg). Repeated side jumps (n).	Forward bending: →. Grip strength: →. Quadriceps strength: →. Repeated side jumps: →.
Suda et al. (45)	*N* = 12	Vertical jumps. 50-m sprint. Repeated side jumps.	Eszopiclone 2 mg.	Immediately before going to bed (11.00 pm).	**Secondary**: Vertical jumps (cm). 50-m sprint (s). Repeated side jumps (n).	Vertical jumps: →. 50-m-sprint: →. Repeated side jumps: →.
Tafti et al. (9)	*N* = 8	Standing jump test. Running time test.	Zopiclone 7.5 mg.	11 pm the night before exercise testing.	**Secondary:** Standing jump. Running time.	Standing jump: →. Running time: →.

N, total sample size; RPE, rating of perceived exertion; →, no changes; ↑, increase/longer time; ↓, decrease/shorter time.

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TABLE 5 Stimulants: experimental testing, drug and measured performance parameters.

References	Sample size	Experimental testing	Drug	Time of drug intake	Performance and physical parameters *(primary/secondary)*	Statistical outcome *(data compared to placebo/all trials)*
King et al. (47)	*N* = 15	Muscle-fatiguing handgrip task during functional magnetic resonance imaging.	Methylphenidate 20 mg.	Before the start of the exercise testing	**Primary:** Mean grip force.	Mean grip force: ↑.
Klass et al. (34)	*N* = 10	60-min cycling at 55% of (Wmax) followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible). Neuromuscular measurements of knee extensors (rectus femoris, vastus medialis, and biceps femoris).	Methylphenidate 40 mg.	On arrival in the lab on experiment day.	**Primary:** Exercise time. **Secondary:** Heart rate. RPE. Mean power output. MVC torque.	Exercise time: →. Mean power output: →. Heart rate: ↑. RPE: →. MVC torque: ↓.
Roelands et al. (48)	*N* = 8	60-min cycling at 55% of Wmax followed by a time trial until the participants completed a predetermined amount of work (equal to about 30 min cycling at 75% Wmax as fast as possible) in temperate (18°C) or warm (30°C) conditions.	Methylphenidate 20 mg.	1 h before the start of exercise.	**Primary:** Exercise time. **Secondary:** Power output. Heart rate. RPE.	**18°C:** Exercise time: →. Heart rate: →. RPE: →. **30°C:** Exercise time: ↓ (16% faster). Power output: ↑. Heart rate: ↑. RPE: →.
Westover et al. (49)	*N* = 245	Treadmill exercise test until exhaustion.	An amphetamine- or methylphenidate-type (AMP/MPH) stimulant.	Dosage and duration of medication use was not provided.	**Primary:** Peak heart rate. **Secondary:** Peak systolic blood pressure (SBP). Average rise in systolic blood pressure. Estimated VO_2max.	Peak heart rate: ↓. Peak SBP: →. Average SBP: →. Estimated VO_2max: →.

N, total sample size; MVC, maximal voluntary contraction; RPE, rating of perceived exertion; →, no changes; ↑, increase/longer time; ↓, decrease/shorter time.

Blood lactate concentration during exercise testing was only measured in one study (27). Lactate increased throughout exercise but was not influenced by fluoxetine. Another study examined further SSRI and showed that the isokinetic muscle performance of depressed middle-aged patients (m/w) was improved after a 3-month treatment with different SSRI (fluoxetine, sertraline, fluvoxamine, or citalopram) (28).

Effects of bupropion

Six publications examined the effects of bupropion (6, 20, 29–32). One clinical trial showed that the acute administration of a single dose of bupropion (2 × 300 mg) during prolonged exercise cycling in a temperate conditions had no effect on performance in well-trained male cyclists (31). But in warm conditions (30°), acute bupropion administration enabled endurance-trained males to 9% faster completed time trials (cycling) in the bupropion condition compared to placebo (6). Two further trials supported this finding, both in physically active women (29) and in well-trained male cyclists (32). Continuous administration of bupropion (10 days of medication) caused no differences in cycling performance in trained males (20). Neuromuscular data showed that maximal voluntary contraction and voluntary activation were unaffected by the administration of bupropion (2 × 300 mg) during cycling in temperature (20°) and warm (32°) conditions in physically active males (30). Heart rates increased over time during exercise cycling (6, 20, 31, 32) and exercise intensity (30), but were not influenced by drug administration. The results of Cordery et al. (29) showed significant changes in heart rate, but only at the end of the exercise test. Blood lactate concentration was not influenced by bupropion (31). The subjects of all six studies were of similar age (mid-late 20s).

Effects of reboxetine

We identified five randomized controlled trials with reboxetine (33–37). All drug administration of reboxetine were given as a single-dose, examined in young physically active males. One study showed no differences in cycling performance between reboxetine (8 mg) intake and placebo (36). Nearly all other studies showed decreases in exercise performance after reboxetine (16 mg) (33–35, 37). Lactate blood concentration (36) and heart rate (33, 36) changed but were not influenced by reboxetine intake. But in one study, heart rate was significantly higher in the reboxetine condition compared to placebo in cooler environment (18°) (37). This drug-induced effect could not be replicated in the heat (30°) (37). Blood pressure was not influenced by drug. At the end of the time trials and after recovery in reboxetine (18°), the blood lactate concentrations were significantly lower than during placebo (18°) (37).

Effects of a further antidepressant drug

The results of one study showed that a specific centrally acting 5-HT$_{2A/2C}$ antagonist (5-Hydroxytryptamin/Serotonin, single-dose Ritanserin, 0,3 mg/kg) did not influenced the time to exhaustion in cycling in trained males (38). Respiratory quotient at the end of exercise was significantly higher in Ritanserin group, while the increase during exercise was comparable in all groups (38).

Antipsychotics

Our search resulted in three publications using the antipsychotic drugs oxypertine (17) (rarely used in clinical practice), clozapine (39), olanzapine and risperidone (40). There are 2/3 studies that recruited mixed participant and 1/3 study was only with male participants. In all studies the subjects were approximately between 20 and 30 years old. Oxypertine was examined in different single-doses from 0 to 40 mg. Physical performance in several exercise tests (muscular force, muscular endurance) in trained athletes (gender unknown) declined progressively as the dosage was increased (17). Negative effects were also found with olanzapine and risperidone (no single-dose) in several physical exercise tests (flexibility, balance, strength, and aerobic condition) examined in a cross-sectional study with middle-aged patients (m/w) (40). Clozapine treatment (no single-dose) was associated with reduced cycling performance in middle-aged patients (m/w) with schizophrenia or schizoaffective disorder compared with non-clozapine antipsychotics (39).

Sedatives

Our search resulted in nine studies using benzodiazepines (18, 41–44) and z-drugs (8, 9, 44–46). For sedatives there are 4/7 studies that recruited mixed participants and 3/7 were only with males. In all studies the subjects were approximately between 18 and 26 years old.

Benzodiazepine

One study applied temazepam 30 mg, nitrazepam 10 mg and placebo for 9 days in young university students (m/w) (18). On day 2, maximal attained exercise levels in cycling with temazepam 30 mg and nitrazepam 10 mg were comparable to placebo, on day 9, physical performance with nitrazepam was lower than with temazepam and placebo (18). One study showed that 4 h after drug intake, a single-dose of lorazepam 1 mg impaired anaerobic peak power and induced a significant decrease in blood lactate concentration during a Wingate test in healthy volunteers (m/w) (41), while another study found that 3 h after a single-dose of lorazepam 1.5 mg time of cycling was not significantly changed in young male triathletes (42). Diazepam 5 mg (exact time of intake was not provided) was shown to not significantly change shooting performance in Turkish archers (m/w) (43). Ten hours after night-time administration, a further study showed no significant impairment of physical performance in sprint, agility and running after a single-dose of loprazolam 2 mg, but drug intake resulted in a greater hangover effect physically active volunteers (m/w) (44).

Z-drugs

Five further studies examined the effects of z-drugs on physical performance with no significant adverse effects on performance. Two RCTs could not identify impaired athletic performance measured with a vertical jump and a 50-m sprint after taking zolpidem 10 mg (8), as well as no increased endurance time after a running test with zopiclone 7,5 mg (9), both with two doses over two nights in young male athletes. As well, 10 h after night-time administration of single-dose zopiclone 7.5 mg physical performance in sprint, agility and running was not significantly impaired in physically active volunteers (m/w) (44). A recent study assessed the residual effects of a single-dose eszopiclone 2 mg on physical performance in male athletes and resulted in no significant differences in vertical jump, 50-m sprint and repeated side jumps (45), as well as a single-dose of zaleplon 10 mg that did not affect physical performances in forward bending, grip strength, quadriceps strength and side jumps (46).

Stimulants

For stimulants there are 2/4 studies that recruited mixed participants and 2/4 were only with males. In all studies the subjects were approximately between 26 and 42 years old. In contrast to sedatives, stimulants could possibly enhance physical performance. This hypothesis was supported by the results of two studies with acute administration of methylphenidate 20 mg after a handgrip task (in young healthy volunteers m/w) and cycling (in young well-trained males) (47, 48), while one study revealed no significant changes in cycling performance after single-dose methylphenidate 40 mg in well-trained males (34). A cross-sectional study examined stimulant medication use and maximal exercise running test outcomes in a large community sample (49). Stimulant medication use was not associated with increases in peak systolic blood pressure (SBP) and average SBP rise, nor did it impact cardiorespiratory fitness (VO_2max). Dosage and duration of use of medications were not available (49). Heart rate significantly increased by methylphenidate in warm condition (48) and was higher at the end of the time trial for methylphenidate than for the placebo (34). But it was also shown, that stimulant medication users had a significantly lower peak heart rate (49).

Discussion

With 33 included studies, this is the first systematic review examining the effects of psychiatric medication on physical performance in physically healthy adult humans. Differentiated by their medical compound, dose and period of use, psychotropic drugs can have performance-limiting or performance-enhancing effects. These findings can help to provide further information about the medication to the patients and thereby lead to reduced discontinuation rates. In the following, we discuss four medication groups separately (antidepressants, antipsychotics, sedatives, and stimulants).

Antidepressants

Within the antidepressants, nine studies have been conducted examining the effects of SSRI on exercise performance using paroxetine (21–26) and fluoxetine (19, 27). Three studies (22, 23, 26) with comparable dosages and application times of paroxetine led to contradictory conclusions. Two studies (23, 26) showed reduced total exercise time, one did not observe any difference after the intake of paroxetine (22). In contrast, another study (22) using the same dose and same time of administration did not observe any difference in total exercise time. The major difference in the study protocols and therefore a possible explanation for the different findings was the manipulation of the ambient temperature (30°C) (22) at which the exercise was performed compared to that of the previous studies (23, 26). It has been suggested that serotonin may play a role in thermal regulation and elevated body temperature is a major factor in the development of fatigue during prolonged exercise (50). The results suggest that oral administration of 20 mg paroxetine did not significantly influence the thermoregulatory factors that may limit exercise capacity (22). Based on these results, the authors of a later published study (24) hypothesized that the dose of 20 mg paroxetine might be insufficient to consistently influence the serotonergic system and consequently physical performance. In their study, they tested doses ranging from 10 to 40 mg of paroxetine. Surprisingly, the higher dose of 40 mg did not affect physical performance. Physical performance only decreased after administration of 20 mg of paroxetine (24). The authors explained this difference based on the pharmacological profile of this agent. Paroxetine increases the extracellular concentration of brain 5-HT, which can promote the release of dopamine (51). A higher dose of 40 mg paroxetine may result in a higher stimulation of 5-HT3 receptors compared to 20 mg of paroxetine, thus increasing dopamine release into the synaptic cleft (24). Furthermore, the authors assumed that 5-HT receptor responses could be influenced by an individual's aerobic capacity level. They suggest that individuals with higher aerobic capacity would be less affected by psychiatric medication than those with a low aerobic capacity level. However, their results revealed decreased physical performance in the high aerobic capacity group which suggested that individuals with higher aerobic capacity might be more responsive to pharmacological activation of the serotonergic system during exercise (24). The authors discussed various explanations for this observed phenomenon, such as higher body fat content in volunteers with lower aerobic capacity, differences in thermoregulation or changes in carbohydrate availability or acid-basic balance between the groups, but they could not postulate a 'one-size-fits-all' hypothesis (24).

Two studies observed no impact of fluoxetine on physical performance, neither after acute (19, 27) nor after continuous drug administration (19). The authors of another study grappled with the *central fatigue hypothesis*, which states that an increased concentration of brain 5-HT as a result of a long-term exercise may contribute to the perception of central fatigue. However, their results showed that subjects were not hindered by the central fatigue hypothesis during the 80 and 90% VO_2max trials (19) also not in the previously mentioned study during 65% Wmax (27). This can possibly be attributed to peripheral mechanisms that contribute to fatigue during short duration exercise training (52). A previously published study showed that, at a lower intensity, there is an earlier onset of fatigue during 70% VO_2max cycle ergometer test, after the administration of a SSRI (paroxetine) (26). Similarly, subjects expressed a greater perceived exertion during a cycle ergometer test after receiving fluoxetine (5). Both of the cited studies indicated that SSRI administration may play a role in fatigue during endurance exercise. Interestingly, the results of the chronic study (cycling at 90% VO_2max) showed reduced ventilation (7.5%) during the fluoxetine trial with no alteration in performance (19). The authors discussed that this may have been caused by inhibitory and excitatory 5-HT receptors that have been identified in the respiratory system of the cat (53). The role of the 5-HT metabolism during exercise is very complex which was also discussed in Kavanagh et al. (21) and Thorstensen et al. (25). The studies showed that with increased 5-HT availability voluntary muscle activation and torque generation increased during unfatigued maximal contraction and in contrast, the ability to generate maximal torque was compromised under fatigue conditions (21). The authors suggested that serotonergic drive, that occurred with prolonged maximal contractions, provided a spinal mechanism by which higher concentrations of 5-HT may contribute to central fatigue (21). Interestingly, during sustained submaximal contractions, enhanced availability of 5-HT did not directly influence motor performance (25). Only strong fatiguing contractions causing strong serotonergic drive may cause 5-HT-associated reductions in motor output. It should be further studied to understand its mechanisms of action during exercise and especially its role in the onset of fatigue. However, the serotonergic system (could potentially) impact fatigue during exercise, but the mechanisms underlying this relationship remain elusive. Of the mentioned studies investigating how 5-HT concentration affects exercise performance, most of them used well-trained/physically active subjects (19, 22–24, 26, 27). In fact, only one publication included patients in their study. Its results showed that isokinetic muscle performance in patients with major depressive disorder was reduced compared to healthy controls. After 3 months of antidepressive treatment (comprising a trial of fluoxetine), muscle performance improved and the patients approached levels similar to the healthy control group. The authors suggested that this may be related to an increasing metabolism in brain structures, such as prefrontal cortex and basal ganglia (28). Although two other studies identified SSRI-mediated changes in central fatigue during sustained isometric contraction, their participants had no training history (21, 25), SSRI responses may be associated with the type of exercise as well as the individual's fitness level which was discussed earlier (24). In conclusion, it can be stated that the here presented studies have mostly shown limitations in physical performance. The explanations for the mentioned impairments may relate to the modification of central fatigue, which has not been adequately investigated so far. Moreover, there is no data on the nowadays commonly used preparations citalopram, escitalopram and sertraline.

With its norepinephrine dopamine reuptake inhibitor function, bupropion does not typically cause weight gain or sedation (54). The included studies suggest that there may be performance enhancement in heat (6, 29) but not in temperate conditions (31). Similar performance and thermoregulatory effects did not occur after continuous administration of bupropion over several days, which might be due to an adaptation of central neurotransmitter homeostasis (20). Further examinations (32) investigated a dose-response relationship. The study demonstrated that an ergogenic effect occurred when the highest dose (600 mg) of bupropion was taken, which is consistent to prior findings (6). Bupropion was shown to cause a suppressed sensation of heat enabling humans to push themselves to higher temperature without perceiving greater effort (6). This may potentially increase the risk of developing heat illness (6). Because of its ergogenic effect, which can lead to enhanced performance, it is included in the Monitoring Program of WADA (World Anti-Doping Agency) competition but is not prohibited in competition (54).

Similar examinations have been conducted with the norepinephrine reuptake inhibitor reboxetine. One study (36) found no effect of reboxetine 8 mg on performance (36). In contrast, two other studies showed that this medication may limit performance (33, 37). To identify the mechanisms that contributed to the decrease in performance after reboxetine 16 mg (37), other researchers analyzed the potential link between neural impairments and changes in brain neurotransmission (34, 35). Their results suggest that noradrenaline reuptake inhibition could contribute to the development of supraspinal fatigue observed after a prolonged cycling exercise (34) and after a fatiguing task involving intermittent submaximal contractions (35). Since corticospinal excitability was not modified after both exercising tests, norepinephrine appears to more specifically affect supraspinal centers located prior to the motor cortex.

In conclusion, the studies of antidepressants on physical performance must be considered heterogeneous and thus the observed effects inconsistent. Possible reasons for this include differences in study protocols (doses and acute versus continuous intake of the medication) and limitations (e.g., usually very small sample sizes). Only bupropion 600 mg resulted in performance enhancement in heat (6, 29, 32) but not in temperate conditions (31) with risk of contracting heat illnesses. Other antidepressants (paroxetine, fluoxetine, and reboxetine) led to impairments or showed no medication-induced changes during exercise. The mentioned drugs are usually not related to sedation. Therefore, further research is needed to elucidate the effects of psychotropic drugs that can cause greater sedation (e.g., mirtazapine or tricyclic antidepressants).

Antipsychotics

The effects of antipsychotics are more consistent and point to limited physical performance, even though only three studies could be included in this review (17, 39, 40). One study showed dose-dependent effects, with a gradual impairment as the dose level of oxypertine was increased from 5 to 40 mg (17). Another study showed that olanzapine had negative effects on muscle strength, balance and aerobic endurance and risperidone had negative effects on the amount of physical activity (40). The authors assumed that patients with severe psychiatric symptoms have a decrease in their activity levels and physical fitness in general. These facts may also be explained by side-effects such as increased fatigue or sedation, both of which might affect physical performance (40). These data confirm previous findings from a study that was not included in our review (different population), but showed that adults with severe mental illness (SMI) who were taking antipsychotic medication were less physically active and had lower body balance as well as muscular strength compared with unmedicated patients (12). Another study from our review showed that cardiovascular fitness was impaired during clozapine treatment which might be explained by the higher antagonistic activity at alpha-adrenergic receptors. This antagonism could lead to limited blood flow in the working skeletal muscle and compromise cardiovascular stability during exercise (39). We found no articles on the use of antipsychotic medication in athletes but based on the assumptions from the cited studies (12, 40), this collective might expect less limitations compared to those previously mentioned in patients. Due to a favorable side-effect profile, aripiprazole or lurasidone are recommended for this special collective (2). In addition, an important difference to the results from the antidepressants should be emphasized. The presented studies using antipsychotics have mostly included patients with a mental illness who have been taking the medication for a longer time period (39, 40). This may explain the consistent deterioration in physical performance with antipsychotic treatment. For antidepressants, mostly acute administration and well-trained subjects were investigated.

Sedatives

Sedatives are mostly used in clinical practice to treat insomnia and other sleep disturbances (55). They are a common issue for athletes after jet lag or as isolated symptoms in stressful situations. Commonly used sleep aids among the general population include benzodiazepines and z-drugs.

It would seem obvious that the intake of sedating medication at night may result in residual morning drowsiness, which may impair the participant's motivation and may increase perceived exertion. However, these assumptions were not confirmed by the identified studies in our review. The intake of loprazolam (2 mg) and zopiclone (7.5 mg) at 10 pm the night before the exercise test resulted in unchanged physical performance (44). The authors suggested that zopiclone may have a weaker (self-reported) hangover effect compared to loprazolam, but both drugs did not significantly impair objectively measured physical performance (44). A greater number of subjects reported feeling alert after the ingestion of zopiclone without having any residual drowsiness the morning following the night-time administration. This can possibly be attributed to the different half-lives of zopiclone [4–5 h, (56)] and loprazolam [6–12 h, (57)]. Previously published studies that were not included in our review (missing data about physical fitness) supported that finding and stated that due to the relatively short half-life of zopiclone, the hangover effect the morning after night-time administration was minimal (56) and a 7.5 mg dose of zopiclone has been shown to have the optimum sedative properties with negligible side-effects (58). Similar effects are shown with three further 'z' agents that were used in double-doses but showed no adverse effect on physical performance (8, 9, 46). This can possibly be explained by their short plasma half-life and limited duration of action (59). Zaleplon is characterized by an ultrashort half-life (approximately 1 h). Zolpidem and zopiclone have longer half-lives (1.5–2.4 h and 4–5 h) (59). These properties, together with the low risk of residual effect, may explain the limited negative influences on physical performance (59). Instead, the authors concluded that zopiclone and zolpidem have useful hypnotic activity without disturbing physical performance on the following day (8, 9), suggesting that zolpidem may be used in healthy humans to adjust sleep disturbances (8).

Similar results were shown by another study evaluating psychomotor and physical performances on the following day after taking eszopiclone (half-life 5–6 h) at bedtime (45). The authors did not identify any impairment. Another study examined the longer acting benzodiazepines temazepam [half-life of 5.3 h (60)] and nitrazepam [half-life of 30 h (61)] and their effects on exercise performance using two separate study designs (study 1: drug for two nights, study 2: drugs for nine nights) with night-time administration (18). In study 1, at all work-loads both drugs showed an increase in ventilation, gas exchange and heart rate when compared to placebo suggesting that the subjects were working harder at all work loads and this might have reduced the maximum load they could achieve. In study 2, a similar trend in the maximal exercise load was displayed with a significant difference in the nitrazepam group on day 9 compared to temazepam and placebo. The authors attributed this finding to a probable hangover effect of nitrazepam (18).

Two further studies investigated the effects of benzodiazepines on physical performance (41, 42). Subjects who had been treated with lorazepam (1.5 mg) 4 h before cycling at 85% of their VO_2max (submaximal exercise) showed no difference when compared to placebo but exhibited significantly lower values in selected hormones and lactate (42). On the other hand, subjects treated with lorazepam (1.0 mg) 3 h before exercising a Wingate Test (supramaximal exercise) showed significantly lower values in peak power and maximal lactate when compared to placebo (41). Authors in both studies suggested that the lower lactate values may be due to either a decrease in muscle glycogenolysis or a change in lactate removal (41, 42) but in Collomp et al. they did not find a clear association between drug effects and impairment in peak power (41). Melatonin is one of the most studied sleep aids among athletes (55), but no study met our inclusion criteria due to an inappropriate study design. However, one study indicated no impairment of performance the following day after intake (62).

In summary, due to the heterogeneous study designs (drug, dosage, and exercise testing) of the studies included in our review, it is difficult to derive consistent findings about sedatives and their effects on physical performance. Sedatives may result in residual morning drowsiness, which may impair the participant's motivation but not directly physical performance which may be explained by different half-lives. Especially with regard to their use in sleep disorders or stage fright, sedatives should be further investigated, since reduced muscle strength and poorer running times in the endurance sport have already been reported (63).

Stimulants

Stimulants are known to be performance-enhancing and they are banned (only) in competition (64). This was first reported in the Journal of the American Medical Association (JAMA) (65). Since then, further studies have reported similar effects with performance enhancements in anaerobic capacity, strength, time to exhaustion, acceleration, and maximum heart rate (66). Some researchers suggest that athletes taking stimulants (e.g., methylphenidate) may be able to exercise to higher core temperature without any change in the perception of effort or thermal stress. The ergogenic effect was confirmed by one of our included studies (48). Subjects showed improved performance in the heat but not in temperate conditions without any greater perception of effort or thermal stress. Concerning this matter, stimulants might not only be ergogenic but also harmful in the heat as athletes may be unaware of increasing thermal/heat stress promoting heat illness (6, 48).

In another experiment, subjects demonstrated enhanced force and changes in brain connectivity throughout a muscle-fatiguing handgrip test using acute ingestion of 20 mg methylphenidate at room temperature (47). The authors discussed, that given agents may affect dopamine transmission and consequently cause an increase in fatigue and a decrease in motivation (67), methylphenidates influence on neurotransmission make subjects more willing to exert forces closer to their maximum (68). The ergogenic mechanism of methylphenidate remained elusive in this study, further experiments were proposed to detect the neurochemical underpinnings of motivation and muscle fatigue.

One RCT tested the effects of acute noradrenaline (reboxetine 8 mg) and acute dopamine (methylphenidate 40 mg) reuptake inhibitors on prolonged cycling exercise and supraspinal fatigue in a temperate environment (34). Compared to reboxetine, methylphenidate did not affect exercise performance and did not contribute to the development of supraspinal fatigue. It can be speculated that compared to dopamine, norepinephrine has an inhibitory effect on performance. The effects of reboxetine have already been discussed in the paragraph regarding antidepressants (34).

We were further able to identify a cross-sectional study examining stimulant medication use and maximal exercise test outcomes in a large community sample (49). In contrast to previous studies that have shown an increase in heart rate associated with acute application of methylphenidate (34, 48), this study showed a lower peak heart rate in stimulant medication users compared to non-users (49). The reasons were unclear, however, authors suggested that unmeasured confounding of stimulant use or confounding by contraindication and survivor bias caused lower peak heart rates.

Conclusion

This is the first systematic review evaluating the effects of psychiatric medication on physical performance. We identified studies with antidepressants, antipsychotics, sedatives and stimulants. Antipsychotics seemed to be performance impairing, while the findings for antidepressants and sedatives were more inconsistent. Stimulants were the only group with consistent performance-enhancing effects.

Several issues impede the formulation of generalized conclusions for treatment regimes and should therefore be further considered in future studies. Most studies were conducted in populations of athletes, limiting general transferability of the results. Although 27 of our included studies have powered their sample size calculation to the primary sport outcome, most of them were conducted in small sample sizes ($N < 10$). To get an impression of sample sizes for future studies, we made some assumption using G*Power (69). Assuming a two-sided independent t-test for a respective analysis, a power of 0.8 and an α-prolity of 0.05, a sample size of 34 subjects per group would be valid to identify a moderate effect size $d = 0.5$ and 19 subjects per group to identify a large effect size of $d = 0.7$ between two groups in a conservative between-group design. A within-group design using pared sample t-tests would results in slightly smaller sample sizes. Of our included studies five out of 36 included >26 subjects. Thus, most studies may have been underpowered and we recommend larger sample sizes for future studies. Moreover, most study protocols used single dose medication, which does not reflect real-world settings in clinical practice. Within the different medication groups, there was a bias toward specific drugs (e.g., six studies with paroxetine and none for the often-used venlafaxine). In addition, there were 17/21 studies for antidepressants, that only recruited male participants. This shows good comparability among these studies, since the age of the participants was almost identical, but there is only one study with female and just 2/21 studies with mixed participants. For antipsychotics, there are 2/3 studies, for sedatives there are 4/7 studies and for stimulants there are 2/4 studies that recruited mixed participants. However, future studies especially with antidepressants in female and mixed participants are necessary to be able to make sex-related conclusions and to state more details for the treatment reality.

Further research with longitudinal studies and therapeutic doses is recommended to focus on precisely these issues to be able to derive even more well-founded data and clinically reliable recommendations for therapy. We would suggest adding physical performance parameters such as e.g., exercise time, oxygen consumption, heart rate, muscle contraction or blood lactate concentration to the safety assessments in future clinical and approval studies for psychopharmacological compounds. On the one hand, one could assume that with an approval in psychopathology also physical performance parameters may improve. However, the here evaluated outcomes from mainly single-dose studies imply that a worsening of physical performance parameters need to be defined and evaluated as compound-specific side-effects. Moreover, with a deeper understanding of these effects of psychopharmacological compounds on physical performance parameters, medication prescriptions could become more tailored to individual requirements and addressed by specific side-management interventions. Less side effects due to impairments of physical performance (which might be misinterpreted as sedation) could lead to reduced discontinuation rates of treatment and therefore more successful treatments in terms of less discontinuation-based relapses.

Author contributions

AHi, DL, and AR conceived the study and performed the qualitative analyses. AHi wrote the first draft of this manuscript. AR and AlH supervised the project. EW provided methodological advice. All authors were involved in reviewing the manuscript and approved the final version of the manuscript.

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Conflict of interest

Within the last 5 years, AlH has received paid speakerships from Janssen, Otsuka, Recordati, and Lundbeck. He was member of Rovi, Recordati, Otsuka, Lundbeck, and Janssen advisory boards. He is the editor of the German AWMF S3 and the WFSBP schizophrenia guidelines.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.985983/full#supplementary-material

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The influence of exercise interventions on cognitive functions in patients with amnestic mild cognitive impairment: A systematic review and meta-analysis

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Introduction: Patients with amnestic mild cognitive impairment (aMCI) are more likely to develop dementia compared to patients with non-aMCI (naMCI). Among the mixed samples of aMCI and naMCI, exercise interventions are effective for patients with MCI to improve cognitive functions. However, the influence of exercise interventions on patients with aMCI is still unclear.

Objective: The objective of this systematic review and meta-analysis is to evaluate the influence of exercise interventions on cognitive functions in patients with aMCI.

Methods: Four literature databases (PubMed, Web of Science, EBSCO, and Cochrane Library) and three Chinese databases (China National Knowledge Infrastructure, Wanfang, and China Science and Technology Journal Database) were searched from their inception to August 31, 2022. Based on the preliminary search of seven databases and their cited references, a total of 2,290 records were identified. Finally, 10 studies with a total of 28 data points involving 575 participants with aMCI were included in this meta-analysis. If the measurements of outcomes were different among studies, the effect size was synthesized using the standardized mean difference (SMD) with a 95% confidence interval (CI). If the measurements were the same, the weight mean difference (WMD) with a 95% CI was used to integrate the effect size.

Data synthesis: The results showed that exercise interventions had no significant effects on improving several specific domains of cognitive functions including working memory (WMD = −0.05; 95% CI = −0.74 to 0.63; $p = 0.88$; $I^2 = 78\%$) and attention (SMD = 0.20; 95% CI = −0.31 to 0.72; $p = 0.44$; $I^2 = 60\%$). Additionally, exercise interventions had a significant effect on global cognitive function (SMD = 0.70; 95% CI = 0.50–0.90; $p < 0.00001$; $I^2 = 29\%$) and some specific cognitive domains including immediate recall (SMD = 0.55; 95% CI = 0.28–0.81; $p < 0.0001$; $I^2 = 0\%$), delayed recall (SMD = 0.66; 95% CI = 0.45–0.87; $p < 0.00001$; $I^2 = 37\%$), and executive function (SMD = 0.38; 95%

CI = 0.16–0.60; p= 0.0006; I^2 = 4%). Furthermore, subgroup analysis based on the intervention forms indicated that multi-component interventions (SMD = 0.44; 95% CI = 0.11–0.77; p = 0.009; I^2 = 0%) appeared to be less effective than the single-component intervention (SMD = 0.85; 95% CI = 0.60–1.10; $p < 0.00001$; $I^2 = 10\%$) in terms of boosting global cognitive function.

Conclusion: This meta-analysis suggests that the exercise can help patients with aMCI improve global cognitive function. And exercise interventions have positive influence on enhancing several specific cognitive domains such as immediate recall, delayed recall, and executive function.

Systematic review registration: http://www.crd.york.ac.uk/PROSPERO, identifier: CRD42022354235.

KEYWORDS

exercise, cognitive function, mild cognitive impairment, amnestic, meta-analysis, physical activity

Introduction

Recently, the population aging has become a global concern. World Health Organization (WHO) claims that the Western Pacific region has more than 245 million people over the age of 65 years and this number is projected to double by 2050 (1). The advanced age exacerbates the deterioration of the physical health and mental soundness of the elderly. Especially, the risk of developing dementia among older adults caused by aging is increasing rapidly. The estimated number of individuals with dementia has been predicted to reach 82 million worldwide by 2030 (2). The dementia severely impairs the quality of the life and the well-being of older adults and places a heavy burden on families and societies (3). Thus, there is an urgent need to find targeted treatments for slowing the progression of dementia.

In recent years, the increasing attention has been paid to populations with mild cognitive impairment (MCI) in order to prevent the occurrence of the dementia. MCI is a transitional condition that occurs between normal cognitive aging and dementia (4). According to the relevant data, the MCI prevalence in older adults between 60 and 84 years old is 6.7–25.2% (5). A meta-analysis (6) suggests that 12.2% of over 55-year-old Chinese people meet the diagnostic criteria for MCI and the elderly have a higher rate of MCI as their age increases. Patients who are diagnosed as MCI are worse in terms of the overall health and the balance than people without MCI (7). Also, it has been reported that patients with MCI are detected to have a higher chance of getting neuropsychiatric symptoms such as depression, anxiety, irritability, agitation, and apathy compared to healthy people (8, 9). Several studies have presented that MCI individuals who are accompanied by the symptoms of depression, apathy, and anxiety are more likely to develop Alzheimer's disease (AD) (10–12). In view of the above, it is vital to implement cost-effective and efficient treatments for MCI patients as early as possible.

Currently, there's no strong evidence supporting the prominent impact of drug treatments on improving cognitive functions in patients with MCI (13–16). Therefore, utilizing non-pharmacological interventions (e.g., exercise interventions) is a wise choice to increase cognitive levels for MCI individuals. Several original studies have demonstrated that exercise interventions are capable of enhancing cognitive functions (e.g., processing speed, working memory, and executive function) of MCI patients (17–19). For example, a 24-form simplified Tai Chi exercise intervention lasting 1 year contributed to a significant improvement in MCI older adults' delayed recall scores (20). Another study has illustrated that a 6-month resistance training is beneficial for the improvements of the global cognitive function in patients with MCI (21). Baker et al. (22) also have confirmed that the executive function of MCI patients can be ameliorated after a high-intensity aerobic training.

In addition, individuals with MCI can be further classified into amnestic MCI (aMCI) and non-amnestic MCI (naMCI) (23). Compared to naMCI people, patients with aMCI can suffer from more adverse influences in certain aspects. Several studies have proposed that individuals with aMCI have a greater risk of progressing to AD (24–26). Moreover, aMCI patients are more likely to obtain a higher hazard ratio of the death (27, 28). Consequently, we should pay more attention to the non-pharmacological interventions (e.g., exercise interventions) to raise the cognitive functions for aMCI patients.

Plenty of meta-analyses have focused on investigating the effect of different exercise interventions on cognitive functions in mixed samples of aMCI and naMCI (29–33). Specifically, Zhu et al. (31) in their meta-analysis highlighted that an aerobic dance intervention was useful to reinforce the global cognitive function, memory, and executive function of patients who were diagnosed with MCI. Another meta-analysis suggested that the twice-weekly resistance interventions could display a larger improvement in MCI individuals' global cognitive function but not for working memory (33). Although these meta-analyses have discussed the effect of exercise interventions on cognitive functions in mixed samples of MCI individuals, the researchers have not distinguished the subtypes of MCI including aMCI and naMCI. Hence, the separate influence of exercise interventions on the cognitive functions of aMCI individuals or naMCI individuals is still uncertain. Given that patients with aMCI get greater impairment in some aspects, it is important to integrate the relevant data using meta-analysis based on the original studies and comprehensively evaluate the effect of exercise interventions on aMCI patients' cognitive functions.

This systematic review and meta-analysis intends to explore the influence of exercise interventions on cognitive functions in patients with aMCI.

Methods

Search strategy and study selection

Based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we conducted this systematic review and meta-analysis by searching seven databases from their inception to August 31, 2022. PubMed (1978–2022), Web of Science (2010–2022), EBSCO (2005–2022), Cochrane Library (2012–2022), China National Knowledge Infrastructure (CNKI) (2006–2022), Wanfang (2000–2022), and China Science and Technology Journal Database (2016–2022) were searched respectively using several keywords. Two independent authors (RW and HZ) evaluated all titles, abstracts, and full-text articles to filter and identify relevant studies. In order to avoid missing related articles as much as possible, we also screened references and citations from the included studies. Any disagreement was settled by discussion or by consulting a third arbitrator (XH). Table 1 shows the specific search strategy in PubMed.

We registered the protocol on the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number: CRD42022354235. There's no similar review protocol existing.

Inclusion criteria

In accordance with the PICOS principle related to the terms of patient/population, intervention, comparison/control, outcome, and study design, trials that met all of the following criteria were included: (1) participants were over the age of 50 years old; (2) participants were screened or diagnosed with aMCI by neurologists or based on Petersen's criteria (23), or participants with MCI who had memory complaints; (3) participants in the experimental group received exercise interventions or exercise interventions combined with psychological cognitive interventions; (4) participants in the control group maintained their regular lifestyles, received educational classes, or conducted sham exercise interventions (e.g., stretching or toning); (5) the outcomes were the common indicators reflecting cognitive functions such as executive function, memory, or attention; (6) only trials designed as the randomized controlled trials (RCTs) were covered; and (7) the peer-reviewed articles.

Exclusion criteria

Trials were excluded if they met one of the following exclusion criteria: (1) case reports, abstracts, or non-peer-reviewed articles (e.g., academic dissertations and conference posters); (2) trials recruited the mixed participants with different subtypes of MCI and the authors did not report the independent data points for aMCI patients; (3) participants were pregnant women, animals, or individuals who were diagnosed with other mental disorders like anxiety or schizophrenia; (4) participants in experimental and control groups received drug treatments; (5) missing data.

Quality assessment

The Cochrane Collaboration tool was used by two authors to independently examine the seven domain biases: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other bias (34). Three levels of bias risk (i.e., high, low, and unclear) were applied to grade the included studies. Any disagreement was settled by discussion or by consulting a third arbitrator (XH).

Data extraction

From each included study, two authors independently summarized the pertinent information as the following: author(s), country/region, participants' characteristics (e.g., age and gender), sample size, details of interventions (e.g., types, frequency, and duration), and reported outcomes.

Meta-analysis

The meta-analysis was carried out using the Review Manager software (Review Manager 5.3; The Nordic Cochrane Center,

TABLE 1 Search strategy in PubMed.

Step	Search strategy
#1	"Cognit* impair*" OR "MCI" OR "aMCI" OR "memory" OR "amnestic" OR "cognition disorders" OR "cognitive dysfunction" OR "memory impairment" [Title/Abstract]
#2	"Cognition" OR "cognition disorders" OR "cognitive dysfunction" [Mesh]
#3	#1 OR #2
#4	"Exercise" OR "physical activit*" OR "aerobic training" OR "resistance training" OR "circuit-based exercise" OR "combined exercise" OR "Chinese traditional exercise" OR "Chinese exercise" OR "Baduanjin" OR "Tai chi" OR "Taiji*" OR "Qi gong" [Title/Abstract]
#5	"Exercise" OR "resistance training" OR "circuit-based exercise" [Mesh]
#6	#4 OR #5
#7	"Cognition" OR "executive function" OR "memory function" OR "working memory" OR "delayed recall" OR "immediate recall" OR "attention" OR "verbal fluency" OR "visuospatial ability" OR "processing speed" [Title/Abstract]
#8	"Randomized controlled trial" OR "controlled clinical trial" OR "clinical trial" [Publication Type]
#9	"Randomized controlled trials as topic" [Mesh]
#10	#8 OR #9
#11	#3 AND #6 AND #7 AND #10

The Cochrane Collaboration). In this meta-analysis, various cognitive functions were measured using different scales. For example, the global cognitive function was assessed by the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog). The working memory was assessed by the Digit Span Test-Backward (DST-B). The immediate recall was evaluated by the Logical Memory I subtest of the Wechsler memory scale-revised (WMS-LM I) and Rivermead Behavioral Memory Test (RBMT). The delayed recall was evaluated by the Logical Memory II subtest of the Wechsler memory scale-revised (WMS-LM II) and RBMT. The executive function was appraised by the Symbol-Digit Substitution Test (SDST), Trail Making Test Parts B (TMT-B), Trail Making Test B minus A (TMT-B–A), and Stroop Color and Word Test (SCWT). The attention was appraised by the Digit Span Test-Forward (DST-F) and Test of Everyday Attention (TEA). If the reported outcomes were measured by different scales, the effect size would be synthesized using the standardized mean difference (SMD). If the outcomes were measured by the same scales, the effect size would be integrated using the weight mean difference (WMD). If outcomes were measured by reverse scored scales, the inverse of the original data would be used. Additionally, the Cochrane Handbook for Systematic Reviews stated that both post-intervention values ($\text{Mean}_{\text{post-intervention}} \pm \text{SD}_{\text{post-intervention}}$) of the outcome and changes from baseline ($\text{Mean}_{\text{of changes}} \pm \text{SD}_{\text{of changes}}$) could be employed to synthesize the effect size (35).

If studies presented standard error (SE) and the number of subjects (N), the formula "Standard Deviation (SD) $= \text{SE} \times \sqrt{N}$" would be used to compute the SD. If studies provided a confidence interval (CI), the formula "$\text{SD} = \sqrt{N} \times (l_{\text{upper}} - l_{\text{lower}})/c$" would be used to determine the SD. The upper and lower limits of the CI were denoted by the l_{upper} and the l_{lower}. And the constant c depended on the sample size and the CI (36). If studies did not provide the mean and SD of outcomes, we would contact the authors by email. The articles would be removed if we did not receive the reply.

The heterogeneity across the studies was evaluated using the I^2 index. When $I^2 \leq 25\%$, the low heterogeneity was estimated. When $I^2 \leq 50\%$ and $>25\%$, the moderate heterogeneity was assessed. When $I^2 \leq 75\%$ and $>50\%$, the high heterogeneity was identified. When $I^2 > 75\%$, the very high heterogeneity was evaluated (36). A random-effect model would be used to aggregate the outcomes for studies with high heterogeneity ($I^2 \leq 75\%$ and $>50\%$) or very high heterogeneity ($I^2 > 75\%$). Otherwise, a fixed-effect model would be chosen. Possible publication bias was evaluated when $I^2 > 50\%$ by assessing the asymmetry of funnel plots or by applying Egger's test (37). $p < 0.05$ was set as the significant level.

Results

Search results

The search procedure is presented in Figure 1. A total of 2,290 records were found after our preliminary search of seven databases and their cited references. There were 1,937 records left after removing duplicates. There were still 42 eligible articles left after checking titles and abstracts. After examining the full-text papers, 10 articles qualified for inclusion. A total of 28 data points (covering 575 individuals) from the 10 articles were included in this meta-analysis.

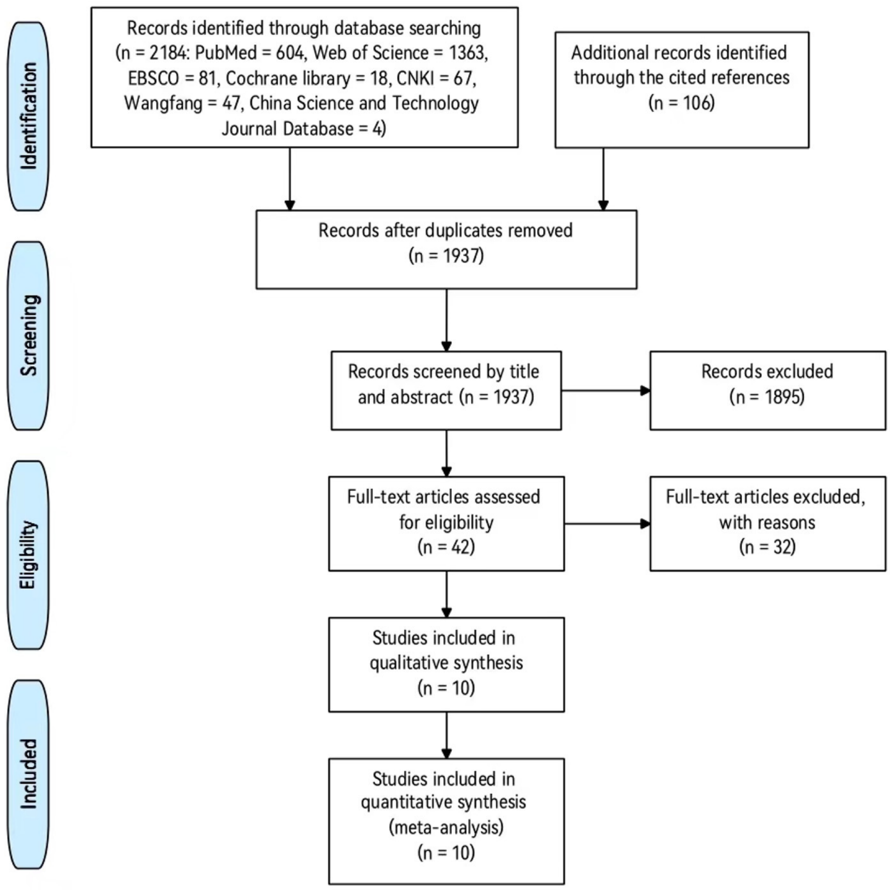

FIGURE 1
The flowchart of search procedure.

Characteristics of included studies

The characteristics of included studies are displayed in Table 2. The subjects in all studies were the aMCI older adults over the age of 50 years. These studies came from different countries around the world. One study (10%) was carried out in America (38). One study (10%) was conducted in China (39). One study (10%) was carried out in Greece (40). Two studies (20%) were performed in Japan (41, 42). Two studies (20%) were conducted in Korea (18, 43) and three studies (30%) were performed in Thailand (44–46).

Among these 10 studies, three studies (30%) conducted multi-component interventions (e.g., exercise interventions combined with psychological cognitive interventions). The other seven studies (70%) conducted single-component interventions (i.e., the isolated exercise intervention). For multi-component interventions, two studies performed the aerobic exercise (AE), resistance exercise (RE), postural balance retraining, and dual-task training programs. Another study performed physical activity (PA) promotion and behavior modification, AE, and dual-task training programs. For single-component interventions, subjects in two studies received the AE training. Subjects in two studies performed the RE training and subjects in three studies received other forms of the exercise (e.g., Tai Chi and traditional Thai exercise).

Additionally, the quality of included studies was evaluated according to the guidelines established by Higgins (34). As shown in Figure 2, these studies have relatively high qualities and the greatest source of bias was the blinding of participants and personnel (performance bias).

Global cognitive function

Seven data points from seven studies reported the influence of exercise interventions on global cognitive function in aMCI individuals. As depicted in Figure 3, there was a significant difference between the experimental and control groups based on a fixed-effect model (SMD = 0.70; 95% CI = 0.50–0.90; $p < 0.00001$; $I^2 = 29\%$). Except that, a

TABLE 2 Characteristics of included studies.

No.	Author (Ref)	Country	Participant age	The proportion of females (EG/CG)	Sample size	Intervention type	Intervention frequency	Intervention duration	Outcomes (measurements)
1	Suzuki et al. (42)	Japan	Age: 65–92 years	48/44%	**EG:** 24 **CG:** 23	**EG:** multi-component intervention (AE, RE, postural balance retraining, dual-task training program: subjects performed concurrent cognitive tasks during exercise) **CG:** education classes	**EG:** 90 min/day; 2 days/week **CG:** two education classes over 6 months	6 months	Global cognitive function (MMSE); immediate recall (WMS-LM I); delayed recall (WMS-LM II)
2	Park et al. (43)	Korea	Age: 50–85 years	68/71%	**EG:** 25 **CG:** 24	**EG:** multi-component intervention (PA promotion and behavior modification, AE, dual-task training program: subjects performed concurrent cognitive tasks during exercise) **CG:** none	**EG:** 110 min/day; 2 days/week	24 weeks	Global cognitive function (MMSE); working memory (DST); executive function (SDST)
3	Hong et al. (18)	Korea	Age: >65 years	70/75%	**EG:** 10 **CG:** 12	**EG:** RE (10-min warm-up, 40-min RE at 65% of 1RM, 10-min cool-down) **CG:** maintain regular lifestyle	**EG:** 60 min/session; 2 sessions/week	12 weeks	Global cognitive function (MoCA); working memory (DST-B); attention (DST-F)

(Continued)

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TABLE 2 (Continued)

No.	Author (Ref)	Country	Participant age	The proportion of females (EG/CG)	Sample size	Intervention type	Intervention frequency	Intervention duration	Outcomes (measurements)
4	Lü et al. (39)	China	Age: ≥65 years	73/70%	**EG:** 22 **CG:** 23	**EG:** RE (5-min warm-up, 50-min dumbbell-spinning exercises, 5-min cool-down) **CG:** maintain regular lifestyle	**EG:** 60 min/session; 3 sessions/week	12 weeks	Global cognitive function (ADAS-cog); working memory (DST-B); attention (DST-F); executive function (TMT-B)
5	Suzuki et al. (41)	Japan	Age: 65–93 years	48/44%	**EG:** 25 **CG:** 25	**EG:** multi-component intervention (AE, RE, postural balance retraining, dual-task training program: subjects performed concurrent cognitive tasks during exercise) **CG:** education classes	**EG:** 90 min/day; 2 days/week **CG:** three education classes over 12 months	12 months	Global cognitive function (MMSE); immediate recall (WMS-LM I); delayed recall (WMS-LM II); executive function (SCWT)
6	Sungkarat et al. (45)	Thailand	Age: 65–92 years	94/79%	**EG:** 33 **CG:** 33	**EG:** TC (10-min warm-up, 30-min TC exercise, 10-min cool-down) **CG:** maintain regular lifestyle	**EG:** 50 min/session; 3 sessions/week	15 weeks	Delayed recall (WMS-LM II); executive function (TMT-B–A)
7	Lazarou et al. (40)	Greece	Mean age: 66.8 years	80/76%	**EG:** 66 **CG:** 63	**EG:** international ballroom dancing [5-min warm-up, 45 min of new material (figures/dances), 10-min cool-down] **CG:** maintain regular lifestyle	**EG:** 60 min/session; 2 sessions/week	40 weeks	Global cognitive function (MMSE); immediate recall (RBMT1); delayed recall (RBMT2); attention (TEA)

(Continued)

TABLE 2 (Continued)

No.	Author (Ref)	Country	Participant age	The proportion of females (EG/CG)	Sample size	Intervention type	Intervention frequency	Intervention duration	Outcomes (measurements)
8	Sungkarat et al. (46)	Thailand	Mean age: 67.9 years	94/79%	**EG:** 33 **CG:** 33	**EG:** TC (10-min warm-up, 30-min TC exercise, 10-min cool-down) **CG:** education classes	**EG:** 50 min/session; 3 sessions/week **CG:** a 1-h presentation	6 months	Delayed recall (WMS-LM II); executive function (TMT-B–A)
9	Khanthong et al. (44)	Thailand	Age: 50–80 years	89/69%	**EG:** 35 **CG:** 36	**EG:** traditional Thai exercise (Ruesi Dadton: 15 postures with 10 repetitions for each posture) **CG:** maintain regular lifestyle	**EG:** 60 min/session; 3 sessions/week	12 weeks	Global cognitive function (MoCA); executive function (TMT-B)
10	Thomas et al. (38)	America	Age: 55–80 years	47/47%	**EG:** 15 **CG:** 15	**EG:** moderate to vigorous AE **CG:** stretching and toning	**EG&CG:** the former 10 weeks: 25–30 min/session; 3 sessions/week; 11–26 weeks: 30–35 min/session; 3–4 sessions/week; the latter 22 weeks: 30–40 min/session; 4–5 sessions/week	12 months	Delayed recall (WMS-R)

TC, Tai Chi; EG, experimental group; CG, control group; WMS-R, Wechsler memory scale-revised; AE, aerobic exercise; RE, resistance exercise; MMSE, mini-mental state examination; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; DST, digit span test; DST-B, digit span test-backward; DST-F, digit span test-forward; RM, repetition maximum; MoCA, montreal cognitive assessment; RBMT, rivermead behavioral memory test; SDST, symbol-digit substitution test; SCWT, stroop color and word test; TMT-B, trail making test parts B; TMT-B–A, trail making test B minus A; PA, physical activity; WMS-LM I, logical memory I subtest of the Wechsler memory scale-revised; WMS-LM II, logical memory II subtest of the Wechsler memory scale-revised; TEA, test of everyday attention.

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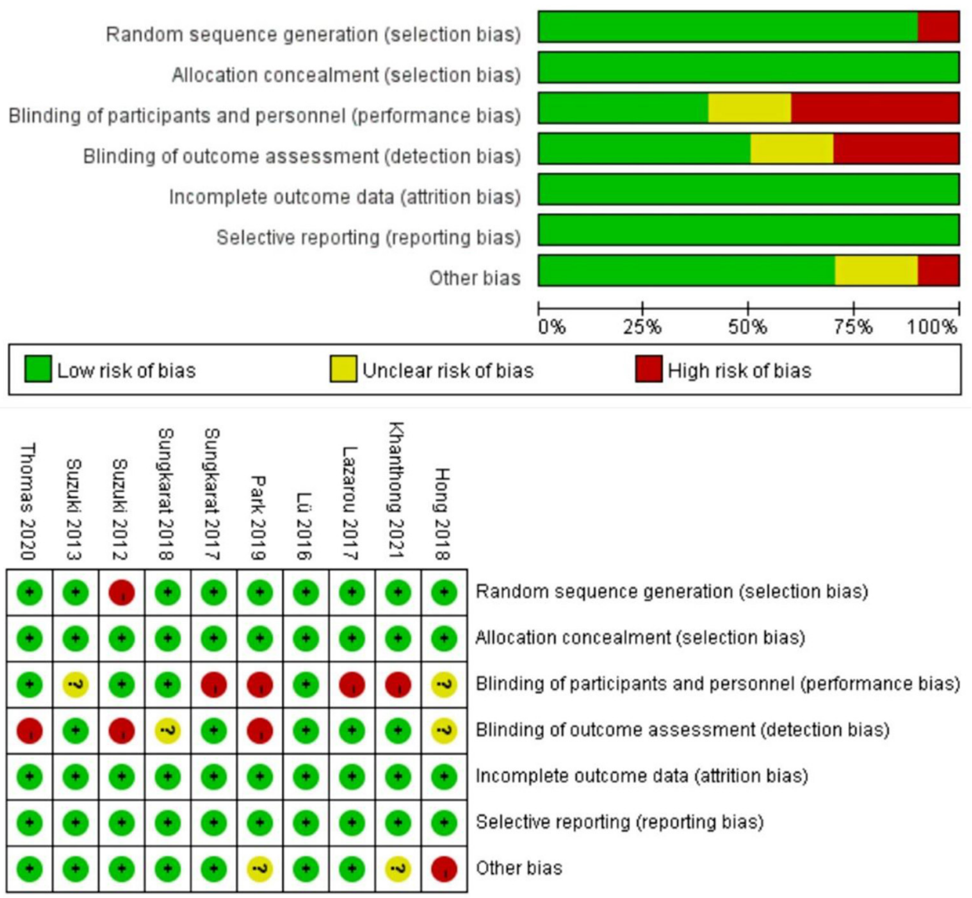

FIGURE 2
Details of bias of the included studies.

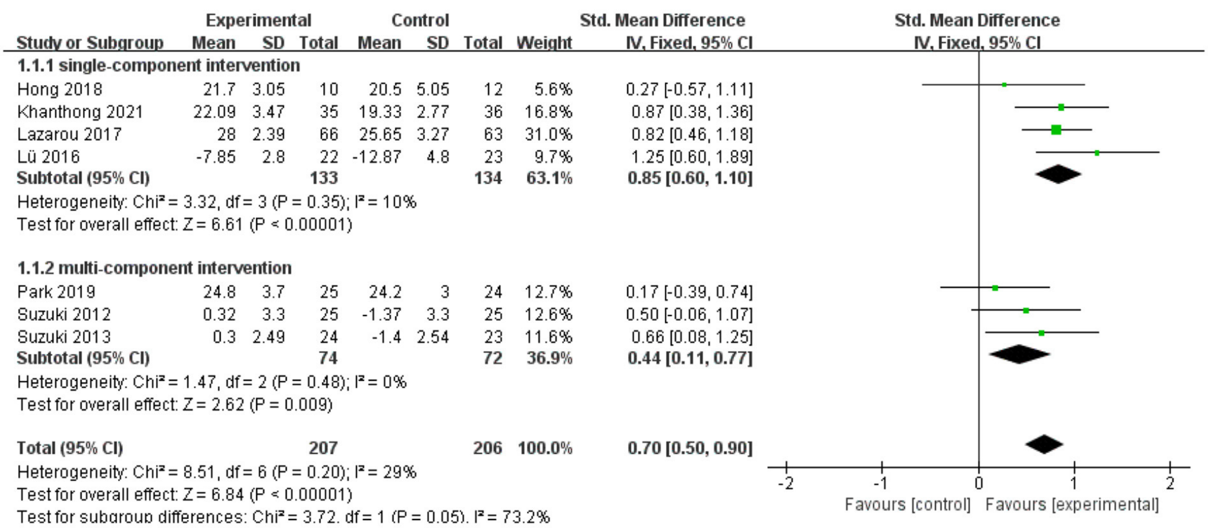

FIGURE 3
The influence of exercise interventions on global cognitive function.

subgroup analysis was performed based on the forms of interventions (i.e., the single-component intervention and the multi-component interventions). Figure 3 presents that the single-component intervention is effective for aMCI patients to enhance the global cognitive function (SMD = 0.85; 95% CI = 0.60–1.10; $p < 0.00001$; $I^2 = 10\%$). And the multi-component interventions are also conducive to improving the global cognitive function (SMD = 0.44; 95% CI = 0.11–0.77; $p = 0.009$; $I^2 = 0\%$). According to the effect size in different intervention forms, the single-component intervention (SMD = 0.85) seems have a better improvement effect on global cognitive function than multi-component interventions (SMD = 0.44).

Working memory

Three data points from three studies were synthesized to describe the influence of exercise interventions on working memory in aMCI individuals. As depicted in Figure 4, no significant difference was found between the experimental and control groups based on a random-effect model (WMD = −0.05; 95% CI = −0.74 to 0.63; $p = 0.88$; $I^2 = 78\%$).

Immediate recall

Three data points from three studies were combined to evaluate the influence of exercise interventions on immediate recall in patients with aMCI. As shown in Figure 5, there was a significant difference between the experimental and control groups based on a fixed-effect model (SMD = 0.55; 95% CI = 0.28–0.81; $p < 0.0001$; $I^2 = 0\%$).

Delayed recall

Six data points from six studies were pooled to investigate the influence of exercise interventions on delayed recall of patients with aMCI. As shown in Figure 6, there was a significant difference between the experimental and control groups based on a fixed-effect model (SMD = 0.66; 95% CI = 0.45–0.87; $p < 0.00001$; $I^2 = 37\%$).

Executive function

Six data points from six studies were merged to evaluate the influence of exercise interventions on the executive function of individuals with aMCI. As depicted in Figure 7, there was a significant difference between the experimental and control groups based on a fixed-effect model (SMD = 0.38; 95% CI = 0.16–0.60; $p = 0.0006$; $I^2 = 4\%$).

Attention

Three data points from three studies were integrated to assess the influence of exercise interventions on attention in patients with aMCI. As shown in Figure 8, no significant difference was found between the experimental and control groups based on a random-effect model (SMD = 0.20; 95% CI = −0.31 to 0.72; $p = 0.44$; $I^2 = 60\%$).

Discussion

To the best of our knowledge, this is the first meta-analysis investigating the influence of exercise interventions on the cognitive functions of patients with aMCI. The findings of this review suggested that exercise interventions had a positive effect on enhancing global cognitive function, immediate recall, delayed recall, and executive function of aMCI patients. And the single-component intervention seemed to show greater improvements in global cognitive function than multi-component interventions. By contrast, aMCI patients' several specific domains including working memory and attention could not be significantly improved by exercise interventions.

The findings demonstrated that exercise interventions could improve global cognitive function in patients with aMCI. The improvement of the global cognitive function induced by exercise interventions may be associated with neuroplasticity. Neuroplasticity is also known as brain plasticity, which refers to the ability of the brain to change, develop, and adapt functionally and structurally in response to environmental factors (47–49). Several studies have reported that exercise interventions can promote the process of neurogenesis, which directly leads to an increase in the number of new neurons (50–53). The increase of new neurons has been proved to be highly positive related to the enhancement of cognitive performance (54). Besides, exercise interventions are also helpful to enhance synaptic plasticity, which strengthens the connection between different nerve cells and may contribute to the improvement of cognitive levels (55, 56). Therefore, patients with aMCI may obtain significant benefits from exercise interventions in terms of global cognitive function.

Similar to exercise interventions, cognitive interventions are also proved to be conducive to increasing the new neurons' survival and guiding these new neurons to integrate into the existing brain networks (50, 51). Hence, we conducted a subgroup analysis based on the intervention forms (i.e., single-component interventions and multi-component interventions) and speculated that the multi-component interventions might bring a more obvious and comprehensive improvement in cognitions for aMCI individuals than the single-component intervention. However, the results were opposite to our initial hypothesis. Our results suggested that the single-component intervention might provide greater enhancement in global

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hong 2018	2.17	1.52	10	1.08	0.91	12	21.4%	1.09 [0.02, 2.16]
Lü 2016	3.82	0.91	22	4	1.13	23	33.7%	-0.18 [-0.78, 0.42]
Park 2019	2.4	0.2	25	2.9	0.2	24	44.8%	-0.50 [-0.61, -0.39]
Total (95% CI)			**57**			**59**	**100.0%**	**-0.05 [-0.74, 0.63]**

Heterogeneity: Tau² = 0.27; Chi² = 9.29, df = 2 (P = 0.010); I² = 78%
Test for overall effect: Z = 0.15 (P = 0.88)

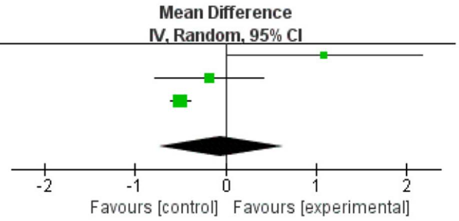

FIGURE 4
The influence of exercise interventions on working memory.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Lazarou 2017	12.53	4.78	66	9.89	5.4	63	57.4%	0.52 [0.16, 0.87]
Suzuki 2012	3.83	5.87	25	0.6	5.97	25	22.1%	0.54 [-0.03, 1.10]
Suzuki 2013	3.8	5.1	24	0.5	4.97	23	20.5%	0.64 [0.06, 1.23]
Total (95% CI)			**115**			**111**	**100.0%**	**0.55 [0.28, 0.81]**

Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 4.03 (P < 0.0001)

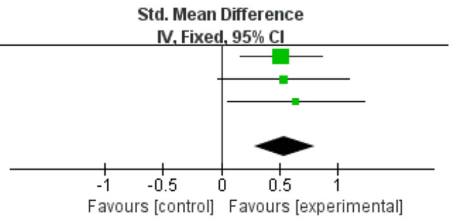

FIGURE 5
The influence of exercise interventions on immediate recall.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Lazarou 2017	11.09	4.38	66	8.38	4.28	63	35.5%	0.62 [0.27, 0.98]
Sungkarat 2017	31.8	7.4	30	25.6	8.9	29	15.8%	0.75 [0.22, 1.28]
Sungkarat 2018	33.5	9.5	29	21.9	7.6	27	13.1%	1.32 [0.74, 1.91]
Suzuki 2012	3.79	5.58	25	2.09	5.67	25	14.3%	0.30 [-0.26, 0.86]
Suzuki 2013	3.8	4.62	24	2.1	4.74	23	13.3%	0.36 [-0.22, 0.93]
Thomas 2020	13.8	2.6	15	11.1	4.2	15	8.0%	0.75 [0.01, 1.50]
Total (95% CI)			**189**			**182**	**100.0%**	**0.66 [0.45, 0.87]**

Heterogeneity: Chi² = 7.89, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 6.17 (P < 0.00001)

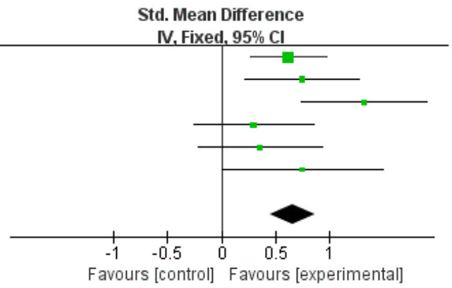

FIGURE 6
The influence of exercise interventions on delayed recall.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Khanthong 2021	-133.11	69.6	35	-172.61	83.88	36	21.4%	0.51 [0.03, 0.98]
Lü 2016	-95.45	45	22	-117.85	54.01	23	13.7%	0.44 [-0.15, 1.03]
Park 2019	36.3	8.7	25	34.7	8.1	24	15.2%	0.19 [-0.37, 0.75]
Sungkarat 2017	-71.4	34.2	30	-107.9	63.3	29	17.2%	0.71 [0.18, 1.24]
Sungkarat 2018	-76.2	46.7	29	-101.1	60.8	27	17.0%	0.46 [-0.08, 0.99]
Suzuki 2012	2.61	19.45	25	4.57	19.74	25	15.6%	-0.10 [-0.65, 0.46]
Total (95% CI)			**166**			**164**	**100.0%**	**0.38 [0.16, 0.60]**

Heterogeneity: Chi² = 5.22, df = 5 (P = 0.39); I² = 4%
Test for overall effect: Z = 3.42 (P = 0.0006)

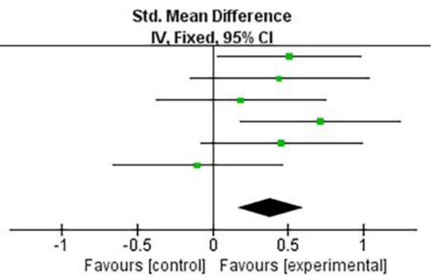

FIGURE 7
The influence of exercise interventions on executive function.

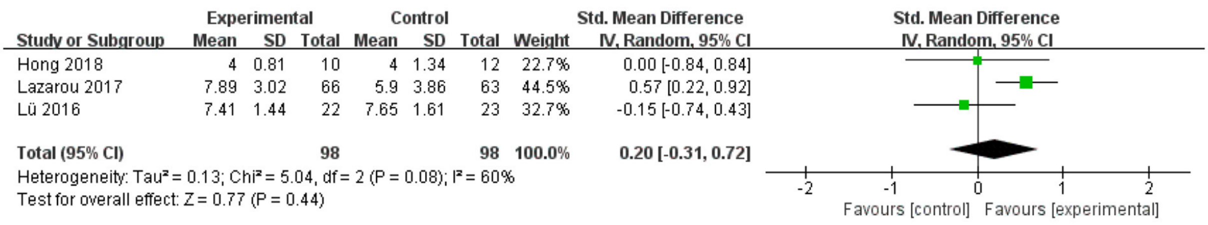

FIGURE 8
The influence of exercise interventions on attention.

cognitive function than multi-component interventions. The poorer effect of the multi-component interventions may be related to the over-stress under dual-task stimulation. For patients with cognitive disorders, especially those old adults with aMCI, performing concurrent cognitive tasks while doing exercises is a great challenge (e.g., subjects were required to invent their poems while walking). Facing the dual challenge of physical exercise and mental tasks may prompt them to experience the excessive pressure, which weakens the cognitive benefits (21). This might partly explain that multi-component interventions may be less effective for aMCI patients to improve global cognitive function than the single-component intervention.

In addition, our results showed that exercise interventions were useful to improve some specific domains of cognitive functions including immediate recall and delayed recall of patients with aMCI. The enhancement of memory might be affected by the activation of noradrenergic. One study has found that both normal old individuals' and aMCI patients' memory can be consolidated due to the significant elevation of endogenous norepinephrine induced by a 6-min aerobic stationary bicycle exercise at 70% VO_2max (57). Alternatively, it is well-known that the hippocampus is also involved in memory consolidation (58, 59). Some researchers have suggested that even mild physical exercise can facilitate the functional connection between the dentate gyrus/CA3 of the hippocampus and cortical regions (e.g., parahippocampal), which may contribute to memory improvement (60). Another explanation may be associated with the size of the hippocampus increasing after exercise interventions. It has been implied that exercise interventions (e.g., moderate-intensity AE) are able to enlarge the hippocampal volume and lessen memory decline in late adulthood (61).

Another finding in this meta-analysis was exercise interventions could improve the executive function of patients with aMCI. The better performance of executive function has been proved relevant to prefrontal cortex activation (62–64). An RCT study manifested that an AE intervention could increase bilateral prefrontal cortex activity, which contributed to a great improvement in executive function (63). Similarly, Chen et al. (62) adopted the near-infrared spectroscopy (NIRS) technique and indicated that a Chinese traditional exercise intervention Baduanjin lasting 8 weeks (90 min/day, 5 days/week) could promote a significant increase in oxygenated hemoglobin in the left prefrontal cortex and enhance executive function. Furthermore, moderate-vigorous-intensity PA has been demonstrated to be effective to ameliorate executive function by increasing the alpha band power and reducing beta-3 band power significantly (65). Hence, it may be possible to interpret the reason why the exercise is helpful to increase the performance of the executive function.

Exercise interventions couldn't alleviate the decline of working memory and attention in patients with aMCI. In the included articles that reported the outcomes of working memory and attention, the most common intervention duration was 12 weeks. Compared to other longer intervention periods related to other cognitive function domains (e.g., Park et al. conducted a 24-week intervention for improving executive function, and Lazarou et al. performed a 40-week intervention for preventing immediate recall and delayed recall decline), exercise interventions lasting 12 weeks may not be sufficient to improve working memory and attention. Therefore, exercise interventions beyond 12 weeks might be better. But further scientific evidence is needed to find a protocol (minimal or optimal) that is effective in enhancing cognition when providing exercise interventions in aMCI. In addition, it is believed currently that the enhancement of working memory mainly depends on visual and auditory training rather than exercise interventions. A previous meta-analysis (33) assessing the effect of the RE on working memory in mixed samples including aMCI individuals and naMCI individuals also obtained similar results that RE had no effect on improving working memory. The isolated AE didn't play a significant role in enhancing the working memory of people without dementia as well (66). Thus, it is possible that the benefits of exercise interventions for different cognitive domains are selective. Depending on different cognitive domains, exercise interventions should be selectively applied.

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the influence of exercise interventions on cognitive functions in one of the specific subtypes of MCI (i.e., patients with aMCI). Nevertheless, there are also some inevitable limitations in our study. First, we didn't use the funnel plot analysis to evaluate the publication bias due to the small number of studies for each cognitive outcome (fewer than 10 studies). Second, although aMCI consisted of the single-domain amnestic subtype and the multiple-domain amnestic subtype, further subgroup analysis was not performed, because few included articles in our meta-analysis distinguished the subtypes of aMCI. Third, we did not explore the effect of exercise interventions on other cognitive domains beyond the reported results, which was attributed to the limited included articles. Fourth, some cognitive domains have only been investigated by very few studies (e.g., working memory, immediate recall, and attention). So, any conclusion drawn (positive or negative) should still be speculative and more studies are likely needed to confirm the results. Finally, some unpublished articles or relevant studies using other languages except for English or Chinese may not be identified. This might reduce the comprehensiveness of this study.

Conclusion

This review and meta-analysis demonstrates that exercise interventions are helpful for patients with aMCI to improve global cognitive function and several specific cognitive domains, such as immediate recall, delayed recall, and executive function. And the single-component intervention seemed to show a greater effect on improving global cognitive function than multi-component interventions. On the contrary, aMCI patients' working memory and attention can't be enhanced by exercise interventions.

Data availability statement

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

Author contributions

XH, HL, and HR: conceptualization. RW and HZ: methodology and investigation. RW: formal analysis and writing-original draft preparation. TS, LX, and YL: resources. XH and RW: writing-review and editing and visualization. XH: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Health benefits of physical activity for people with mental disorders: From the perspective of multidimensional subjective wellbeing

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This paper uses a large scale and nationally representative dataset, Chinese General Social Survey, to empirically examine the role of physical activity in reducing the negative effects of depression among people with mental disorders. Empirical results demonstrate that physical exercise could help to alleviate depression's adverse consequences on work and life for depressed individuals. The impact mechanism is that physical activity may decrease the severity of depression, enhance life satisfaction, improve mood, and make people have a better sense of purpose and meaning in life. Therefore, from the perspective of multidimensional subjective wellbeing, evaluative wellbeing, experienced wellbeing and eudaimonic wellbeing all play mediating roles in the reduction of depression's adverse effects. Heterogeneity analysis shows that there are no significant gender differences in the health benefits of physical exercise, but its impact tends to be more prominent for depressed individuals who are younger and higher educated, with better health status, and live in urban areas. It is also found that socioeconomic status may play an important moderating role. The health benefits of physical activity seem to be greater for depressed people who have lower income, work in the secondary labor market, and have lower levels of social capital and assets. In addition, the instrumental variable approach is used to identify the causal impact of physical activity, which further proves a significant effect of it based on tackling the endogeneity problem. Meanwhile, this paper uses different explanatory and explained variables, different statistical models, as well as machine learning and placebo techniques to conduct robustness tests, all of which lend credence to above findings.

KEYWORDS

physical activity, people with depression, health benefits, multidimensional subjective wellbeing, psychiatric treatment

Introduction

Mental health awareness has taken hold over the recent years and psychiatric health is widely regarded as important as physical health (1). Depression is a typical manifestation of mental disorders, decreasing people's quality of life and working ability. Studies have shown that depression is strongly associated with lower life satisfaction, poorer overall health and even higher risk of death (2–4). At the same time, those with mental disorders are faced with more difficulties to obtain job opportunities in the labor market, forcing them to accept lower wages and thus bear greater financial burdens, which in turn exacerbates depressive disorders (5). In addition, depression brings about stigma to patients due to misconceptions in the public. Such an effect not only causes them to feel humiliated, but also drives them out of social contacts (6). Therefore, effective treatment of depression is very essential for improving people's mental health and achieving the goal in the United Nations' *2030 Agenda for Sustainable Development*, that is "ensuring healthy lives and promoting wellbeing for all" (7).

Existing studies have examined the effectiveness of multiple treatments for mental disorders, such as antidepressants (8), psychotherapy (9, 10), and lifestyle improvement (3, 4). Although medication is effective and necessary in many cases, studies have shown that antidepressants bring about notable side effects (11, 12). Therefore, it is necessary to explore alternative solutions for the treatment of mental disorders. In recent years, there has been growing interest in whether physical activity contributes to the welfare of people with depression. Physical activity is believed to have fewer side effects and is widely accepted, with significant correlations with both physical and mental health (13–19). In terms of mental health, maintaining a regular exercise routine can improve people's healthy living habits and help them reduce emotional exhaustion (15). Studies have shown a correlation between physical activity and mental health, and that physical exercise may reduce the risk of depression to some extent (20–22). In terms of the duration of physical activity, research shows that 3–5 times per week of moderate-intensity training is sufficient to reduce depression levels (4, 23). In recent years, COVID-19 has increased depressive disorders as people have less opportunity to participate in exercise due to isolation and limited social activities (16, 24). Existing studies have examined the effect of physical exercise in impacting people's health status during the epidemic both psychologically and physiologically (17, 23). In addition, it is found that team sports increase the frequency of interpersonal interactions, which can have a positive effect on mental health (18, 19). This echoes findings that physical activity helps people effectively deal with negative emotions caused by limited interactions (25). Furthermore, physical activity can also improve people's physical and cognitive abilities, thereby improving their capability to cope with negative emotions (26). Subjective wellbeing is also an important factor affecting mental health (27) and research has demonstrated that exercise contributes to people's wellbeing (28). The main reason for this is the positive effect of exercise on body image (29), and this conclusion holds for various types of physical activities (30).

In addition, existing studies have shown that there may exist heterogeneities in the effects of physical activity across different groups. As regards sociodemographic characteristics, it is found that exercise's effect is heterogeneous in terms of gender and age (31, 32). For example, regular exercise is an effective way to maintain a good psychological state and its benefits are more prominent for older people (33). Among the elderly, moderate exercise is very helpful in promoting mental health (34, 35). In addition, women exhibit higher levels of depression and therefore are more likely to gain health benefits from regular exercises (17, 32). Compared to men's preference for vigorous exercise, women are more likely to engage in low-intensity activities, such as walking, jogging and yoga (36). For example, square dancing, which is widely practiced among older people in China, can effectively reduce mental disorders (37). In terms of personality traits, people with high self-efficacy are generally more active in sports and mentally healthier (38). With regards to occupational characteristics, it is found that jobs that require long periods of sedentary work are more likely to cause anxiety and depression in workers, and physical activity has a more significant effect on them (39).

Compared with the existing research, the significance and value of this paper are mainly reflected in three aspects. First, this paper confirms the benefits of physical activity for people with mental disorders. Existing studies indicate that there is a correlation between physical activity and depression (20–22), but systematic empirical tests are still needed concerning whether exercise weakens the adverse effects of depression on the life and work among people with mental disorders. Specifically, the causal effect of physical activity awaits scientific examination. Second, this paper detects the mechanisms by which physical activity exerts its positive effect on people with mental disorders from multidimensional wellbeing. In terms of how exercises affect mental disorders, existing research suggests the relationship between exercises and subjective wellbeing (28–30), as well as associations between mental health and wellness (27). However, it remains to be investigated whether physical activity reduces the negative effects of depression by improving people's subjective wellbeing. Third, this paper systematically examines the heterogeneity of benefits brought by physical activity. Literature demonstrates variations in exercise habits among people with different characteristics (31–39), but it is unclear whether there also exist heterogeneities in the health benefits of physical activity. Based on this, this paper systematically examines whether physical exercise brings health benefits to people with depressive disorders using a large-scale representative micro dataset in China, and conducts mechanism analysis from the perspective of multidimensional subjective wellbeing. In addition, this research deals with endogeneity to test causality using the instrumental variable approach, and conducts heterogeneity analysis as well as robustness checks in multiple aspects.

Materials, measures, and methods

Data source

Data used in this research is the Chinese General Social Survey (CGSS) from 2017 to 2018, which is one of the most important national microdata in China. CGSS is in the world General Social Survey family, mainly carried out by Renmin University of China. CGSS aims to systematically and comprehensively reflect living conditions of Chinese people. Detailed information of CGSS is provided in Supplementary materials and can also be accessed through http://cgss.ruc.edu.cn/English/Home.htm. The reasons for using CGSS in this paper are mainly due to three aspects. First, CGSS asks respondents whether they are depressed and the extent to which depression adversely affects their lives and work. It also comprehensively contains factors relevant to mental health discussed in the existing literature. This not only enables us to construct control variables, but also facilitates an in-depth heterogeneity analysis. Second, CGSS examines people's exercise habits, which facilitates the construction of explanatory variables for this study. Third, CGSS includes different dimensions of people's subjective wellbeing in the extension module including evaluative wellbeing, experienced wellbeing and eudaimonic wellbeing. This allows us to systematically examine physical activity's impact mechanisms from the perspective of multidimensional subjective wellbeing.

Measures

Participants of this research are those who report that they suffer from depressive disorders in CGSS. The main explained variable is the extent to which people's life and work are negatively affected by depression, denoted as *Problem_depression*. This variable is based on the Likert scale to classify the severity of depressive disorders, where points from 1 to 5 represent depression never, seldom, sometimes, often and always exerting negative effects on their life and work. The explanatory variable in this paper is the frequency of participating in physical activity, denoted as *Physical_activity*. This variable comes from the question: "In the past 12 months, how many times did you usually engage in physical activity that lasts at least 30 min and makes you sweat per week?".

Based on literature concerning depressive disorders and its consequences on people's lives and work (1–3, 6, 10, 15), in order to avoid the omitted variable bias, this paper comprehensively controls factors related to effects of depression, including variables of demographic characteristics, human capital characteristics, social characteristics, working characteristics, family characteristics, and regional and time characteristics. (1) Demographic characteristics include age, the squared term of age and gender. (2) Human capital characteristics include educational level and whether the respondent is a migrant. (3) Social characteristics include whether her/his Hukou[1] is in urban, whether being ethnic minorities, whether having religious beliefs and whether being the Communist Party of China (CPC) member. (4) Working characteristics include personal income, whether working in the system[2] and whether having pension and medical insurance. (5) Family characteristics include marital status, family size, number of children and number of housing assets. (6) Regional and time features include provincial and year dummies. The descriptive statistics results of above variables are shown in Supplementary Table 1.

Methods

Because the explained variable, which is the extent to which life and work are adversely affected by depression, is an ordered variable, we use the Ordered Probit model to conduct regression. Specifically, based on $Problem\_depression_i$, the sample is divided into 5 different groups. Groups $g = 1$ to 5 represent those whose life and work are never, seldom, sometimes, often and always negatively affected by depression, respectively. The probability of a given observation i for the Ordered Probit model p_{gi} is

$$\begin{aligned} p_{gi} &= \Pr\left(Problem\_depression_i = g\right) = \Pr\left(\chi_{g-1} < \alpha \right. \\ &\quad \left. + \beta Physical\_activity_i + \mathbf{x}_i^{'}\gamma + \varepsilon_i \le \chi_g\right) \\ &= \Phi(\chi_g - \alpha - \beta Physical\_activity_i - \mathbf{x}_i^{'}\gamma) - \Phi(\chi_{g-1} \\ &\quad - \alpha - \beta Physical\_activity_i - \mathbf{x}_i^{'}\gamma) \end{aligned}$$

where $Problem\_depression_i$ and $Physical\_activity_i$ are the dependent and explanatory variables, $\mathbf{x}_i^{'}$ is a vector of controls introduced above, χ_0 is $-\infty$, χ_5 is $+\infty$ and $\Phi(\cdot)$ is the standard normal cumulative distribution function.

1 Hukou is a system of household registration used in mainland China, mainly identifying a person as a rural or urban resident.

2 Working in-system in China refers to having jobs in Communist Party of China organizations, governments and state-owned corporations. Compared with out-of-system jobs, in-system jobs bring better social security and additional hidden benefits. Therefore, in-system is traditionally regarded as the primary labor market in China, while out-of-system means the secondary labor market.

Accordingly, the log likelihood of the maximum likelihood estimation (MLE) is

$$lnL = \sum_{i=1}^{N}\sum_{g=1}^{5} I_g(Problem\_depression_i)\ ln\ p_{gi}$$

where $I_g\left(Problem\_depression_i\right) = \begin{cases} 1, \ if\ Problem\_depression_i = g \\ 0, \ if\ Problem\_depression_i \neq g \end{cases}$ and N is the sample size. Based on this, β and γ are estimated by $\max lnL$. The data analysis software used in this paper is Stata 17.0.

Results

Benchmark results

Table 1 shows the regression results by the above Ordered Probit model. Column (1) is the estimation without including any control variables, showing that *Physical_activity* is significantly and negatively correlated with *Problem_depression*. In Columns (2)–(6), control variables of demographic characteristics, human capital characteristics, social characteristics, working characteristics, family characteristics, and regional and time characteristics are sequentially added into the regressions. Results demonstrate that the estimated coefficients of physical activity are significantly negative at the 1% level in all regressions. It means that for people with mental disorders, the higher the frequency of physical exercise, the less their work and daily life are adversely affected by depression problems. In addition, the estimated coefficient of physical activity decreases slightly but remains very stable as different aspects of characteristics are controlled. This shows that the significant relationship between *Physical_activity* and *Problem_depression* can hardly be affected by other factors and is very robust. The estimates of control variables are basically in line with theoretical expectations and are consistent with the existing research. In terms of gender, women are more likely to suffer from depression in their work and life, consistent with findings in Lyttelton et al. (40). The estimated coefficient of the squared term of age is significantly negative, while that of age is positive. This implies an upward trend in depression symptoms as people get older and a negative relationship after a turning point (41, 42). In terms of working characteristics, lower income level and inadequate social security will increase the adverse impacts of mental disorders. In addition, married individuals have lower levels of depression, especially among those with higher marital quality (43, 44). Raising children requires people to bear more time and financial costs, so the greater the number of children, the more prominent the problems in terms of mental disorders (45).

Mechanism analysis

Studies have shown that physical activity helps to increase people's enthusiasm for life and improve their subjective wellbeing (28–30). The question naturally arises that whether physical exercise reduces the extent to which people suffer from depression by reducing the severity of depression and improving the subjective wellbeing. To test this hypothesis, firstly, we use respondents' answers to the question "To what extent do you feel depressed?" to characterize the severity of depression to conduct the mechanism analysis. Responses to this question include "not depressed," "mildly depressed," "moderately depressed," "very depressed" and "severely depressed." Second, based on the measures of multidimensional subjective wellbeing in the existing literature (46–48), we test the mediating roles of evaluation wellbeing (life satisfaction), experienced wellbeing (the emotions that people experience in their lives) and eudaimonic wellbeing (sense of purpose and meaning in life). The variable of Evaluative wellbeing comes from the respondents' degree of agreement on "In general, how are you satisfied with your life?". Experienced wellbeing_1, Experienced wellbeing_2 and Experienced wellbeing_3 come from the respondents' degree of agreement on "I feel that the society is providing more and more opportunities for people to develop themselves," "I am content with my life compared to others around me" and "I am satisfied with my family's income level," respectively. Furthermore, Eudaimonic wellbeing_1 , Eudaimonic wellbeing_2 and Eudaimonic wellbeing_3 come from the respondents' degree of agreement on "I have goals in life and they motivate me to live better," "I am currently doing my best to pursue my goals in life" and "When things are uncertain, I usually expect them to go in the good direction" respectively. These questions are all based on the 5-Point Likert Scale, with higher values representing higher levels of wellbeing. The Cronbach's Alpha for the multidimensional sub-scales of subjective wellbeing is 0.891, indicating good internal consistency.

Results of the mechanism analysis using above variables are shown in Table 2. Column (1) demonstrates that physical activity helps reduce the severity of depression among people with mental disorders. Besides, other odd-numbered columns in Table 2 display that physical exercise has a significant positive effect on depressed individuals' subjective wellbeing in all of the three dimensions. This means that the more frequently they participate in exercises, the higher their wellness will be, including the evaluative wellbeing, experienced wellbeing and eudaimonic wellbeing. Specifically, it is demonstrated that exercises help to increase the life satisfaction of people with depressive disorders, improving emotions in their lives and helping them have a better sense of purpose and meaning in life. Results of even-numbered columns in Table 2 show that when the mediators are included in the regressions, their estimated coefficients are all significantly positive at the 1% level.

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TABLE 1 Benchmark regression results.

Model	(1) Oprobit	(2) Oprobit	(3) Oprobit	(4) Oprobit	(5) Oprobit	(6) Oprobit	(7) Oprobit
Variable	Problem_ depression	Problem_ depression	Problem_ depression	Problem_ depression	Problem_ depression	Problem_ depression	Problem_ depression
Physical_ activity	−0.042*** (0.003)	−0.042*** (0.003)	−0.040*** (0.003)	−0.034*** (0.003)	−0.033*** (0.003)	−0.033*** (0.003)	−0.031*** (0.003)
Age		0.039*** (0.003)	0.032*** (0.003)	0.032*** (0.003)	0.038*** (0.003)	0.045*** (0.003)	0.042*** (0.003)
Age_squared		−0.000*** (0.000)	−0.000*** (0.000)	−0.000*** (0.000)	−0.000*** (0.000)	−0.000*** (0.000)	−0.000*** (0.000)
Whether female		0.114*** (0.016)	0.112*** (0.016)	0.100*** (0.016)	0.061*** (0.017)	0.056*** (0.017)	0.075*** (0.018)
Education level			−0.177*** (0.029)	−0.027 (0.031)	−0.002 (0.033)	0.005 (0.034)	0.047 (0.034)
Whether migrants			−0.245*** (0.026)	−0.239*** (0.026)	−0.219*** (0.028)	−0.232*** (0.028)	−0.127*** (0.030)
Whether Hukou in urban				−0.236*** (0.018)	−0.184*** (0.019)	−0.183*** (0.020)	−0.111*** (0.021)
Whether ethnic minorities				0.145*** (0.032)	0.143*** (0.033)	0.142*** (0.033)	0.061 (0.038)
Whether religious believer				−0.054* (0.028)	−0.050* (0.029)	−0.047 (0.029)	0.012 (0.030)
Whether CPC member				−0.192*** (0.030)	−0.155*** (0.031)	−0.135*** (0.031)	−0.130*** (0.031)
ln_Income					−0.028*** (0.002)	−0.028*** (0.002)	−0.024*** (0.002)
Whether working in the system					0.003 (0.038)	0.003 (0.038)	−0.010 (0.039)
Whether having pension					−0.048** (0.021)	−0.040* (0.021)	−0.010 (0.021)
Whether having medical insurance					0.061* (0.035)	0.087** (0.036)	0.071** (0.036)
Whether married						−0.115*** (0.022)	−0.112*** (0.023)
Family size						−0.028*** (0.006)	−0.027*** (0.006)
Number of children						0.027*** (0.008)	0.017** (0.008)
Number of houses						−0.089*** (0.015)	−0.075*** (0.015)
Year dummies	No	No	No	No	No	No	Yes
Province dummies	No	No	No	No	No	No	Yes
Observations	17,840	17,840	17,786	17,740	16,721	16,559	16,559
Pseudo R^2	0.005	0.058	0.061	0.066	0.068	0.070	0.079

The values in parentheses are standard errors robust to heteroskedasticity. Yes means the corresponding variables are controlled in the regression, while No means not controlled.
***, **, and * indicate significance at the levels of 1, 5, and 10%, respectively.

TABLE 2 Mechanism analysis.

Model	(1)Oprobit	(2)Oprobit	(3)Oprobit	(4)Oprobit	(5)Oprobit	(6)Oprobit	(7)Oprobit	(8)Oprobit
Variable	**Depression**	**Problem_ depression**	**Evaluative wellbeing**	**Problem_ depression**	**Experienced wellbeing_1**	**Problem_ depression**	**Experienced wellbeing_2**	**Problem_ depression**
Physical_ activity	−0.018*** (0.003)	−0.027*** (0.003)	0.025*** (0.008)	−0.037*** (0.008)	0.015** (0.007)	−0.038*** (0.1008)	0.036*** (0.007)	−0.035*** (0.008)
Depression		0.452*** (0.013)						
Evaluative wellbeing				−0.194*** (0.026)				
Experienced wellbeing_1						−0.047** (0.024)		
Experienced wellbeing_2								−0.057** (0.023)
Controls	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	16,579	16,559	2,734	2731	2,678	2,675	2,681	2,678
Pseudo R^2	0.028	0.111	0.039	0.107	0.027	0.101	0.029	0.101

Model	(9) Oprobit	(10) Oprobit	(11) Oprobit	(12) Oprobit	(13) Oprobit	(14) Oprobit	(15) Oprobit	(16)Oprobit
Variable	**Experienced wellbeing_3**	**Problem_ depression**	**Eudaimonic wellbeing_1**	**Problem_ depression**	**Eudaimonic wellbeing_2**	**Problem_ depression**	**Eudaimonic wellbeing_3**	**Problem_ depression**
Physical_ activity	0.045*** (0.007)	−0.034*** (0.008)	0.024*** (0.007)	−0.036*** (0.008)	0.036*** (0.007)	−0.035*** (0.008)	0.019*** (0.007)	−0.039*** (0.008)
Experienced wellbeing_3		−0.107*** (0.018)						
Eudaimonic wellbeing_1				−0.108*** (0.024)				
Eudaimonic wellbeing_2						−0.050*** (0.016)		
Eudaimonic wellbeing_3								−0.068** (0.033)
Controls	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	2,707	2,704	2,643	2,640	2,626	2,623	2,710	2,707
Pseudo R^2	0.041	0.104	0.030	0.103	0.061	0.102	0.039	0.101

*** and ** indicate significance at the levels of 1, 5, and 10%, respectively.

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This suggests that multidimensional subjective wellbeing plays a mediating role in the health benefits of exercise for people with depression. Therefore, participation in physical activity alleviates the adverse effects of mental disorders on life and work by both decreasing depression levels and increasing people's subjective wellbeing. It is worth pointing out that the sample size is smaller in the regressions testing multidimensional subjective wellbeing since relevant questions come from the extension module, where only some of the randomly selected respondents are asked to answer questions therein. Despite the sample loss, it is obvious that all of these mechanism analysis results are significant and the conclusions are robust.

Heterogeneities analysis

In order to further examine the heterogeneous effects of *Physical_activity*, we conduct moderating effects analysis in multiple aspects. Regression results are shown in Table 3. Here we primarily focus on the estimated coefficients of the interactions between the moderating variables and physical activity. If the interaction term's estimate is significantly negative, it means that the moderator would increase the health benefits of physical exercise in reducing depression's adverse effect. Otherwise, the opposite result would mean that the factor reduces physical activity's impact.

First, we examine the heterogeneities in terms of two demographic characteristics, which are gender and age. With regard to gender, results in column (1) of Table 3 show that the interaction term between gender and physical exercise is not significant, meaning that there is no obvious difference in *Physical_activity*'s role to lower *Problem_depression* for men and women. In respect of age, column (2) of Table 3 demonstrates that if the depressed individuals are under the age of 50, the effect of physical activity on reducing depression's consequences is more prominent. This may be due to the fact that younger individuals are more physically active and more likely to engage in physical activities with higher intensity and longer duration. Therefore, the health benefits of physical exercise for younger depressed people are more prominent. Furthermore, columns (3) and (4) show that, in terms of human capital characteristics, the interaction terms of both education level and health status with *Physical_activity* are significantly positive[3]. This demonstrates that rewards from exercise are greater for those with higher levels of human capital. In addition, regarding social characteristics, column (5) shows that the health benefits of physical activity are greater for depressed residents in urban areas, which is consistent with the theoretical expectations because there are more sports venues and better sports infrastructure in urban areas. Thus, compared with their rural counterparts, urban residents have more access to professional physical exercises, which is more helpful to reduce the adverse effects of depression on their life and work. However, results in columns (6) and (7) indicate that whether the individuals are religious believers and whether they belong to ethnic minorities do not alter physical activity's benefits.

It is also found that socioeconomic status plays an important moderating role in the relationship between *Physical_activity* and *Problem_depression*. Specifically, we examine the heterogeneities in aspects of income, job characteristics, social capital, assets, and social security among depressed individuals. First, results in column (8) of Table 3 show that physical activity alleviates the negative effects caused by depression in the lower-income subgroup more prominently. Besides, working in-system in China refers to having jobs in Communist Party of China organizations, governments and state-owned corporations. Working in these sectors is perceived as having higher social status and social capital. Therefore, in-system work is traditionally regarded as the primary labor market in China, while out-of-system means the secondary labor market. We conduct heterogeneity analysis from the perspective of social status according to this employment characteristic. Meanwhile, we use respondents' answers to "how often you use your work to help your family and friends" (ranging from 1 to 5) as an indicator of social capital. Results of columns (9) and (10) demonstrate that for depressed individuals who work outside the system and whose social capital is lower, the role of physical activity in reducing depression's detrimental effects is more pronounced. In addition, columns (11) and (12) indicate that the effect of exercise is greater for depressed people not owning cars and commercial medical insurance. Overall, heterogeneity analysis in terms of socioeconomic status reveals that for depressed individuals with lower socioeconomic status, *Physical_activity* has a greater effect in reducing *Problom_depression*. The reason behind it may be attributed to the fact that the negative impact of depression on work and life is significantly higher for groups with lower socioeconomic status. For example, the averages of *Problom_depression* among depressed respondents with lower incomes and working outside the system are, respectively, 2.49 and 2.13, which are significantly higher than their counterparts, which are 1.86 and 1.62, respectively. Therefore, the health benefits gained from physical activity for them tend to be greater.

3 The education level is classified from 1 to 13: 1-without any education, 2-kindergarten, 3-primary school, 4-junior high school, 5-vocational high school, 6-ordinary high school, 7-techinical secondary school, 8-technical high school, 9-junior college (adult education), 10-junior college (regular education), 11-undergraduate (adult education), 12-undergraduate (regular education), 13-postgraduate and above. Health status is based on the self-rated health levels from 1 to 5: 1-very unhealthy, 2-relatively unhealthy, 3-medium, 4-relatively healthy, 5-very healthy.

TABLE 3 Heterogeneities analysis.

Model	(1) Oprobit	(2) Oprobit	(3) Oprobit	(4) Oprobit	(5) Oprobit	(6) Oprobit
Moderator variable	**Whether female**	**Whether younger than 50**	**Education level**	**Health condition**	**Whether Hukou in urban**	**Whether religious believer**
Interaction between physical_activity and moderator	0.002 (0.006)	0.033*** (0.006)	0.002** (0.001)	0.017*** (0.003)	−0.013** (0.006)	−0.013 (0.010)
Physical activity	−0.031*** (0.004)	−0.045*** (0.004)	−0.039*** (0.005)	−0.072*** (0.010)	−0.024*** (0.004)	−0.029*** (0.003)
Moderator variable	0.072*** (0.021)	−0.617*** (0.024)	−0.030*** (0.005)	−0.725*** (0.012)	−0.116*** (0.024)	0.039 (0.036)
Other controls	Yes	Yes	Yes	Yes	Yes	Yes
Observations	16,559	16,559	16,559	16,554	16,559	16,559
Pseudo R^2	0.080	0.070	0.080	0.190	0.080	0.080
Model	**(7) Oprobit**	**(8) Oprobit**	**(9) Oprobit**	**(10) Oprobit**	**(11) Oprobit**	**(12) Oprobit**
Moderator variable	**Whether ethnic minorities**	**ln_Family_ income**	**Whether working in the system**	**Social capital**	**Whether owning cars**	**Whether having commercial medical insurance**
Interaction between physical_activity and moderator	−0.017 (0.013)	0.003** (0.001)	0.023** (0.010)	0.019*** (0.004)	0.021*** (0.006)	0.027*** (0.010)
Physical activity	−0.029*** (0.003)	−0.060*** (0.015)	−0.033*** (0.003)	−0.056*** (0.006)	−0.036*** (0.004)	−0.033*** (0.003)
Moderator variable	0.088** (0.043)	−0.057*** (0.005)	−0.147*** (0.041)	−0.073*** (0.017)	−0.194*** (0.026)	−0.169*** (0.040)
Other controls	Yes	Yes	Yes	Yes	Yes	Yes
Observations	16,559	15,843	16,559	16,537	16,547	16,452
Pseudo R^2	0.080	0.080	0.080	0.080	0.080	0.080

Other controls include all the controls other than the moderator variable. In column (8), personal income is not controlled to avoid multicollinearity as family income is controlled as the moderator variable.
*** and ** indicate significance at the levels of 1, 5, and 10%, respectively.

Dealing with endogeneity

To examine the causal effect of physical activity on reducing the adverse effect of depression for people with mental disorders, this paper uses the instrumental variable method to tackle the endogeneity problem. Specifically, we construct the following two-stage least squares (2SLS) statistical model, applying the degree of automation's replacement of tasks in work as the instrumental variable.

$$Physical\_activity_i = \gamma_0 + \gamma_1 Automation_i + x_i^{'}\psi^1 + \mu_i^1$$
$$Problem\_depression_i = \delta_0 + \delta_1 \widehat{Physical\_activity}_i + x_i^{'}\psi^2 + \mu_i^2$$

In the model, $\mathbf{x_i^{'}}$ is a vector of a set of control variables described above. $Automation_i$ is the automation indicator, which is the instrumental variable constructed by Mihaylov and Tijden (49). This measure is the extent to which the tasks in individual *i*'s occupation are replaced by automation. The higher this index, the fewer time people need to spend in working (50) and thus the more time they can participate in sports. Therefore, this instrumental variable satisfies the correlation prerequisite. Statistical tests on this are shown in Supplementary Table 2. Furthermore, automation depends on exogenous technology change, independent of the micro individual's personal characteristics. Consequently, this instrumental variable meets the requirement of exogeneity. Regression results are shown in Table 4, and due to space limitations the full table of estimations is shown in Supplementary Table 3. It is noted that 2SLS estimates with the instrumental variable are basically consistent with that of benchmark regressions. With gradually adding different characteristics, estimated coefficients of physical activity are all significantly negative at the 1% level. This means that the health benefits of physical activity for depressed people are not subject to endogeneity problems. Results using other IV approaches demonstrate consistent findings with that applying 2SLS and are provided in Supplementary Table 4.

TABLE 4 Endogeneity treatment: instrumental variable regressions.

Model	**(1) 2SLS**	**(2) 2SLS**	**(3) 2SLS**	**(4) 2SLS**	**(5) 2SLS**	**(6) 2SLS**	**(7) 2SLS**
Variable	**Problem_ depression**	**Problem_ depression**	**Problem_ depression**	**Problem_ depression**	**Problem_ depression**	**Problem_ depression**	**Problem_ depression**
Physical_activity	−0.846*** (0.115)	−0.450*** (0.077)	−0.437*** (0.082)	−0.473*** (0.128)	−0.384*** (0.110)	−0.402*** (0.122)	−0.378*** (0.138)
Demographic characteristics	N	Y	Y	Y	Y	Y	Y
Human capital characteristics	N	N	Y	Y	Y	Y	Y
Social characteristics	N	N	N	Y	Y	Y	Y
Working characteristics	N	N	N	N	Y	Y	Y
Family characteristics	N	N	N	N	N	Y	Y
Year dummies	N	N	N	N	N	N	Y
Province dummies	N	N	N	N	N	N	Y
Constant	3.759*** (0.219)	1.990*** (0.219)	2.004*** (0.205)	2.074*** (0.256)	2.057*** (0.211)	2.024*** (0.220)	1.690*** (0.237)
Observations	8964	8964	8934	8916	8460	8406	8406

*** indicate significance at the levels of 1, 5, and 10%, respectively.

Robustness checks

We examine the robustness of physical activity's role in reducing the negative effects of depression among depressed individuals in the following five ways. First, we use the dummy variable representing "whether the life and work are often or frequently affected by depression" as the explained variable. This indicator is corresponding to *Problem_depression* from the same question in CGSS. Supplementary Table 5 shows that when this variable is used to characterize depression's adverse impacts, the estimated coefficients of physical exercise are also significantly negative at the 1% level, further proving the robustness of findings in the benchmark analysis. Second, we use a dummy variable "whether doing physical exercise per week" as the explanatory variable. Results of Supplementary Table 6 demonstrate that when using this indicator to reflect people's physical activity habits, it is also proved that exercise has a significant impact in reducing the adverse effects of depression. Third, we perform regressions using other statistical models, including the Ordinary Least Squares (OLS) and the Ordered Logit (Ologit) model. Supplementary Tables 7, 8 indicate that regardless of which model is applied and which variables are controlled in the regression, estimates of physical activity are all significantly negative at the 1% level.

Fourth, we further examine the explanatory power of physical activity on the explained variables using the machine learning method. Results in Supplementary Table 9 show that in all penalized machine learning models, physical activity consistently serves as the key indicator for predicting the explained variables. In Supplementary Figures 1, 2, the coefficients paths of independent variables illustrate that the explanatory power of physical activity is very robust. Fifth, we perform a placebo analysis of the results. Specifically, we randomly reallocate the *Physical_activity* variable in the sample and perform regressions using the generated new sample. Supplementary Figure 3 exhibits that estimates of physical activity in 1,000 such kind of new samples are all greater than that in the benchmark regression. Besides, their mean value is close to 0 and almost all the corresponding P-values are >0.1. This further proves that results in this paper are not affected by endogeneity caused by omitted random factors.

Conclusion and discussion

This paper empirically investigates the role of physical activity in reducing the negative effects of depression among people with mental disorders. Empirical results show that physical exercise can help to mitigate depression's adverse consequences on work and life for depressed individuals. We find that the mechanism of this effect is that physical activity helps to reduce the severity of depression, enhance life satisfaction, improve mood, and make people have a better sense of purpose and meaning in life. Consequently, from the perspective of multidimensional subjective wellbeing, evaluative wellbeing, experienced wellbeing and eudaimonic wellbeing play mediating roles in the reduction of depression's adverse effects. Heterogeneity analysis shows that there are no significant gender differences in the health benefits of physical exercise, but the positive impact is more prominent for people with mental disorders who are younger and higher educated, with better health status, and live in urban areas. We also find that socioeconomic status plays an important moderating role. The health benefits of physical activity are greater for depressed people who have lower income, work in the secondary labor market, and have lower levels of social capital and assets. In addition, the instrumental variable approach is applied to identify the causal impact of physical activity, which further proves a significant effect of it based on tackling the endogeneity problem. Meanwhile, this paper uses different explanatory and explained variables, different regression models, as well as machine learning and placebo techniques to conduct robustness tests, all of which lend credence to above findings.

This study confirms the positive impact of physical activity on people with mental disorders. The existing research has generally discussed the relationship between physical exercise and mental health. For example, studies based on adolescents have found that physical exercise can alleviate depression caused by interpersonal problems (25), and higher levels of exercise have a positive effect on mental health (19, 26). At the same time, other studies have found that exercises help to reduce the frequency of smoking and develop a lifestyle conducive to both physical and mental health (15). When people are physically inactive, they are more likely to have physical diseases as well as psychological disorders (16, 17, 20). For example, because people worked at home for a long time during the COVID-19 epidemic, physical constraints of space reduce the exercise frequency and increase negative emotions as a result (40, 51). In addition, physical exercise can improve people's sense of happiness (28, 29). Research has also found that a healthy lifestyle brought by physical activities can help reduce the decline in abilities caused by aging (52). Regular exercise reduces the morbidity and improves the quality of life (53). However, it remains to be tested whether physical activity helps to improve the wellbeing of individuals already suffering from depression. Therefore, this paper extends the research on the relationship between exercise and mental health in the existing literature, demonstrating that it plays an important and positive role in alleviating depression's adverse effects on the work and life among depressed individuals. The more depressed individuals participate in physical activities, the less frequently they suffer from depression problems. This conclusion is robust to different explanatory and explained variables, various regression models, as well as machine learning and placebo tests.

In addition, as a typical manifestation of mental disorders, depression is strongly associated with lower living satisfaction, poorer overall health and even higher risk of death (2–4). Higher levels of recreational physical activity can help improve people's physical fitness and happiness in life (54). It is also found that lower levels of exercise frequency increase people's psychological distress (21, 22). In this paper, we support and expand the conclusion that exercises can reduce the mental burdens by reducing the severity of depression among those suffering from mental disorders. At the same time, based on the classification of subjective wellbeing in existing literature (46–48), this paper deepens the research on this issue. We further discover the mechanism of multidimensional subjective wellbeing in physical activity's impact on mental disorders. Specifically, this study reveals that exercises can reduce the negative effects of depression on people's work and life by enhancing life satisfaction, improving mood, and making them have a better sense of purpose and meaning in life. Depression and happiness are the two most important opposite emotions (55), and this paper demonstrates that exercises can reduce the negative effects of mental disorders by improving people's happiness.

At the same time, compared with previous studies that support the positive effects of exercises (19, 25, 26, 28, 29), we further systematically examine the heterogeneities in physical activity's benefits among different subgroups. Heterogeneity analysis shows that there is no significant gender difference in the health benefits of physical exercise, but its impact is more prominent for people with mental disorders who are younger and higher educated, with better health status, and live in urban areas. We also find that socioeconomic status plays an important moderating role. The health benefits of physical activity are greater for depressed people who have lower income, work in the secondary labor market, and have lower levels of social capital and assets. These findings not only enrich our understanding of the positive effects of physical activity, but also help us to better target our recommendations to specific subgroups to reduce depression's consequences on their work and life.

This research has important clinical implications for applying physical exercise to alleviate the adverse effects of depression on people's life and work. First, this paper proves the important role of physical activity in reducing depression levels and increasing the sense of wellbeing among people with mental disorders. This implies that the health benefits of exercise should be emphasized in clinical practice in addition to conventional treatment measures, such as antidepressants and psychotherapy. Second, the heterogeneity analysis results have important implications. For example, depressed patients who are younger, higher educated, in better physical condition, and with lower socioeconomic status should be advised more to gain greater health benefits from physical activity. The shortcomings of this paper mainly include two aspects. First, this paper uses the instrumental variable method to solve the endogeneity problem. Because this instrumental variable is only available for individuals with jobs, this approach results in sample loss. Therefore, randomized controlled experiments would be a better way to deal with endogeneity. Second, this paper uses a cross-sectional dataset, which is not as advantageous as longitudinal data in controlling individual fixed effects. Therefore, conducting randomized controlled experiments on physical activity among those with depression would be a very valuable research direction.

Data availability statement

The data that support the findings of this study are available from Chinese General Social Survey (CGSS, http://cgss.ruc.edu.cn/English/Home.htm). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of CGSS.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board, Renmin University of China. The participants provided their written informed consent to participate in the survey.

Author contributions

CL contributed to the conception and design of the study and performed the statistical analysis. YX generated the tables and figures, respectively, based on CL's analysis. CL and GN wrote the first draft of the manuscript. GN and QL worked on revisions of the manuscript. All authors provided critical feedback and approved the final submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1050208/full#supplementary-material

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An exercise prescription for patients with lung cancer improves the quality of life, depression, and anxiety

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Introduction: Lung cancer has the highest rates of morbidity and mortality among all cancers. Patients with lung cancer inevitably confront psychosocial discomforts and progressively experience depression and anxiety that potentially impact the clinical outcomes [e.g., quality of life (QoL)]. These mental disorders in patients with lung cancer may effectively be alleviated with prescribed Chinese traditional mind-body exercises. This study aimed to determine the effect of the exercise prescription containing Chinese traditional mind-body exercise on QoL, depression, and anxiety in patients with lung cancer.

Methods: In this study, 52 patients with non-small cell lung cancer (NSCLC) recruited from the China-Japan Friendship Hospital were divided into two groups, namely, the experimental group ($N = 26$) and the control group ($N = 26$). The experimental group was treated with an 8-week exercise prescription containing aerobic and resistance training. The control group received the usual care during the study period. The QoL, depression, and anxiety were separately investigated using EORTC QLQ-C30, EORTC QLQ-LC13, the Self-Rating Depression Scale (SDS), and the Self-Rating Anxiety Scale (SAS) at baseline and post-intervention. The scores of questionnaires were analyzed using the paired sample and independent sample t-tests to explore the intragroup and intergroup differences, respectively.

Results: The EORTC QLQ-C30 scores for physical functioning, role functioning, emotional functioning, and global QoL in the experimental group at post-intervention were significantly higher than those at baseline. The EORTC QLQ-C30 scores for fatigue, pain, dyspnea, and insomnia in the experimental group at post-intervention were significantly lower than those at the baseline. The SDS scores (baseline: 57.74 ± 8.77 vs. post-intervention: 51.42 ± 7.31, $p < 0.05$) and the SAS scores (baseline: 56.63 ± 9.39 vs. post-intervention: 49.16 ± 7.83, $p < 0.05$) in the experimental group at post-intervention were significantly lower than those at baseline.

Conclusions: The 8-week exercise prescription containing moderate-intensity Baduanjin (5 days per week) can effectively alleviate QoL, depression, and anxiety in patients with NSCLC. Our exercise prescription is an effective supportive treatment for lung cancer patients with depression and anxiety.

Clinical trial registration: Chinese Clinical Trial Registry (ChiCTR1900025121).

KEYWORDS

exercise prescription, lung cancer, depression, anxiety, quality of life

Introduction

Lung cancer has the highest rates of morbidity and mortality among all cancer types in the world (1–3). In 2003–2009, the 5-year relative survival rate for patients diagnosed with lung cancer was only 18.2% (1). In China, lung cancer is the most common type of cancer and the leading cause of death (3, 4). With the sharp rise in smoking rates in China, the incidence of lung cancer may still be increasing (5–7). According to the statistics of the World Health Organization, the annual lung cancer mortality rate in China may reach 1 million by 2025.

Due to the disease deterioration and side effects of treatment, patients with lung cancer not only experience physiological discomforts, including pain, weight loss, and dyspnea (8), but also inevitably confront psychosocial problems, which progressively develop into depression and anxiety (9–11). For example, Linden et al. (12) found that anxiety and depression levels vary widely in patients diagnosed with different cancers, and the depression level in patients with lung cancer is the highest. A 6-month prospective study found that 29% of patients with lung cancer have depression after thoracotomy, leading to a poorer emotional QoL (11). Moreover, a recent study also showed that patients with lung cancer who suffer from emotional problems have a lower QoL and heavier symptom burdens than those who report no emotional problems (13). Thus, the negative effects of depression and anxiety should be seriously considered during the implementation of treatment for patients with lung cancer.

Physical exercise has been recognized as a feasible and effective way to improve clinical outcomes in patients with lung cancer after surgery (14). Although different combinations of exercise types (e.g., aerobic exercise, resistance training, and high-intensity interval training) have been proven to improve different physical capacities, such as peak rate of oxygen uptake (VO_2peak), respiratory muscle strength, 6-min walking test (6MWT) distance, fatigue, and health-related QoL (15–18) of the patients with lung cancer, the effect of exercise interventions on alleviating depression and anxiety in patients with lung cancer remains unclear (19, 20). Only a few studies considered the impact of exercise on the emotional problems of patients with lung cancer, and most of their exercise prescriptions failed to alleviate depression and anxiety (21–23).

Baduanjin, a moderate-intensity aerobic exercise derived from Tai Chi/Qigong, contains eight serial movements designed for people of all ages to maintain both mental and physical health. Because of its simplicity, cost-effectiveness, and utility, Baduanjin has been popular in China for over 800 years. Furthermore, it can be considered a Chinese traditional mind-body exercise involving body relaxation, mental imagery, and mindfulness (24, 25). These mental processes may potentially improve cognition, attention, and mood by retaining a pattern of activation of brain regions and connectivity of brain networks (26). It has been demonstrated that Baduanjin shows effectiveness at both physical and mental levels on mental disorders and some other specific diseases, such as depression, anxiety (27), insomnia (28), musculoskeletal pain (29), chronic obstructive pulmonary disease (30, 31), and cancers (32). However, these studies mainly focused on patients with breast cancer (33, 34) rather than those with lung cancer. There is still no scientific evidence supporting the effect of Baduanjin exercise prescriptions on the mental health of patients with lung cancer.

Given that depression and anxiety can negatively impact the clinical outcomes of patients with lung cancer, there is an urgent need for effective and targeted exercise prescriptions for patients with lung cancer who have mental disorders. The aim of this study was to determine the effect of the exercise prescription with Baduanjin on QoL, depression, and anxiety in patients with lung cancer. We hypothesized that our exercise prescription with Baduanjin had a significant benefit on the QoL, depression, and anxiety in patients with lung cancer.

Methods

Study design and participants

This was a parallel, pseudorandomized, controlled, and single-center trial conducted at the China-Japan Friendship Hospital in Beijing, China. A convenience sample was assigned to the control group (CG) and the experimental group (EG). The EG was treated with an 8-week exercise prescription containing Baduanjin. The CG received the usual care during the study period. The recruitment started from June 2019 to December 2019.

The inclusion criteria for participants were as follows: (1) individuals aged between 18 and 75 years; (2) those with histologically confirmed stage I-IIIB non-small cell lung cancer (NSCLC) and in a medically stable condition for the last 8 weeks; (3) those with the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores $\leq$2; (4) those with a life expectancy of $\geq$12 weeks; (5) those who performed <150 min of moderate-intensity exercise per week; (6) those who were suggested no further medical examination by ACSM's Pre-activity Screening Questionnaire (PASQ); (7) those who were able to complete the exercise prescription with normal neuromuscular and cognitive functions; and (8) those who for completed all definitive therapy (i.e. surgery, radiation, or chemotherapy) more than 1 week without severe complications related to these therapies.

The exclusion criteria for participants were as follows: (1) individuals with symptomatic spinal cord compression or brain metastasis; (2) aberrant cardiac function or any cardiac case history; (3) severe systemic disease; (4) autoimmune disease; (5) cancer-related active bleeding within 3 months; (6) psychiatric disorder history or contraindications for exercise (i.e., severe osteoporosis and musculoskeletal disorders); (7) positive blood or urine pregnancy tests within 3 days before the intervention; (8) disease related to cortisol increment; (9) individuals scheduled to have surgery or chemotherapy within 12 weeks; and (10) in situations where the doctor recommended not to be involved in any form of exercise.

The participants were considered dropout subjects when they (1) were unable to continue the experiment because of the deteriorated disease progression; (2) declined to continue; (3) had an adherence rate of intervention of $\leq$80%; (4) died; and (5) had sports injuries during the experiment.

The research was approved by the Sports Science Experiment Ethics Committee of Beijing Sport University (2019064H).

Procedure

The patients from the respiratory and critical illness medicine department and internal medicine department of China-Japan Friendship Hospital were screened according to the inclusion and exclusion criteria. Eligible patients were informed about the study procedure and invited to participate in this study. All participants provided informed consent and then underwent the baseline assessment. Patients were assigned in the order of their visits. The first 27 patients were assigned to the CG, whereas the following assigned patients were assigned to the EG. The EG was treated with our 8-week exercise prescription, and the CG received the usual care. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 and EORTC QLQ-LC13), the Self-Rating Depression Scale (SDS), and the Self-Rating Anxiety Scale (SAS) were sent to participants by social media after the intervention. For ethical reasons, the participants in CG were given systematic exercise guidance after the experiment.

Intervention

The patients in the EG received detailed movement instructions for the exercise prescriptions from therapists before the intervention. In addition, the brochures and online videos of the movement instructions were distributed to patients for review. In the first 2 weeks, the patients in the EG performed the exercise prescription in the hospital and were supervised by the therapists. In the last 6 weeks, the patients in the EG were asked to exercise at home and to record their training details on their record cards. The therapist checked the training progress online two times a week *via* video call or other social media.

There were two different training schemes in the exercise prescription. The first scheme focused on Baduanjin practice. It contained a 26-min Baduanjin session, a 10-min warm-up session, and a 5-min warm-down session. The second scheme involved resistance training and Baduanjin. It contained a 12-min Baduanjin session, a 23-min elastic band training session, a 10-min warm-up session, and a 5-min warm-down session. Both schemes lasted ~50 min each time. The intervention frequency gradually increased from three times per week to five times per week. In addition, the exercise intensity gradually increased from the rest state to 65%–75% of maximum heart rate (HR_{max}) for Baduanjin and 30%–50%*1RM for resistance training (shown in Table 1). Heart rate was monitored continuously by the heart rate chest belt (Inc. Polar, China) during the exercise. The specific movements of elastic band training are exhibited in Table 2 and Figure 1.

Outcomes

Demographic and clinical characteristics of patients, including age, sex, smoking history, cancer diagnosis, and surgery condition, were collected at baseline. The primary outcomes were the scores of SDS and SAS. Both SDS and SAS cover 20 items corresponding to depression- and anxiety-related symptoms. Points 1–4 represent a few of the times, some of the times, a good part of the time, and most of the time, respectively (35, 36). The scale raw scores were multiplied by 1.25 and rounded to the nearest integer (35). The higher scores indicate a worse status of depression or anxiety. The secondary outcomes of the study were the scores of the EORTC QLQ-C30 and -LC13 subscales. The QLQ-C30 is a reliable and valid approach for evaluating the QoL of patients with cancer (37). It consists of five functional scales, three symptom scales, a global health and quality of life scale, and six single-item symptom scales. The QLQ-LC13 as a supplement to QLQ-C30

TABLE 1 Details of exercise prescription.

	Type	Time	Intensity	Frequency
The former 2 weeks	Baduanjin	Warm-up: 10 min Baduanjin: 26 min Warm-down: 5 min	65%—75%HR_{max}	2 times/week
	Baduanjin and EBT	Warm-up: 10 min Baduanjin: 12 min EBT: 23 min Warm-down: 5 min	Baduanjin: 65%—75%HR_{max} EBT: 30%—50%*1RM, 10–12 reps/set, 3 sets	1 time/week
The latter 6 weeks	Baduanjin	Warm-up: 10 min Baduanjin: 26 min Warm-down: 5 min	65%—75%HR_{max}	3 times/week
	Baduanjin and EBT	Warm-up: 10 min Baduanjin: 12 min EBT: 23 min Warm-down: 5 min	Baduanjin: 65%—75%HR_{max} EBT: 30%—50%*1RM, 10–12 reps/set, 3 sets	2 times/week

EBT, elastic band training; HRmax, maximum heart rate; reps, repetitions.

is developed to measure the cancer-related symptoms and side effects, especially in patients with lung cancer (38). The items of QLQ-C30 and QLQ-LC13 are scored on a 4-point scale. The scores of scales are linearly transformed to a 0–100 scale according to a standardized process (39). The higher scores on the functional scale indicate a better functional status, whereas the higher scores on the symptom scale indicate a worse status of the symptom.

Sample size

The sample size was calculated with an effect size of 0.6, a power of 0.8, and a significance level of 0.05. Considering the dropout rate of 30% in patients with lung cancer, 27 individuals were planned for each group.

Statistical analysis

All data were extracted using the SPSS software for statistical analysis. Demographic and clinical information was described by frequencies. The scores of questionnaires and scales were reported as mean and standard deviation (mean ± SD). The chi-square test was performed in demographic and clinical information for the detection of differences between the groups at baseline. The paired sample t-test was used to analyze the differences between baseline and post-intervention. In addition, the independent sample t-test was used to analyze the differences between the CG and the EG. The level of statistical significance was set at a p-value < 0.05.

Results

A total of 52 participants met the inclusion criteria of this study. In the CG, eight of the 26 participants dropped out during the intervention (one died, four declined to continue, and three were unreachable). In the EG, seven of the 26 participants dropped out during the intervention (one died, three dropped out because of deteriorated disease progression, and three were unreachable). It led to an overall adherence rate of 71.15%. No intervention-related adverse events occurred during the study period (shown in Figure 2).

The demographic and clinical characteristics of participants are shown in Table 3. Most participants were men (63.5%) and were diagnosed with lung adenocarcinoma (48.1%). Participants in the CG were aged 58.03 ± 7.71 years, and those in the EG were aged 56.04 ± 11.67 years. More than half of the participants (63.5%) did not require surgery. There was no significant difference in demographic and clinical characteristics between the CG and the EG.

Primary outcomes

As shown in Table 4, both SDS scores and SAS scores in the EG at post-intervention (SDS: 51.42 ± 7.31; SAS: 49.16 ± 7.83) were significantly lower than those at baseline (SDS: 57.74 ± 8.77, $p < 0.05$; SAS: 56.63 ± 9.39, $p < 0.05$). In addition, the SDS and SAS scores of the EG at post-intervention (SDS: 51.42 ± 7.31; SAS: 49.16 ± 7.83) were also lower than those in the CG at post-intervention (SDS: 56.94 ± 8.54, $p < 0.05$; SAS: 55.33 ± 8.69, $p < 0.05$).

TABLE 2 Movements in elastic band training.

Elastic band training	
Standing elbow flexion	The patient stands in the middle of the elastic band and grabs two ends of the elastic band in each hand. Both hands are moved into an elbow flexion motion and then back to neutral
Standing elbow extension	With the elastic band grabbed in each hand, the patient puts one hand behind the back and the other hand behind the head. Cues are given to pull the elastic band apart
Standing rowing	The patient places one foot a step forward and then puts the midpoint of the elastic band under the front foot. The patient begins by holding the elastic band with both hands. Cues are given to squeeze the shoulder blades together without allowing them to shrug
Standing hip extension	With the two ends of the elastic band tied together, the patient places both legs inside the loop of the band. Keeping the knee slightly bent, and the trunk steady, the patient stabilizes on one leg. The contralateral leg is moved into a hip extension motion and then back to neutral
Standing hip flexion	With the two ends of the elastic band tied together, the patient places both legs inside the loop of the band. Keeping the knee slightly bent, and the trunk steady, the patient stabilizes on one leg. The contralateral leg is moved into a hip flexion motion and then back to neutral
Standing hip abduction	With the two ends of the elastic band tied together, the patient places both legs inside the loop of the band. Keeping the knee slightly bent, and the trunk steady, the patient stabilizes on one leg. The contralateral leg is moved into a hip abduction motion and then back to neutral
Squat	The patient stands on the elastic band and grabs the elastic band in each hand. The patient performs a squatting motion to 45 degrees of knee flexion while keeping his knees behind his feet during the exercise. The patient completes the exercise by returning to the start position

Secondary outcomes

Table 5 shows the total QLQ-C30 scores of patients with NSCLC at baseline and post-intervention. As for functional scales in the EG, there were significant differences in the QLQ-C30 scores of physical functioning (baseline: 67.67 ± 15.18 vs. post-intervention: 90.00 ± 7.95, $p < 0.01$), role functioning (baseline: 66.67 ± 27.57, vs. post-intervention: 87.50 ± 15.17, $p < 0.01$), emotional functioning (baseline: 72.08 ± 21.68 vs. post-intervention: 82.92 ± 15.87, $p < 0.01$), and global QoL (baseline: 26.67 ± 17.85 vs. post-intervention: 46.67 ± 14.15, $p < 0.01$). However, no significant difference was found in the scores of social functioning and cognitive functioning. As for symptom scales in the EG, there were significant differences in the QLQ-C30 scores of fatigue (baseline: 33.33 ± 23.36 vs. post-intervention: 18.89 ± 13.05, $p < 0.01$), pain (baseline: 30.00 ± 32.26 vs. post-intervention: 11.67 ± 16.31, $p < 0.01$), dyspnea (baseline: 31.67 ± 27.52 vs. post-intervention: 20.00 ± 16.75, $p < 0.01$), and insomnia (baseline: 41.67 ± 30.35 vs. post-intervention: 21.67 ± 16.31, $p < 0.01$). However, no significant difference was found in nausea and vomiting, appetite loss, constipation, diarrhea, and financial impact.

Compared with the CG in functional scales, the EG showed higher QLQ-C30 scores of physical functioning (CG: 64.44 ± 18.29 vs. EG: 90.00 ± 7.95, $p < 0.01$), role functioning (CG: 57.41 ± 28.71 vs. EG: 87.50 ± 15.17, $p < 0.01$), emotional functioning (CG: 65.28 ± 19.01 vs. EG: 82.92 ± 15.87, $p < 0.01$), and social functioning (CG: 56.48 ± 17.28 vs. EG: 69.17 ± 18.16, $p < 0.05$). However, no significant difference was found in the scores of cognitive functioning and global QoL. Compared with the CG in symptom scales, the EG showed higher QLQ-C30 scores of fatigue (CG: 43.83 ± 21.04 vs. EG: 18.89 ± 13.05, $p < 0.01$), pain (CG: 43.52 ± 29.23 vs. EG: 11.67 ± 16.31, $p < 0.01$), dyspnea (CG: 44.44 ± 25.57 vs. EG: 20.00 ± 16.75, $p < 0.01$), and sleep disturbance (CG: 55.56 ± 36.16 vs. EG: 21.67 ± 16.31, $p < 0.01$).

In the CG, there was no significant difference in the QLQ-C30 scores of all items except nausea and vomiting (baseline: 29.63 ± 28.3 vs. post-intervention: 19.44 ± 23.04, $p < 0.05$). Table 6 shows the total QLQ-LC13 scores of patients with NSCLC at baseline and post-intervention. The QLQ-LC13 scores of dyspnea showed a significant intragroup (baseline: 8.33 ± 25.10 vs. post-intervention: 26.11 ± 14.98, $p < 0.01$) and intergroup difference (CG: 41.36 ± 22.48 vs. EG: 26.11 ± 14.98, $p < 0.05$). However, no significance was found in the other items.

Discussion

Our results showed that our exercise prescription improved the QoL, depression, and anxiety of patients with lung cancer. To the best of our knowledge, this is the first study to investigate the effect of exercise prescriptions, including both Baduanjin and resistance training, in patients with lung cancer. Compared with previous studies, we stress that exercise intensity and volume must be sufficient for patients with lung cancer. One study reported that the exercise prescription that combined eight-movement Tai Chi, a Chinese traditional exercise similar to Baduanjin, with resistance training for patients with lung cancer improved depression and anxiety but failed to improve most aspects of QoL (40). Compared to our exercise prescription,

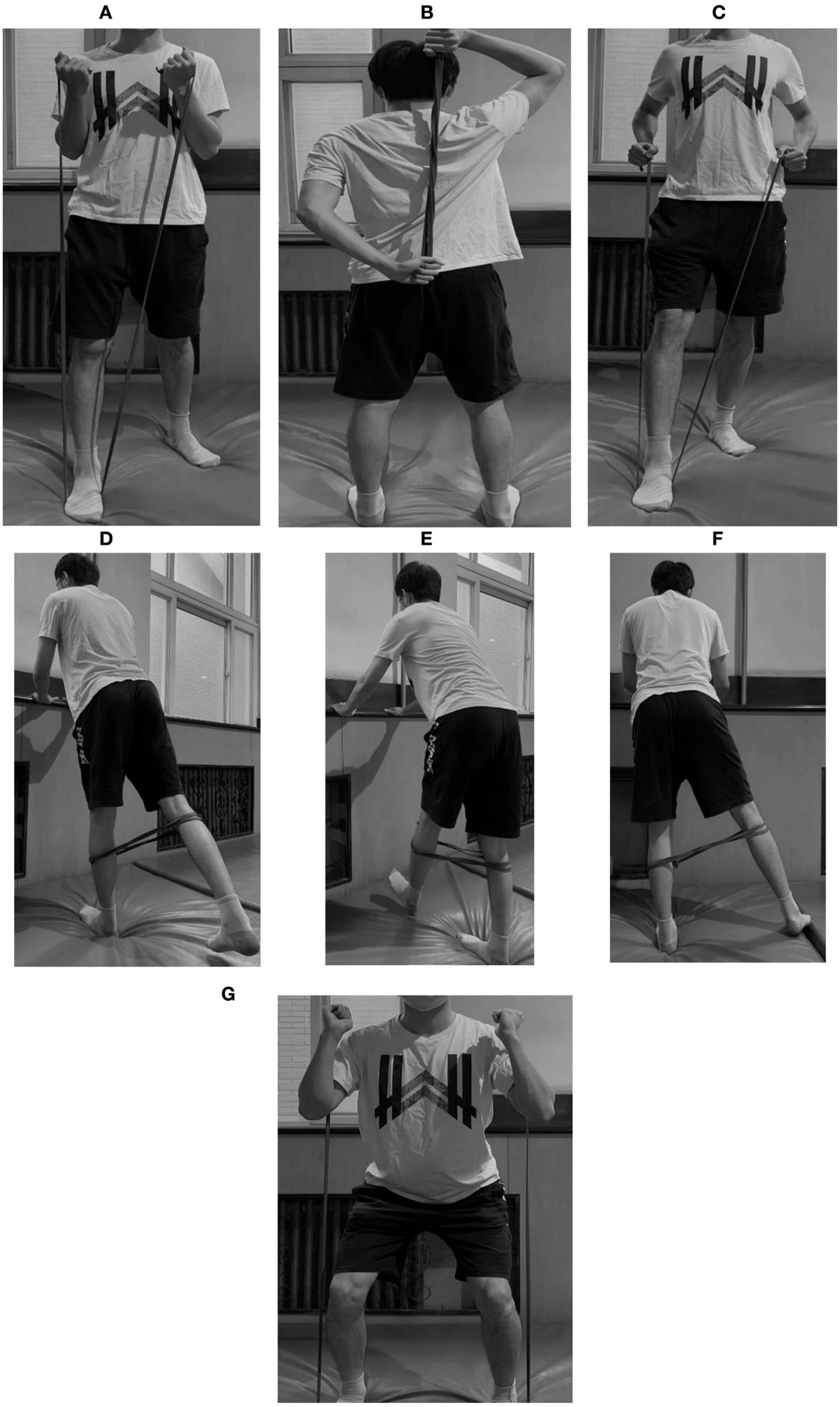

FIGURE 1
Movements in elastic band training. **(A)** Standing elbow flexion. **(B)** Standing elbow extension. **(C)** Standing rowing. **(D)** Standing hip extension. **(E)** Standing hip flexion. **(F)** Standing hip abduction. **(G)** Squat.

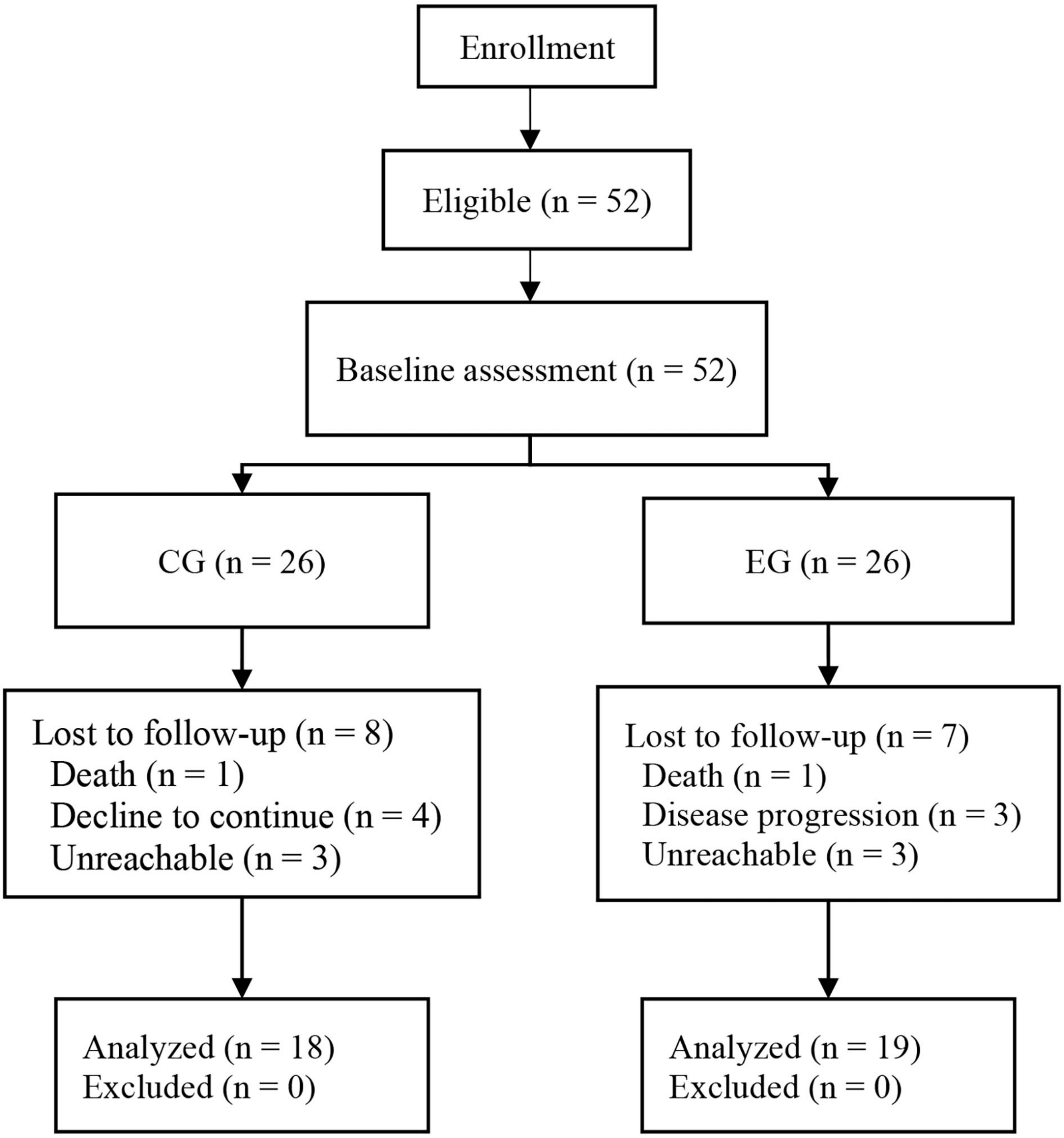

FIGURE 2
Flowchart of the study.

it included a smaller volume of aerobic exercise and a lower frequency of resistance training. These insufficiencies in exercise prescription might account for the unchanged QoL. Furthermore, Chen et al. also found that a 40-min-per-session walking exercise program without resistance training failed to improve cancer-related symptoms (e.g., pain, fatigue, nausea, and sleep disturbance) (41). As their cancer-related symptoms were mild, isolated aerobic walking at a fixed intensity might be monotonous and fail to reach the necessary intensity. We believe that progressive intensity and volume are indispensable elements in an exercise prescription adapted for patients with different physical conditions. Our study recommended a comprehensive exercise prescription that combined mind-body exercises with resistance training because it might include all essential components to treat patients with physical and mental illnesses.

Considering the physical frailty of patients with cancer, the exercises prescribed for them must be safe and easy to learn (42). In our exercise prescription, Baduanjin, a low- to moderate-intensity exercise that includes only eight movements, can be learned easily by patients with worse physical functional status. Systematic reviews demonstrated that Baduanjin effectively improves the QoL and cancer-related symptoms of postoperative breast cancer patients and is unlikely to result in serious adverse events (34, 43). Moreover, the use of elastic bands can modulate the intensity of resistance training in a controlled manner with a simple change in grip width or rubber stiffness (44). Therefore, Baduanjin combined with elastic band training as an exercise prescription might be better than medical treatment. Although patients with cancer who received medical treatment (e.g., nabilone and megestrol acetate) showed higher QoL and improved cancer-related symptoms (45), these medicines may have severe side effects (46–48). Furthermore, as no adverse events were observed during the intervention, our study confirmed the safety and effectiveness of Baduanjin combined with elastic band training. Thus, we suggest that Baduanjin combined with elastic band training is a safe exercise prescription that is easier to implement and promote in patients with lung cancer.

TABLE 3 The demographic and clinical characteristics of participants.

	CG ($n = 26$)	EG ($n = 26$)	p-Value
Age (years)	58.03 ± 7.71	56.04 ± 11.67	0.469
Sex (mean, %)			
Men	16 (61.5%)	17 (65.4%)	0.773
Women	10 (38.5%)	9 (34.6%)	
Smoking history			
Yes	14 (53.8%)	16 (61.5%)	0.266
No	12 (45.2%)	10 (38.5%)	
Surgery			
Yes	8 (30.8%)	11 (42.3%)	0.388
No	18 (69.2%)	15 (57.7%)	
Cancer diagnosis			
Adenocarcinoma	12 (46.2%)	13 (50.0%)	0.852
Squamous carcinoma	12 (46.2%)	10 (38.5%)	
Large cell carcinoma	2 (7.7%)	3 (11.5%)	

p-Values are based on the chi-square test for categorical variables and the t-test for continuous variables.

Our results showed that the exercise prescription containing Baduanjin improved most aspects of the functional scale and most cancer-related symptoms on the QLQ-C30, including fatigue, pain, and sleep disturbance. Its effectiveness is consistent with that reported by a meta-analysis assessing the effect of Baduanjin on QoL in patients with cancer (32). The improvement in emotional function and sleep disturbance may be related to a reduction in cortisol levels. Studies showed that people with depression or sleep disturbances have higher cortisol levels (49, 50). Baduanjin may alleviate the emotional burden and sleep disturbance by reducing cortisol excretion (51). A significant improvement in dyspnea was noted on the QLQ-LC13. As a meta-analysis demonstrated that Baduanjin could effectively improve lung function in patients with chronic obstructive pulmonary disease (52), our results indicate that the benefits of Baduanjin may also apply to patients with lung cancer. Although the scores of other items (i.e., coughing, sore mouth, and peripheral neuropathy) on the QLQ-LC13 did not improve significantly, they showed a downward trend in the EG and an upward trend in the CG post-intervention. The significant improvement of these items on the QLQ-LC13 may require a larger sample size or a longer intervention period to demonstrate. Therefore, we postulate that Baduanjin is a valuable supportive treatment for patients with lung cancer suffering from the side effects of cancer treatment.

It is worth mentioning that the item "nausea and vomiting" on the QLQ-C30 improved significantly in the CG but did not change significantly in the EG. A possible explanation for this might be that patients with comparatively high "nausea and vomiting" scores received medical treatment. Thus, there might be an unexpected factor between the CG (29.63 ± 28.33) and the EG (14.17 ± 18.95), as the "nausea and vomiting" scores were distinctly different at baseline. That is, the significant improvement in the CG may be attributed to medical treatment and the improvement trend in the EG may be attributed to the effect of our exercise prescription. Thus, we suggest a future study that considers the effects of medication to determine whether exercise can improve such symptoms.

TABLE 4 The SDS and SAS scores of the CG and the EG.

Scale	CG ($n = 18$)		EG ($n = 19$)	
	Baseline	Post-intervention	Baseline	Post-intervention
SDS	56.56 ± 8.19	56.94 ± 8.54	57.74 ± 8.77	51.42 ± 7.31*#
SAS	54.89 ± 8.71	55.33 ± 8.69	56.63 ± 9.39	49.16 ± 7.83*#

*Indicates a significant difference ($p < 0.05$) between the baseline and post-intervention.
#Indicates a significant difference ($p < 0.05$) between the CG and the EG.

TABLE 5 The QLQ-C30 scores of the CG and the EG.

QLQ-C30 item	CG ($n = 18$)		EG ($n = 19$)	
	Baseline	Post-intervention	Baseline	Post-intervention
Functional scales				
Physical functioning	64.82 ± 19.10	64.44 ± 18.29	67.67 ± 15.18	90.00 ± 7.95**##
Role functioning	60.19 ± 29.78	57.41 ± 28.71	66.67 ± 27.57	87.50 ± 15.17**##
Emotional functioning	60.65 ± 18.70	65.28 ± 19.01	72.08 ± 21.68	82.92 ± 15.87**##
Cognitive functioning	57.41 ± 21.56	60.19 ± 22.24	70.00 ± 26.27	69.17 ± 18.16
Social functioning	58.33 ± 23.00	56.48 ± 17.28	70.83 ± 24.71	69.17 ± 18.16#
Global quality of life	29.17 ± 14.64	29.63 ± 15.45	26.67 ± 17.85	46.67 ± 14.15**
Symptom scales/items				
Fatigue	43.21 ± 22.83	43.83 ± 21.04	33.33 ± 23.36	18.89 ± 13.05**##
Nausea and vomiting	29.63 ± 28.33	19.44 ± 23.04*	14.17 ± 18.95	9.17 ± 10.08
Pain	41.67 ± 30.92	43.52 ± 29.23	30.00 ± 32.26	11.67 ± 16.31**##
Dyspnea	44.44 ± 25.57	44.44 ± 25.57	31.67 ± 27.52	20.00 ± 16.75**##
Sleep disturbance	55.56 ± 36.16	55.56 ± 36.16	41.67 ± 30.35	21.67 ± 16.31**##
Appetite loss	29.63 ± 37.73	33.33 ± 37.92	25.00 ± 26.21	13.33 ± 16.75
Constipation	22.22 ± 30.25	24.07 ± 29.83	28.33 ± 29.17	20.00 ± 16.75
Diarrhea	24.07 ± 29.83	24.07 ± 29.83	21.67 ± 31.11	15.00 ± 20.16
Financial impact	51.85 ± 32.78	51.85 ± 32.78	38.33 ± 31.11	38.33 ± 31.11

The symbols * and ** indicate a significant difference ($p < 0.05$ and $p < 0.01$, respectively) between the baseline and post-intervention; The symbols # and ## indicate a significant difference ($p < 0.05$ and $p < 0.01$, respectively) between the CG and EG.

TABLE 6 The QLQ-LC13 scores of the CG and the EG.

QLQ-LC13 item	CG ($n = 18$)		EG ($n = 19$)	
	Baseline	Post-intervention	Baseline	Post-intervention
Dyspnea	41.36 ± 26.07	41.36 ± 22.48	38.33 ± 25.10	26.11 ± 14.98**#
Coughing	35.19 ± 24.18	37.03 ± 22.55	38.33 ± 22.36	31.67 ± 17.01
Haemoptysis	16.67 ± 20.61	16.67 ± 20.61	13.33 ± 25.13	13.33 ± 25.13
Sore mouth	16.67 ± 28.58	16.67 ± 28.58	15.00 ± 22.88	13.33 ± 19.94
Dysphagia	18.52 ± 30.73	18.52 ± 30.73	18.33 ± 22.88	16.67 ± 20.23
Peripheral neuropathy	22.22 ± 28.01	24.07 ± 22.30	25.00 ± 26.21	18.33 ± 17.01
Alopecia	46.30 ± 32.62	46.30 ± 32.62	45.00 ± 29.17	45.00 ± 29.17
Pain in chest	22.22 ± 28.01	27.78 ± 32.84	16.67 ± 20.23	16.67 ± 20.23
Pain in arm or shoulder	11.11 ± 16.17	12.96 ± 16.72	15.00 ± 17.01	16.67 ± 17.10
Pain in other parts	5.56 ± 12.78	7.41 ± 14.26	3.33 ± 10.26	5.00 ± 12.21

**Indicates a significant difference ($p < 0.01$) between the baseline and post-intervention. #Indicates a significant difference ($p < 0.05$) between the CG and EG.

The dropout rate in this study was 28.85%, which is not high compared to other studies of patients with lung cancer (16, 23, 40). This could be attributed to the fact that the patients in the present study were older adults. Hence, they were closely cared for by family and not bothered by work. They could then spare more time to perform the exercise prescription. During the follow-up period, we found that the patients' willingness to conduct the exercise prescription was motivated by Baduanjin. In addition, record cards for training and instructive videos reportedly increase adherence (53, 54). However, the occurrence of failure to follow up should be managed. This problem might have been caused by insufficient supervision during the 6-week home exercise program. We suggest offline or online supervised training of patients to increase the adherence rate.

This study has several limitations, and its findings should be interpreted with caution. First, owing to the lack of eligible patients in the hospital, we were unable to conduct a randomized controlled trial. It was difficult to recruit a large number of patients in a short time and implement the intervention on all participants concurrently. Therefore, the patients received the intervention once they participated in the experiment. This is a pseudorandomized procedure that inevitably leads to biased outcomes. Second, due to the nature of the exercise intervention, patient blinding was impossible, and placebo effects could not be eliminated. Third, this study did not record and control the patients' drug intakes, which may have biased the outcomes. Finally, it did not include qualitative measurements such as patient feedback; therefore, comparisons with future studies will be limited.

Conclusion

This study demonstrated that the 8-week exercise prescription containing Baduanjin could effectively improve QoL, depression, and anxiety in patients with NSCLC. Our exercise prescription is an effective supportive treatment for lung cancer patients with depression and anxiety. Baduanjin is a safe and easy-to-learn mind-body exercise that should be included in exercise prescriptions.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Sports Science Experiment Ethics Committee of Beijing Sport University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZB and JX contributed to the concept of the work. JY, JX, LD, and JC contributed to the conduction of this trial. JL and JY contributed to data analysis and the drafting of the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of aquatic exercise on mood and anxiety symptoms: A systematic review and meta-analysis

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Objective: Exercise has beneficial effects on mood and anxiety symptoms. However, the impact of aquatic exercise on mood and anxiety symptoms has not been clearly confirmed. Therefore, this study aimed to synthesize and systematically analyze evidence available on boosting mental health through aquatic exercise.

Method: A systematic review and meta-analysis were conducted under the PRISMA 2020 guidelines. PubMed, BIOSIS Previews, PsycINFO, Medline, SPORTDiscus, Education Source, and Web of Science Core Collection (WoSCC) were searched in May 2022. The research included the influence of aquatic exercises on mood and anxiety symptoms. After assessing trial quality and completing data extraction, a meta-analysis was carried out through R software. The results were presented as a standardized mean difference (SMD) and the corresponding 95% confidence interval.

Results: A total of 18 original trials were included. People who received aquatic exercise intervention had a statistically significant reduction in mental disorder symptoms compared with before. The results were aquatic exercise [SMD = −0.77, 95% CI (−1.08, −0.47), $I^2 = 77\%$, $P < 0.01$], swimming [SMD = −0.51, 95% CI (−1.14, 0.12), $I^2 = 78\%$, $P < 0.01$], aquatic aerobics [SMD = −0.92, 95% CI (−1.32, −0.53), $I^2 = 78\%$, $P < 0.01$], moderate intensity [SMD = −0.75, 95% CI (−1.07, −0.43), $I^2 = 67\%$, $P < 0.01$], and low intensity [SMD = −1.07, 95% CI (−1.08, −0.47), $I^2 = 85\%$, $P < 0.01$].

Conclusion: Aquatic exercise could statistically significantly improve mental health. Light aquatic aerobics probably has a better effect on mood and anxiety symptoms. However, given the number and quality of included research, verifying the aforementioned conclusions requires a larger sample of high-quality studies.

KEYWORDS

swimming, mental health, anxiety, depression, aquatic exercise, mood

Introduction

Mental health is critically important to everyone, everywhere (1). Mood and anxiety significantly diminish the quality of life and happiness of those who suffer from them (2). Some psychological problems become so severe that they can even lead to suicide. More than 90% of suicides in the West have been attributed to mood disorders (3). The prevalence of these conditions has a significant economic impact on society because of the difficulties they cause for affected individuals on a daily basis (4–6). One study from China found that in January and February 2020, 54% of subjects expressed psychological symptoms as severe or moderate, 29% of subjects reported moderate to serious anxiety, and approximately 17% of subjects reported moderate to severe depression (7). Therefore, finding some effective and acceptable intervention methods that can improve mood and anxiety symptoms is significant.

As a non-drug treatment for mental disorders, exercise has become the focus of more and more researchers' attention. Recent studies support that exercise, especially aerobic exercise (8) and physical activity, has beneficial effects on mental health (9). Exercise was promoted as the first level in the Canadian Clinical Guidelines 2016 emotional therapy (10).

Aquatic exercise, as a special aerobic exercise, has been shown to potentially benefit mood and anxiety (11–14). Aquatic exercise has many physiological benefits compared to land-based workouts because of the water's unique properties, such as buoyancy, pressure, resistance, and protection from skin irritation due to temperature and touch (15). As a result, when compared to other forms of exercise, aquatic exercise may prove to be the most effective in terms of its positive impact on mood. However, to our knowledge, no study has been conducted to synthesize the research on the psychological benefits of aquatic exercise. A systematic review of the studies and a meta-analysis are necessary to elaborate on the effect of aquatic exercise on mood and anxiety.

Furthermore, the effect of exercise on mental health is affected by many factors, including differences in individual characteristics and specific parameters of exercise intervention. Aging of both the body and mind may be associated with an increased probability of developing mood disorders (16). Exercise as an intervention to treat chronic diseases is associated with mood elevations in patients with various chronic diseases and disabilities (17). The type, intensity, and duration of exercise also affect the effect of exercise on mood. Specifically, long-time relaxing aerobic exercise may promote greater mood benefits (18–20). Although little evidence supports greater mood improvements in response to exercise among women, (21) some previous studies showed that exercise (dance, yoga, aerobic games, etc.) reduced depressive symptoms, with no moderating effect of sex (22–25). However, it is unclear whether there are differences in age, sex, disease, intensity, and duration in the impact of aquatic exercise on mood.

This study aimed to synthesize and systematically analyze the available evidence to determine the effect of aquatic exercise on mental health.

Methods

The systematic review and meta-analysis followed the guidance of the PRISMA 2020 statement (26).

Eligibility criteria

The eligibility and inclusion criteria of the article are as follows: 1) The study design must only include randomized controlled trials and quasi-experimental studies. 2) The article's full text must be available. 3) The article must be written in English. 4) It must only include peer-reviewed journal articles. 5) The subjects must be limited to humans. 6) Interventions must have included any type of aquatic exercise. 7) Mental health, mood, anxiety symptoms, depression, or related parameters in the study could be clearly extracted.

Aquatic exercise in the encyclopedia was defined as "an activity," and the activity site must be in the water, such as a pool, lake, or ocean (27). Based on this, all types of exercise in water (such as swimming, aquatic exercise, and floating in water) were included in this study. Additionally, demographic restrictions were waived.

Information sources and search strategy

PubMed, BIOSIS Previews, PsycINFO, Medline, SPORTDiscus, Education Source, and Web of Science Core Collection were searched on May 28, 2022, for studies using the following combination of terms: "mental health," "depression,"

TABLE 1 Search strategy in PubMed.

Step	Search strategies
#1	"swim" OR "aquatic" OR "water sport" [Mesh]
#2	"swim" OR "aquatic exercise" OR "water sport" [Text Word]
#3	#1 OR #2
#4	"mental health" OR "depression" OR "anxiety" OR "mood" [Mesh]
#5	"mental health" OR "depression" OR "anxiety" OR "mood" [Text Word]
#6	"POMS" OR "BDI" OR "BAI" [Text Word]
#7	#4 OR #5 OR #6
#8	#3 AND #7

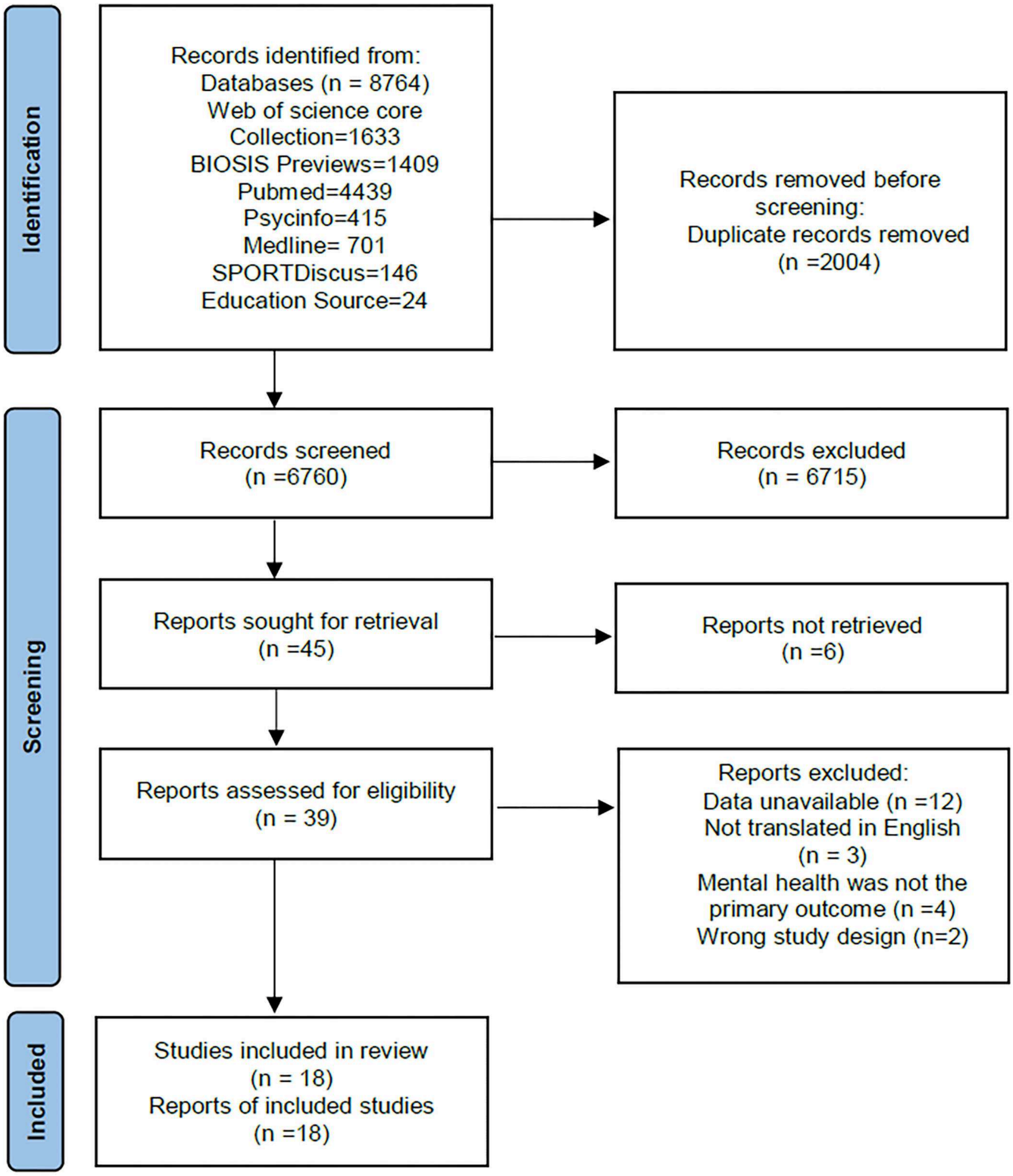

FIGURE 1
PRISMA flow chart. The figure shows the search strategy and selection of articles in this study (18 articles were included at the end).

"anxiety," "mood," "POMS," "BDI," "BAI" in combination with "swim," "aquatic," "water sport," and "aquatic exercise." Table 1 shows the search strategies used for database searches (e.g., PubMed).

Study selection

All of the search results were imported into Endnote. The duplicate was searched by year, title, and author.

TABLE 2 General characteristics.

No.	Year	Author	Country	N	Population characters	Age	Mode	Measurement tool	Duration (week)	Frequency (d/week)	Intensity	Duration of sessions (min)
1	1992	Berger and Owen. (28)	United States	39	College students	21	Swim	Profile of Mood State (POMS)	14	2	Moderate	40
2	1997	Berger et al. (29)	Australia	39	Swimmers	15	Swim	POMS	1	12	High	180
3	1999	Tanaka et al. (30)	United States	12	Obese subjects with stages 1 to 2 essential hypertension	48	Swim	POMS	10	3	Moderate	60
4	2001	Webb and Drummond. (31)	Australia	19	Beach swimming participants	26	Swim	Spielberger State-Trait Anxiety questionnaire	2	N/R[a]	Moderate	240
5	2002	Lindeman et al. (32)	Finland	25	Winter swimming	50	Winter swim	Crown Crisp Experimental Index (CCEI)	32	N/R	N/R	N/R
6	2004	Huttunen et al. (33)	Finland	36	Winter swimming	53	Winter swim	POMS	16	4	N/R	N/R
7	2015	Kim et al. (34)	Korea	25	Elderly women	72	Aquatic aerobics	POMS	24	3	Moderate	60
8	2016	Razazian et al. (35)	Switzerland		Female patients with multiple sclerosis	34	Aquatic aerobics	Beck's Depression Inventory (BDI)	8	3	Moderate	60
9	2018	Aidar et al. (36)	Brazil	19	Persons with stroke	52	Aquatic aerobics	StateTrait Anxiety Inventory & BDI	12	2	Moderate	60
10	2018	Da Silva et al. (37)	Brazil	29	Hypertensive adults & health adults	53	Aquatic aerobics	BDI & Beck's Anxiety Inventory (BAI)	12	2	light	45
11	2018	Delevatti et al. (38)	Brazil	17	Patients with type 2 diabetes	54	Aquatic aerobics	BDI	12	3	high	45
12	2019	da Silva et al. (39)	United States	30	Nondepression elderly & elderly with depression	58	Aquatic aerobics	BDI & BAI	12	2	light	45
13	2019	de Oliveira et al. (38)	Brazil	10	Elderly women	67	Swim	Geriatric Anxiety Inventory (GAI) & Perceived Stress Scale	12	2	light	45
14	2019	Perez et al. (40)	Brazil	10	Patients with Parkinson's disease	67	Aquatic aerobics	Short Geriatric Depression Scale	15	2	light	45
15	2019	Sahin et al. (14)	Turkey	30	People with osteoarthritis	63	Aquatic aerobics	Hospital Anxiety and Depression Scale (HAD)	3	5	Moderate	60
16	2020	Useros et al. (41)	Chile	15	People with cervical dystonia	48	Aquatic aerobics	BDI & State-Trait Anxiety Inventory (STAI)	4	1	light	50
17	2021	da Silva et al. (42)	United States	30	Health adults &people with Type 2 diabetes mellitus	64	Aquatic aerobics	BDI & BAI	12	0.5	light	41
18	2021	Lee et al. (43)	Korea	20	Pre-frailty elderly women	73	Aquatic aerobics	POMS	12	3	Moderate	60

[a] N/R, Not reported.

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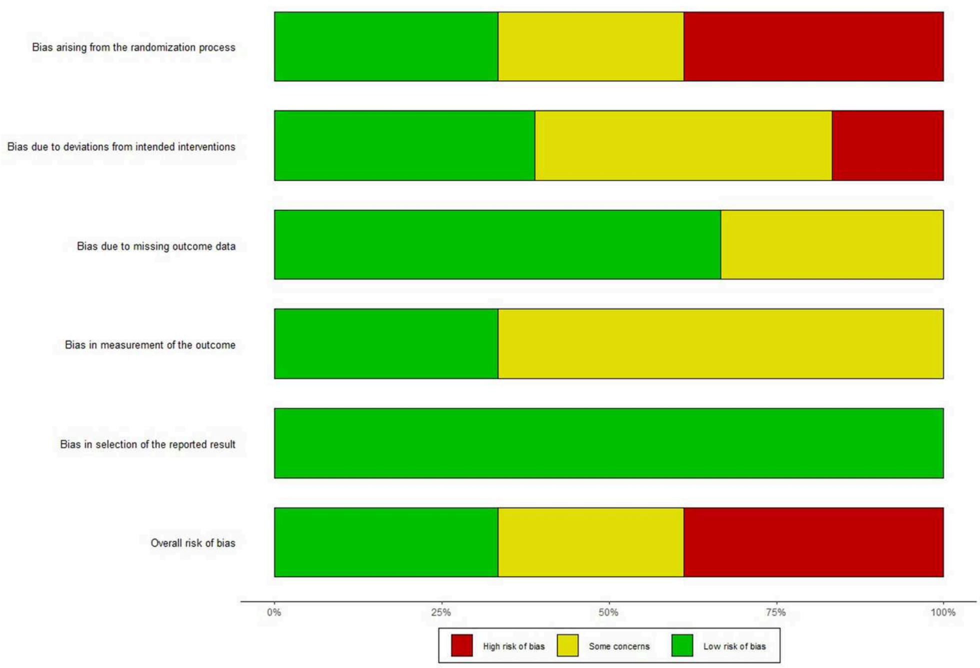


FIGURE 2
Risk of bias summary.

After removing duplicates, two authors (ZYT and JML) independently screened the studies based on the title and the abstract. Only experimental articles defining the effect of aquatic exercise on human mood and anxiety symptoms were included. Following the initial screening, two authors searched the full text and further evaluated the research according to the eligibility criteria. We resolved differences through discussion with another author (YW). The selection process of the study was exhibited by a PRISMA 2020 flow diagram.

Assessment of trial quality and data extraction

Trial quality was assessed from the selected full-text articles by two authors—the studies' risk of bias was in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. At the same time, the data for the article were extracted. The information from the included articles (author, date of publication, country, and study design), the characteristics of subjects (sample size, age, sex, health condition, etc.), and intervention (types of exercises, duration, frequency) were extracted from the included articles. Furthermore, outcomes measured (mean, SD) and measurement tools used (type of questionnaire) were extracted.

Synthesis and analysis

The meta-analysis was performed by R 4.2.1 software ("meta" package). The Chi-square test was performed to determine whether or not there were statistically significant differences between the research results. Multiple similar homogenous studies were considered if $P \geq 0.1$, $I^2 < 50\%$, and meta-analysis using a fixed-effect model. If $P < 0.1$, $I^2 \geq 50\%$, the random-effects model was used. Because of the different ranges and measurement methods of mental health in these studies, standardized mean difference (SMD) and a 95% confidence interval (CI) were used for continuous data.

Subgroup analysis

Subgroup analyses were grouped based on the following factors: age, disease, mode of exercise, type of mental health, duration of exercise, and intensity.

Results

Search strategy results

The PRISMA flow chart (Figure 1) shows the search strategy and details the selection of articles for this review. A total of 8,764 articles were retrieved on a database search. After

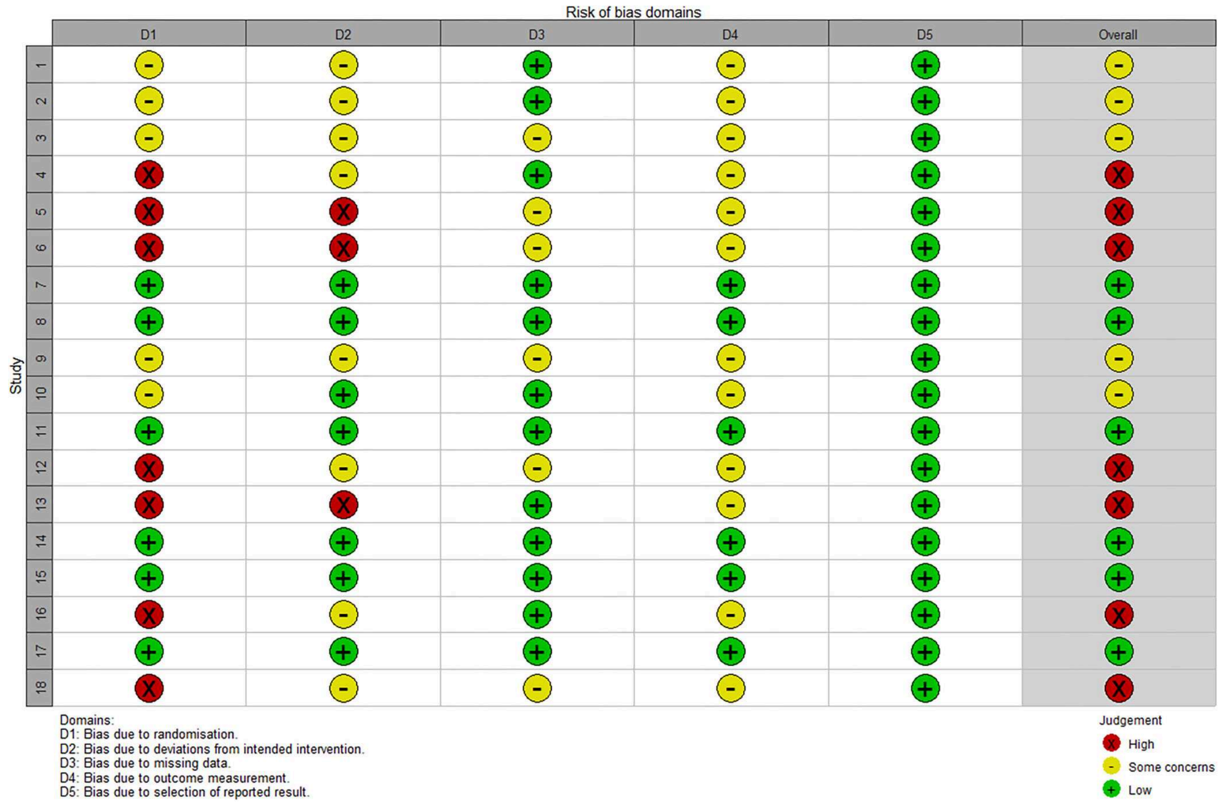


FIGURE 3
Risk of bias graph.

removing duplicates, 6,715 were removed through reviewing the title and abstract. Afterward, of the remaining 45 articles, through the full-text review, 27 were eliminated, and 18 were included.

Study characteristics

Table 2 displays the general characteristics of the 18 articles, including the date of publication, the country, the study design, and the population of subjects.

Quality of the evidence

The assessment of trial quality was performed independently by two authors, according to Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (44). All discrepancies were discussed or consulted with another author. After evaluating the risk of bias in studies, seven studies were considered to have a high bias risk arising from the randomization process, three studies were found to have an ambiguous bias risk due to deviations from intended interventions, and 12 studies were found to have complete data (Figure 2). Overall, six studies have low risk, five have some concerns, and seven have a high risk (Figure 3).

Effects of aquatic exercise on mental health

According to meta-analysis, people who were treated with aquatic exercise showed a statistically significant reduction in mental disorder symptoms compared to pro-intervention [SMD $= -0.77$, 95% CI $(-1.08, -0.47)$, $I^2 = 77\%$, $P < 0.01$]. As depicted in Figure 4, aquatic exercise improves mood and anxiety symptoms.

Subgroup analysis

Subgroup: Age

Based on the age of the subjects, studies were divided into three groups, with an age range of <18 years, 18–64 years,

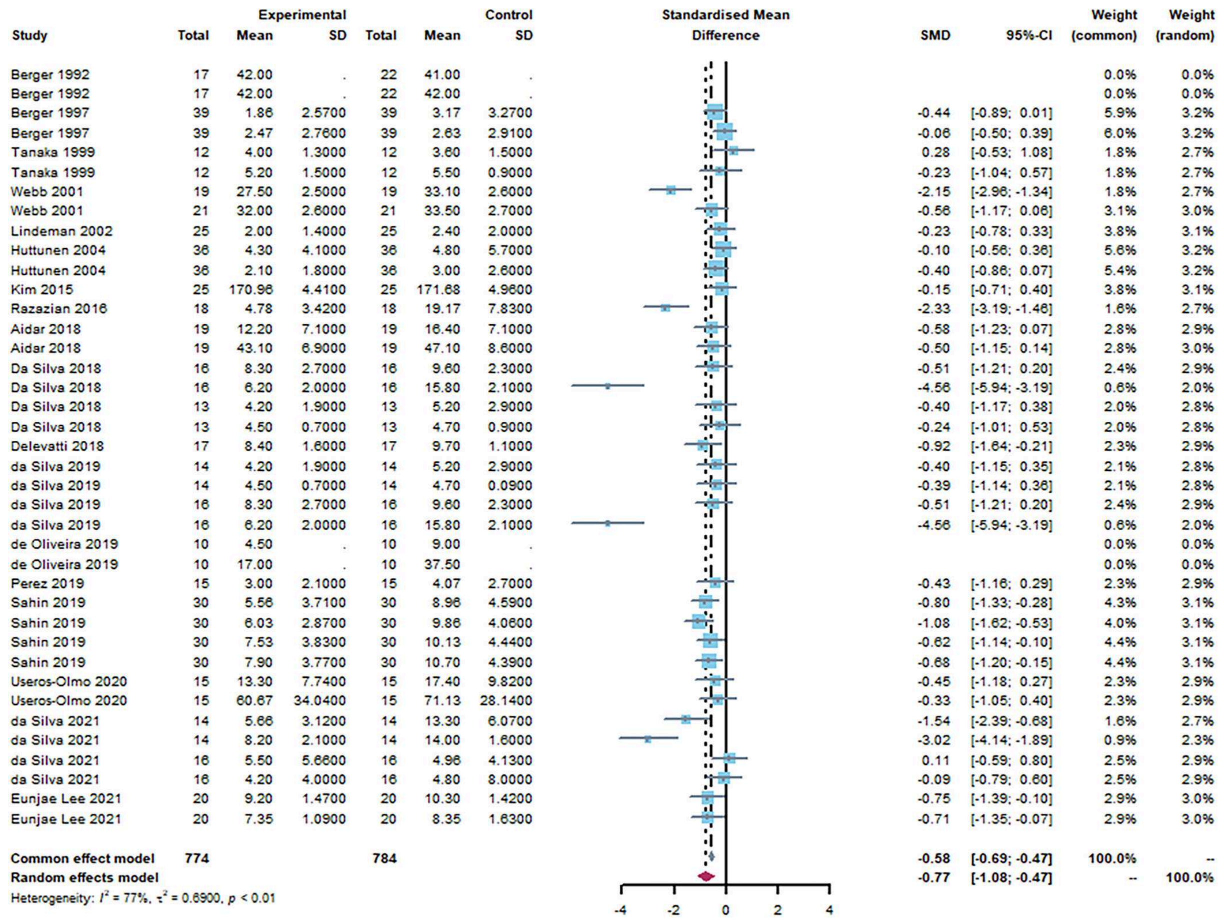


FIGURE 4
Forest plot of aquatic exercise effects on mood. The overall effect of aquatic exercise: [SMD = −0.77, 95% CI (−1.08, −0.47), I2 = 77%, *P* < 0.01].

and>64 years, respectively. Age groups were classified according to WHO standards (45). It can be observed that 18–64 years [SMD = −0.94, 95% CI (−1.34, −0.54), I^2 = 80%, $P < 0.01$] were statistically significant through the subgroup analysis (Figure 5). There was no statistical significance in other groups. There was a statistically significant subgroup effect ($P = 0.02$).

Subgroup: Disease

Studies were divided into ten groups based on the subjects' physical health. It can be observed that the Health group [SMD = −0.64, 95% CI (−1.03,−0.25), I^2 = 74%, $P < 0.01$], Hypertension group [SMD = −1.20, 95% CI (−3.31, 0.91), I^2 = 92%, $P < 0.01$], and Depression group [SMD = −2.49, 95% CI (−6.47, 1.49), I^2 = 96%, $P < 0.01$] were statistically significant through the subgroup analysis (Figure 6). There was no statistical significance in other groups. There was a statistically significant subgroup effect ($P = 0.02$).

Subgroup: Mode of exercise

Based on the exercise mode of intervention, studies were divided into three groups. The swimming group included swimming learning courses, leisure swimming, and swimming training. The aquatic aerobics group included water walking, water gymnastics, and any form of aerobic exercise in water, except swimming. It can be observed that swim [SMD = −0.51, 95% CI (−1.14, 0.12), I^2 = 78%, $P < 0.01$] and aquatic aerobics [SMD = −0.92, 95% CI (−1.32, −0.53), I^2 = 78%, $P < 0.01$] were statistically significant through the subgroup analysis (Figure 7). There was no statistical significance in the winter swim. There was a statistically significant subgroup effect ($P = 0.02$).

Subgroup: Type of mental health

Based on the type of mental health intervention, studies were divided into three groups. It can be observed that anxiety [SMD = −1.28, 95% CI (−2.04, −0.53), I^2 = 87%, $P < 0.01$] and depression [SMD = −0.52, 95% CI (−0.74, −0.30), I^2 = 55%,

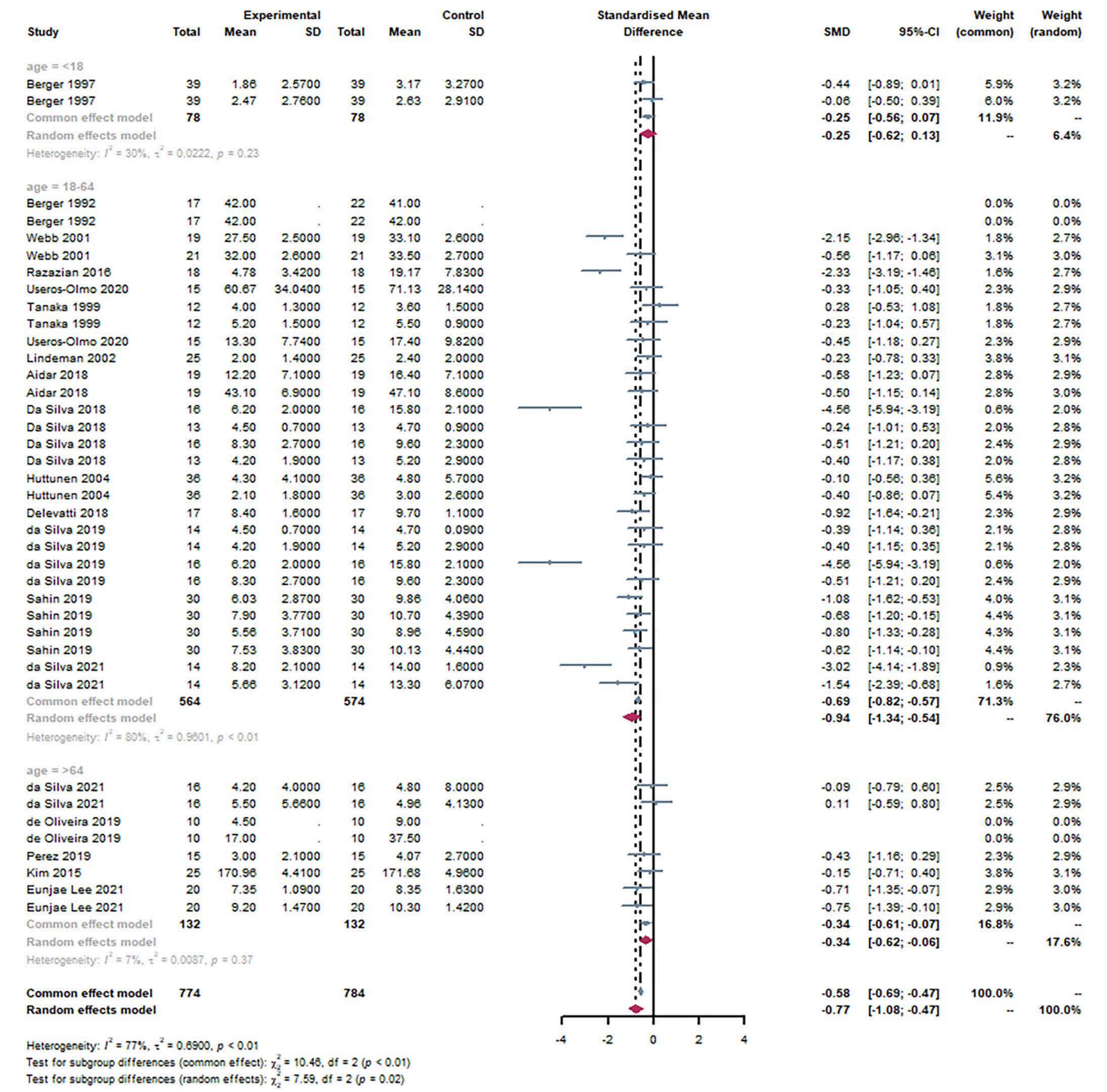


FIGURE 5
Forest plot of age. By subgroup analysis of the age, 18–64 years [SMD = −0.94, 95% CI (−1.34, −0.54), $I^2 = 80\%$, $P < 0.01$] were statistically significant.

$P < 0.01$] were statistically significant through the subgroup analysis (Figure 8). There was a statistically significant subgroup effect ($P = 0.07$).

Subgroup: Duration

Based on the duration of the subjects, studies were divided into three groups, with an age range of <4 weeks, 4–12 weeks, and>12 weeks, respectively. It can be observed that <4 weeks [SMD = −0.74, 95% CI (−1.11, −0.37), $I^2 = 70\%$, $P < 0.01$] and 4–12 weeks [SMD = −0.95, 95% CI (−1.45, −0.45), $I^2 = 82\%$, $P < 0.01$] were statistically significant through the subgroup analysis (Figure 9). There was no statistical significance in the> 12-week group. There was a statistically significant subgroup effect ($P = 0.01$).

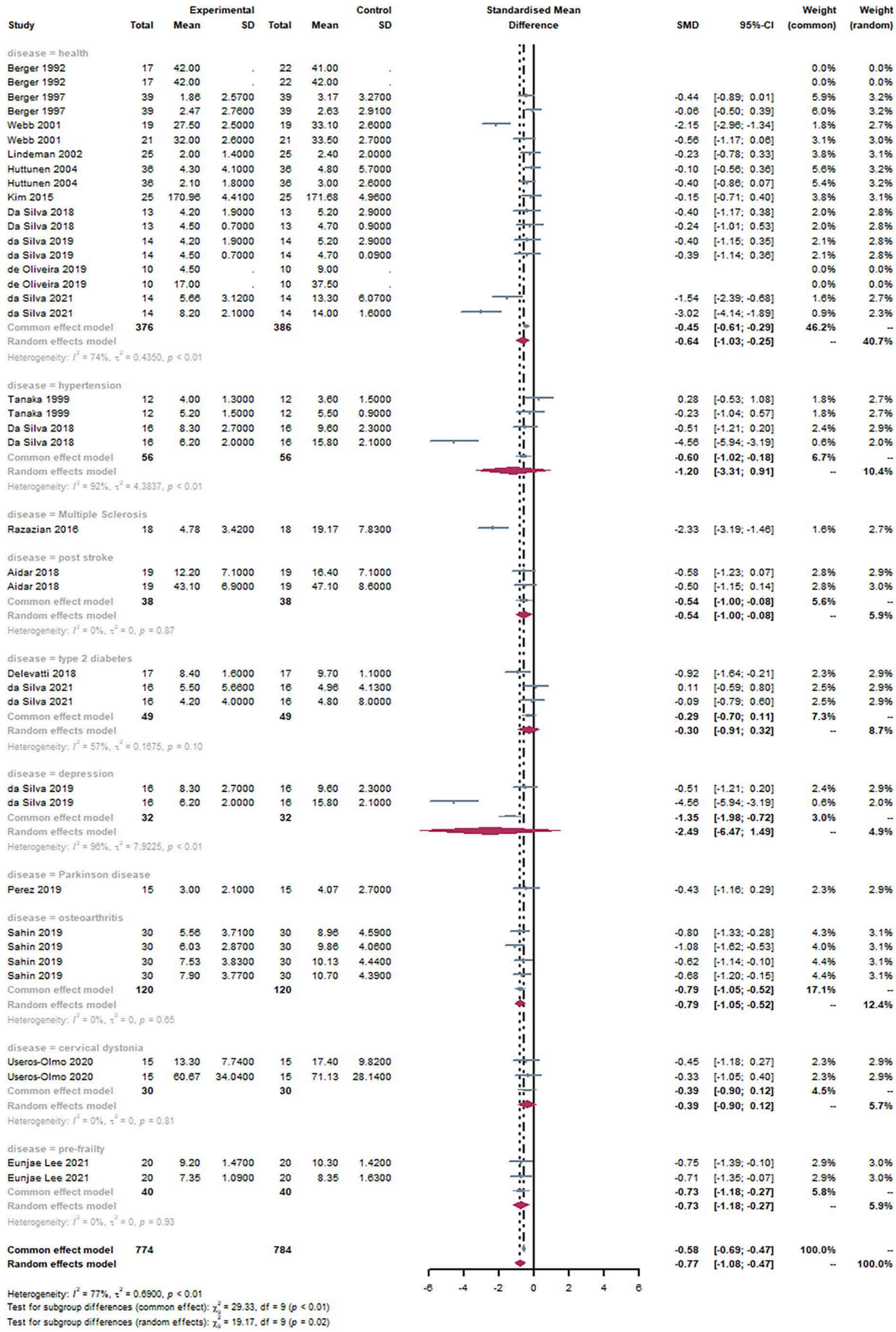


FIGURE 6

Forest plot of disease. By subgroup analysis of the disease, the Health group [SMD = −0.64, 95% CI (−1.03, −0.25), $I^2 = 74\%$, $P < 0.01$], Hypertension group [SMD = −1.20, 95% CI (−3.31, 0.91), $I^2 = 92\%$, $P < 0.01$], and Depression group [SMD = −2.49, 95% CI (−6.47, 1.49), $I^2 = 96\%$, $P < 0.01$] were statistically significant.

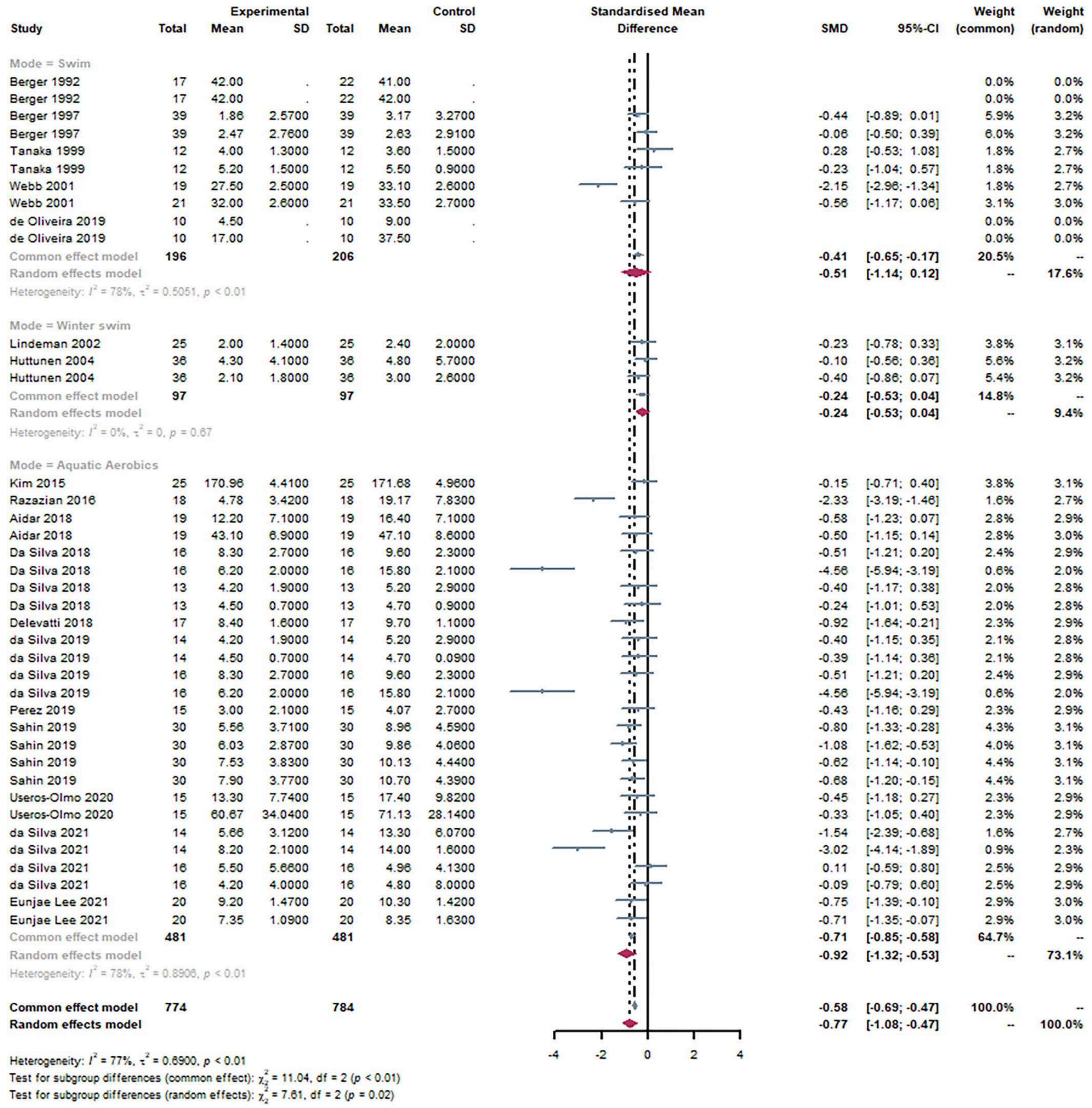


FIGURE 7
Forest plot of the mode of exercise. By subgroup analysis of the disease, swimming [SMD = −0.51, 95% CI (−1.14, 0.12), I^2 = 78%, $P < 0.01$], and aquatic aerobics [SMD = −0.92, 95% CI (−1.32, −0.53), I^2 = 78%, $P < 0.01$] were statistically significant.

Subgroup: Intensity

Intensity was one of the most important parameters of exercise intervention. Heart rate, as the main indicator of intensity, was measured in most studies. Based on the report of the American College of Sports Medicine, < 64% of the maximum was considered low intensity, 64–76% of the heart rate maximum was regarded as moderate intensity, and 77–95% of the heart rate maximum was considered high intensity (46). However, a few studies did not report the measurement of intensity.

According to the intensity of the subjects, studies were divided into three groups, light, moderate, and high, respectively. It can be observed that moderate [SMD = −0.75, 95% CI (−1.07, −0.43), I^2 = 67%, $P < 0.01$] and light [SMD = −1.07, 95% CI (−1.08, −0.47), I^2 = 85%, $P < 0.01$] were statistically significant through the subgroup analysis

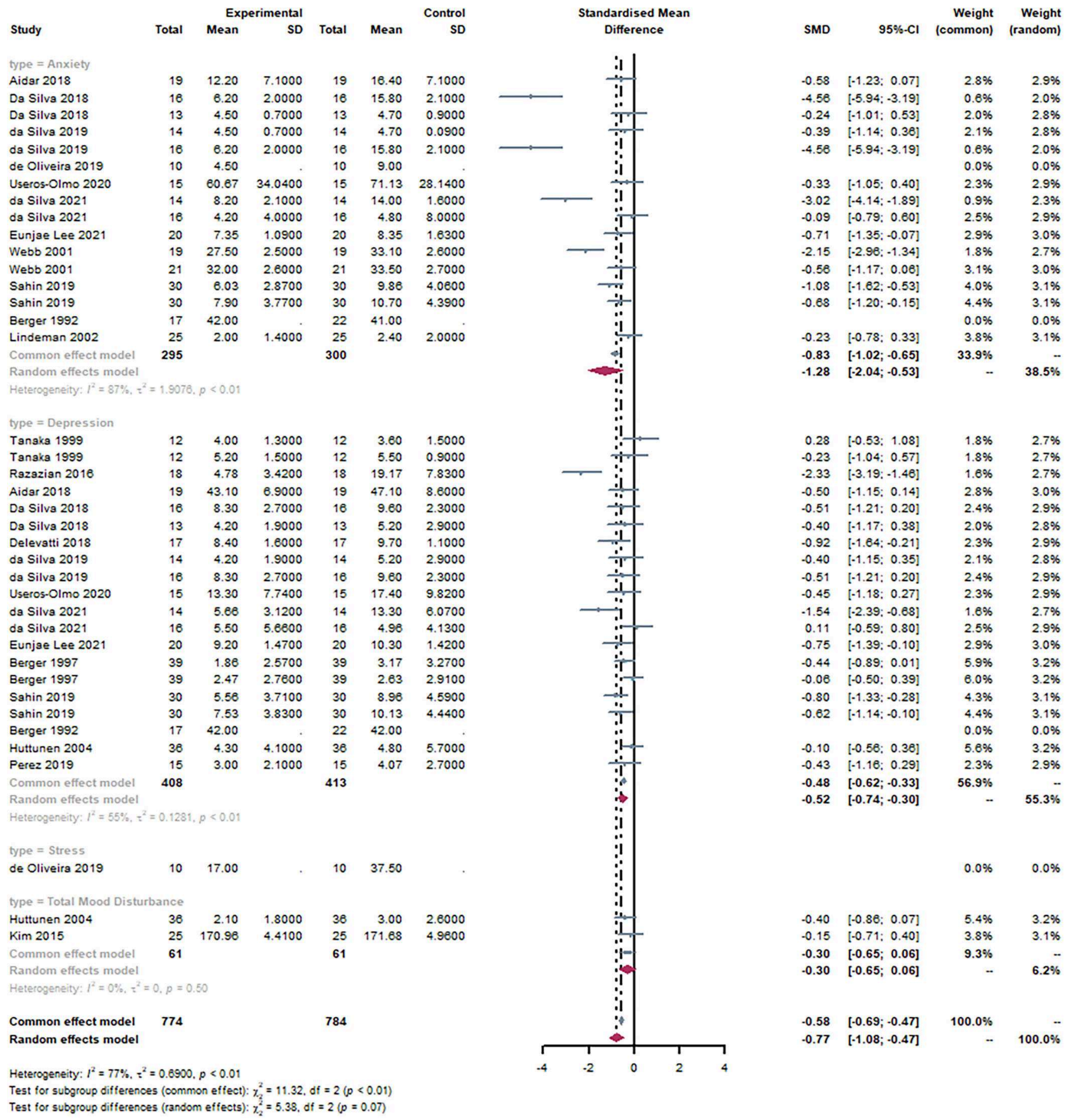


FIGURE 8
Forest plot of the type of mental health. By subgroup analysis of the disease, Anxiety [SMD = −1.28, 95% CI (−2.04, −0.53), I^2 = 87%, $P < 0.01$] and Depression [SMD = −0.52, 95% CI (−0.74, −0.30), I^2 = 55%, $P < 0.01$] were statistically significant.

(Figure 10). There was no statistical significance in the high group. There was a statistically significant subgroup effect ($P = 0.04$).

Publication bias

The funnel plot indicates the possible publication bias (Figure 11). Furthermore, the Egger method was used for analysis. When the linear regression test was $P < 0.01$, the publication bias of studies was statistically significant.

A sensitivity analysis was also conducted. A leave-one-out meta-analysis was used to test the publication bias of a single study (Figure 12). After sequentially removing each study, no studies affecting heterogeneity were found (I^2 = 72%−78%). This analysis confirmed the stability of the results.

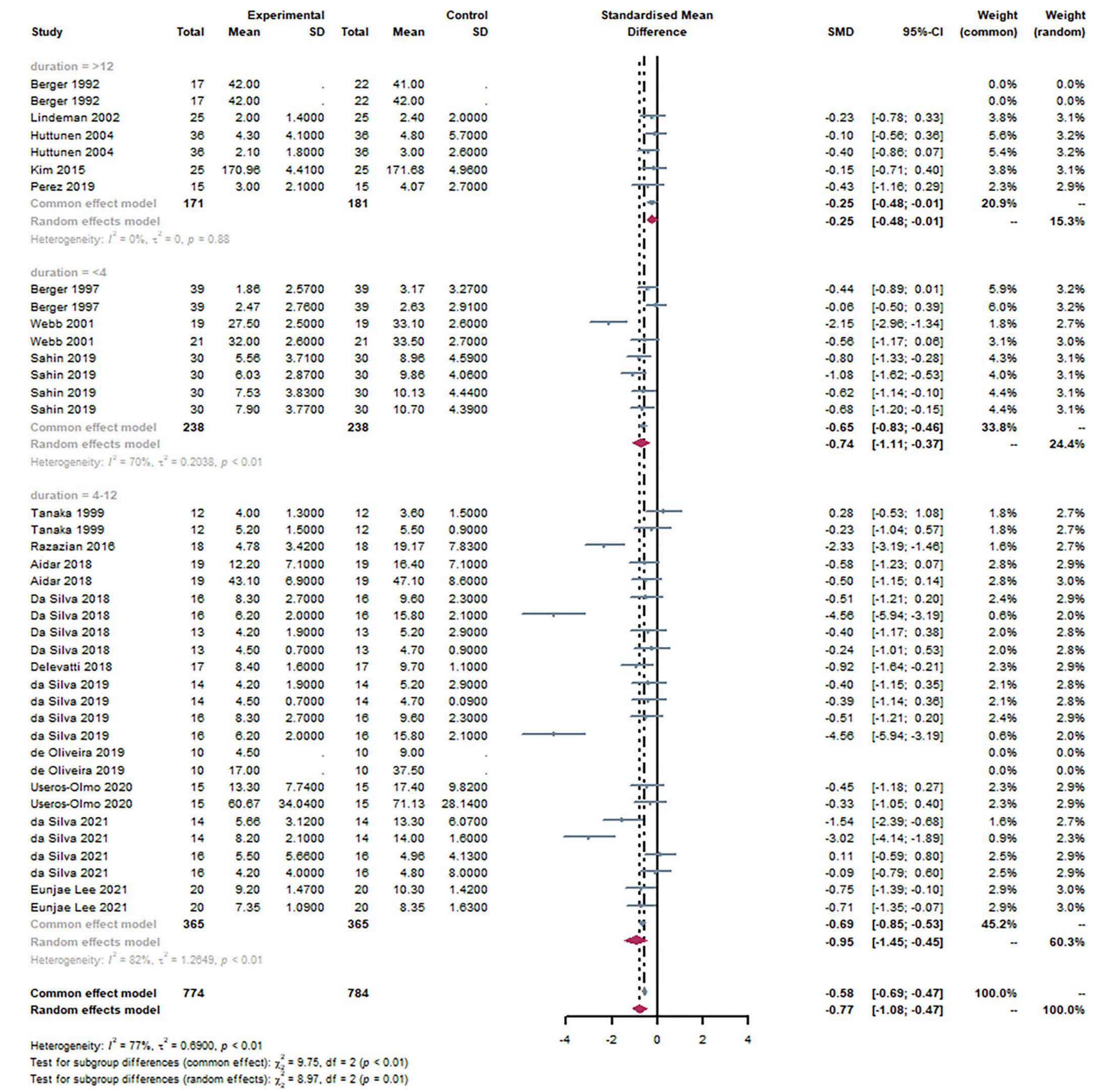


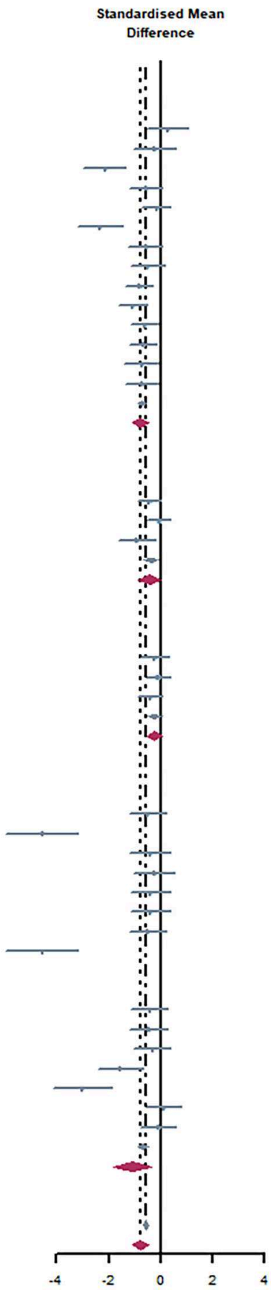
FIGURE 9
Forest plot of duration of exercise. By subgroup analysis of the disease, <4 weeks [SMD = −0.74, 95% CI (−1.11, −0.37), I^2 = 70%, $P < 0.01$] and 4–12 weeks [SMD = −0.95, 95% CI (−1.45, −0.45), I^2 = 82%, $P < 0.01$] were statistically significant through the subgroup analysis.

Discussion

This meta-analysis included 423 people who received aquatic exercise intervention; 18 studies synthesized the benefits of aquatic exercise, and the results revealed that aquatic exercise could statistically significantly improve mood and anxiety symptoms. The overall SMD = −0.77, [95% CI (−1.08, −0.47), I^2 = 77%, $P < 0.01$].

Ten different states of physical health are included in this review. Few comparable studies of a particular disorder made it difficult to determine which states would reap the most benefits from aquatic exercise. Nevertheless, this review found that aquatic exercise may be effective for general states of physical health observed, especially depression and hypertension. It is possible that the exercise increases the secretion of the related release of b-endorphin and dopamine and provides a soothing effect (47), while the muscular resistance of the

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight (common)	Weight (random)
intensity = Moderate										
Berger 1992	17	42.00	.	22	41.00	.			0.0%	0.0%
Berger 1992	17	42.00	.	22	42.00	.			0.0%	0.0%
Tanaka 1999	12	4.00	1.3000	12	3.60	1.5000	0.28	[-0.53; 1.08]	1.8%	2.7%
Tanaka 1999	12	5.20	1.5000	12	5.50	0.9000	-0.23	[-1.04; 0.57]	1.8%	2.7%
Webb 2001	19	27.50	2.5000	19	33.10	2.6000	-2.15	[-2.96; -1.34]	1.8%	2.7%
Webb 2001	21	32.00	2.6000	21	33.50	2.7000	-0.56	[-1.17; 0.06]	3.1%	3.0%
Kim 2015	25	170.96	4.4100	25	171.68	4.9600	-0.15	[-0.71; 0.40]	3.8%	3.1%
Razazian 2016	18	4.78	3.4200	18	19.17	7.8300	-2.33	[-3.19; -1.46]	1.6%	2.7%
Aidar 2018	19	12.20	7.1000	19	16.40	7.1000	-0.58	[-1.23; 0.07]	2.8%	2.9%
Aidar 2018	19	43.10	6.9000	19	47.10	8.6000	-0.50	[-1.15; 0.14]	2.8%	3.0%
Sahin 2019	30	5.56	3.7100	30	8.96	4.5900	-0.80	[-1.33; -0.28]	4.3%	3.1%
Sahin 2019	30	6.03	2.8700	30	9.86	4.0600	-1.08	[-1.62; -0.53]	4.0%	3.1%
Sahin 2019	30	7.53	3.8300	30	10.13	4.4400	-0.62	[-1.14; -0.10]	4.4%	3.1%
Sahin 2019	30	7.90	3.7700	30	10.70	4.3900	-0.68	[-1.20; -0.15]	4.4%	3.1%
Eunjae Lee 2021	20	9.20	1.4700	20	10.30	1.4200	-0.75	[-1.39; -0.10]	2.9%	3.0%
Eunjae Lee 2021	20	7.35	1.0900	20	8.35	1.6300	-0.71	[-1.35; -0.07]	2.9%	3.0%
Common effect model	339			349			-0.72	[-0.88; -0.55]	42.5%	--
Random effects model							-0.75	[-1.07; -0.43]	--	41.1%
Heterogeneity: $I^2 = 67\%$, $\tau^2 = 0.2579$, $p < 0.01$										
intensity = High										
Berger 1997	39	1.86	2.5700	39	3.17	3.2700	-0.44	[-0.89; 0.01]	5.9%	3.2%
Berger 1997	39	2.47	2.7600	39	2.63	2.9100	-0.06	[-0.50; 0.39]	6.0%	3.2%
Delevatti 2018	17	8.40	1.6000	17	9.70	1.1000	-0.92	[-1.64; -0.21]	2.3%	2.9%
Common effect model	95			95			-0.36	[-0.65; -0.07]	14.2%	--
Random effects model							-0.41	[-0.85; 0.03]	--	9.2%
Heterogeneity: $I^2 = 54\%$, $\tau^2 = 0.0831$, $p = 0.11$										
intensity = N/R										
Lindeman 2002	25	2.00	1.4000	25	2.40	2.0000	-0.23	[-0.78; 0.33]	3.8%	3.1%
Huttunen 2004	36	4.30	4.1000	36	4.80	5.7000	-0.10	[-0.56; 0.36]	5.6%	3.2%
Huttunen 2004	36	2.10	1.8000	36	3.00	2.6000	-0.40	[-0.86; 0.07]	5.4%	3.2%
Common effect model	97			97			-0.24	[-0.53; 0.04]	14.8%	--
Random effects model							-0.24	[-0.53; 0.04]	--	9.4%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.67$										
intensity = Light										
Da Silva 2018	16	8.30	2.7000	16	9.60	2.3000	-0.51	[-1.21; 0.20]	2.4%	2.9%
Da Silva 2018	16	6.20	2.0000	16	15.80	2.1000	-4.56	[-5.94; -3.19]	0.6%	2.0%
Da Silva 2018	13	4.20	1.9000	13	5.20	2.9000	-0.40	[-1.17; 0.38]	2.0%	2.8%
Da Silva 2018	13	4.50	0.7000	13	4.70	0.9000	-0.24	[-1.01; 0.53]	2.0%	2.8%
da Silva 2019	14	4.20	1.9000	14	5.20	2.9000	-0.40	[-1.15; 0.35]	2.1%	2.8%
da Silva 2019	14	4.50	0.7000	14	4.70	0.0900	-0.39	[-1.14; 0.36]	2.1%	2.8%
da Silva 2019	16	8.30	2.7000	16	9.60	2.3000	-0.51	[-1.21; 0.20]	2.4%	2.9%
da Silva 2019	16	6.20	2.0000	16	15.80	2.1000	-4.56	[-5.94; -3.19]	0.6%	2.0%
de Oliveira 2019	10	4.50	.	10	9.00	.			0.0%	0.0%
de Oliveira 2019	10	17.00	.	10	37.50	.			0.0%	0.0%
Perez 2019	15	3.00	2.1000	15	4.07	2.7000	-0.43	[-1.16; 0.29]	2.3%	2.9%
Useros-Olmo 2020	15	13.30	7.7400	15	17.40	9.8200	-0.45	[-1.18; 0.27]	2.3%	2.9%
Useros-Olmo 2020	15	60.67	34.0400	15	71.13	28.1400	-0.33	[-1.05; 0.40]	2.3%	2.9%
da Silva 2021	14	5.66	3.1200	14	13.30	6.0700	-1.54	[-2.39; -0.68]	1.6%	2.7%
da Silva 2021	14	8.20	2.1000	14	14.00	1.6000	-3.02	[-4.14; -1.89]	0.9%	2.3%
da Silva 2021	16	5.50	5.6600	16	4.96	4.1300	0.11	[-0.59; 0.80]	2.5%	2.9%
da Silva 2021	16	4.20	4.0000	16	4.80	8.0000	-0.09	[-0.79; 0.60]	2.5%	2.9%
Common effect model	243			243			-0.67	[-0.87; -0.46]	28.5%	--
Random effects model							-1.07	[-1.80; -0.34]	--	40.3%
Heterogeneity: $I^2 = 85\%$, $\tau^2 = 1.8746$, $p < 0.01$										
Common effect model	**774**			**784**			**-0.58**	**[-0.69; -0.47]**	**100.0%**	--
Random effects model							**-0.77**	**[-1.08; -0.47]**	--	**100.0%**



Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.6900$, $p < 0.01$
Test for subgroup differences (common effect): $\chi^2_3 = 11.03$, df = 3 ($p = 0.01$)
Test for subgroup differences (random effects): $\chi^2_3 = 8.11$, df = 3 ($p = 0.04$)

FIGURE 10
Forest plot of the intensity of exercise. By subgroup analysis of the disease, moderate [SMD = −0.75, 95% CI (−1.07,−0.43), $I^2 = 67\%$, P < 0.01] and light [SMD = −1.07, 95% CI (−1.08, −0.47), $I^2 = 85\%$, P < 0.01] were statistically significant through the subgroup analysis.

water is more than ten times higher than the resistance of land. Hence, it requires more activation of the motor cortex in the elderly (39). Besides, people with type 2 diabetes are usually not sufficiently active. Activation of the brain and mood improvement are potentially important motivators for exercise (48). For patients with hypertension, the levels of the cytokines (TNF-α and IL-6) could be reduced by participating in the aquatic exercise program, suggesting the inhibitory effect of aquatic exercise on the production of pro-inflammatory cytokines (37).

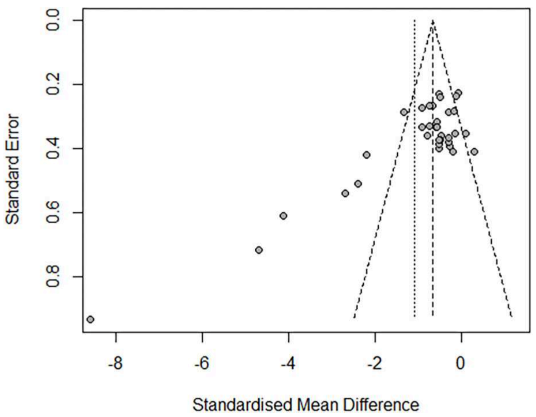


FIGURE 11
Funnel plot of publishing bias.

Aquatic exercise is particularly effective in reducing anxiety. Comparing the results of this study with other studies, a meta-analysis conducted by Song (49) found the effect of land-based aerobic exercise on anxiety (SMD:−0.50), traditional Chinese exercise (SMD:−0.03), and meditation (SMD: −0.15). The above three exercises are lower than aquatic exercises (SMD: −1.28). Several studies have also shown that aquatic exercise can boost mood (35, 40, 50). However, those studies were relatively narrow, focusing primarily on relatively menial land aerobic exercise. The effect of aquatic exercise is different from that of land exercise and needs further research.

Compared with land-based aerobic exercise, aquatic exercise shows its particularity. The sensation of water flowing through the skin when moving in water is difficult to obtain when moving on land. Several studies indicated that touch could reduce stress and improve mood (51–54). The reduction in gravity also reduces the load on the spine, knees, and other pain-prone areas. In addition to physical factors, aquatic exercises are difficult for some people, especially in the sea and other special environments; thus, "confronting challenges" was key to the impact of mood (55). Moreover, aquatic exercise serves to connect and convey a sense of nature. With the function of re-orientating and changing the sense of body, space, and gravity, people can expand their perspectives (56).

Regarding the intervention type of exercise, aquatic aerobics (SMD: −0.92) is better than swimming (SMD: −0.51), but these studies lack consistency. Swimming includes swim-learning programs (28, 38), swimming training for competition (29, 57), and leisure swimming (31, 58, 59). Swimming in different situations affects people's moods differently. Similarly, aquatic aerobics includes various forms. This may be one of the reasons for the high heterogeneity of research. In general, most of the aquatic aerobics' subjects are older or have ordinary diseases. Regarding safety and feasibility, older individuals prefer light, easy, and fun exercises over hard and stressful exercises (60). Therefore, they are more likely to benefit from water aerobics for their mental health than young, healthy adults. However, the trials in this study are insufficient for comparison. The specific impact needs further comparative study through similar samples. Winter swimming has little effect on improving mental health, which may be because the temperature stimulus of cold water is too strong, and then the body tends to remain tense (32, 33). For this reason, winter swimming may not be an effective way to improve mental health.

Based on the results of this study, the low intensity of aquatic exercise causes greater benefits for mental health. It may be that lower intensity makes people more relaxed (49). However, the acceptability of people of different ages and disease conditions to the intensity should also be considered, making it necessary to judge the research results carefully.

The influence of age and sex is not fully reflected in this study. In this study, the impact of exercise on the moods of the elderly was not statistically significant. The influence of age on the effect of exercise intervention is still controversial. A study of land-based exercise intervention shows that there were no significant differences in the amount of improvement between the younger and older exercise groups (61). However, some researchers find that exercise has greater distinct effects on brain activity and mood improvement in young people than in older people (62). Although the trials included in this investigation indicated the sex of the subjects, most studies were not classified by sex in the results, making sex-specific subgroup analysis challenging. Although some research (19, 25, 63, 64) suggests no difference in the positive effects of exercise based on sex, some evidence suggests that males may get greater advantages from exercise on their mood than females (65). Thus, more study is required to determine whether aerobic exercise has different effects on mood depending on gender and age.

There are a few limitations to this study. First, the between-study heterogeneity is significant, and our subgroup and sensitivity analyses cannot entirely account for it. Second, this study only selected articles published in English to limit the risk of bias. There may be influential publications written in languages other than English that were not included. Finally, non-randomized controlled trials were included, which may lead to selection bias. Given the limitations in our review, more large-scale research should be conducted in the future.

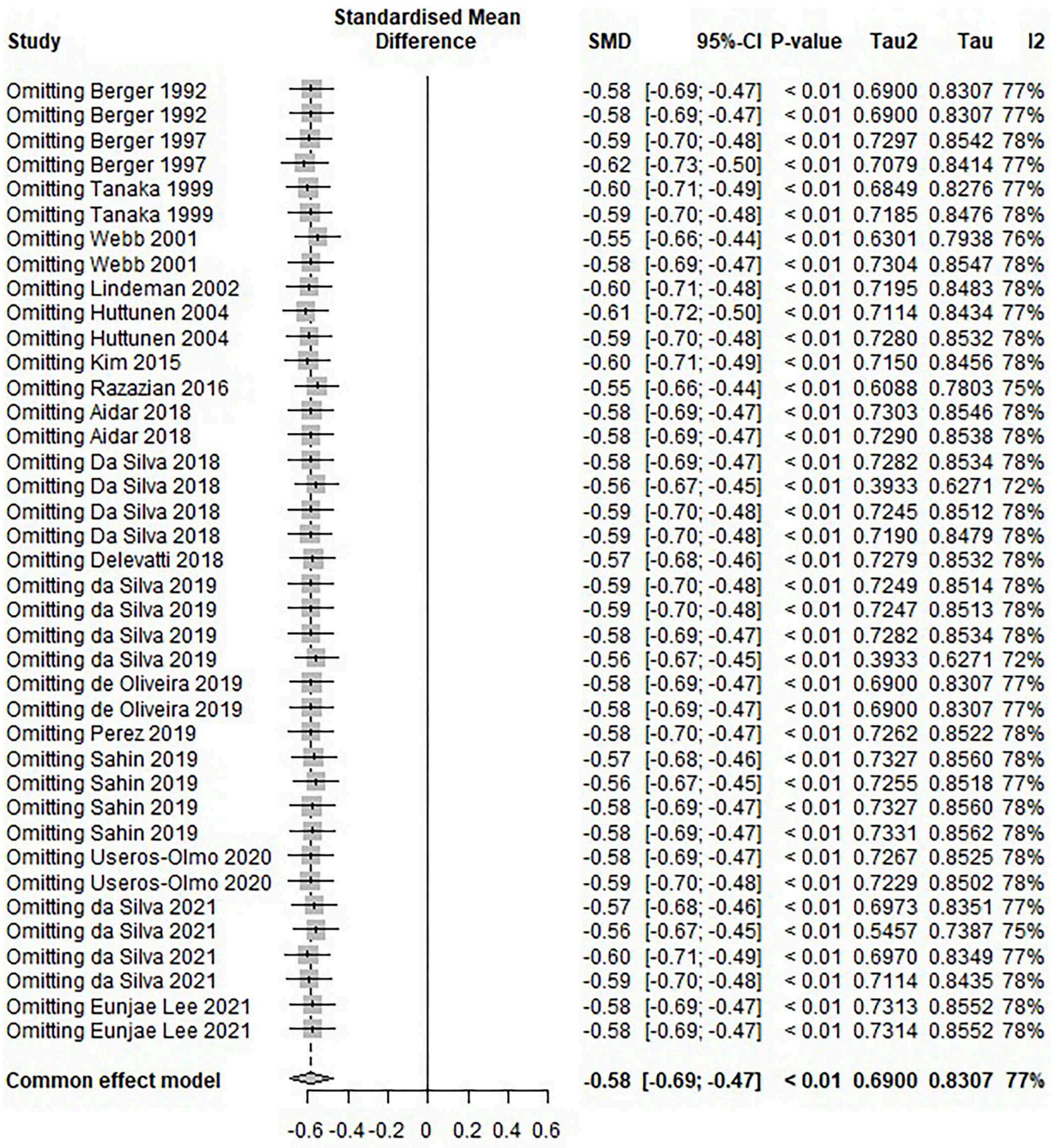


FIGURE 12
Sensitivity analysis plot. A leave-one-out meta-analysis was used to test the publication bias of a single study. No studies affecting heterogeneity were found (I^2 = 72–78%).

Conclusion

Aquatic exercise could statistically significantly improve mental health. Light aquatic aerobics may have a better effect on mood and anxiety symptoms. However, given the number and quality of included research, verifying the above conclusions requires a larger sample size of high-quality studies.

Data availability statement

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

Author contributions

ZT and YW conceived of the idea and designed the study protocol. YL conducted statistical analysis. ZT and JL drafted the manuscript. ZT, YW, JL, and YL participated in the revision of the manuscript of the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The relationship between motor development and social adaptability in autism spectrum disorder

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Objectives: Autism spectrum disorders(ASD)describe a wide range of pervasive developmental disorders by core symptoms including deficits in social communication and interaction, as well as restricted, repetitive, and stereotyped behaviors. At the same time, some children with autism are accompanied by motor development disorder. Many studies have confirmed that the motor development impairment was significantly associated with the social problems associated with ASD. Thus, this study aimed to investigate how motor development affects social adaptability in children with ASD to provide references for early ASD intervention.

Materials and methods: The case data of children's health care were selected in 2021. Motor development was assessed with the Developmental Behavior Assessment Scale for Children Aged 0–6 years. Social adaptability was measured using the Japanese S-M Social Living Skills Scale. Statistical analysis was conducted with SPSS 22.0 software package. Data were analyzed using independent samples *t*-test and logistic regression.

Results: A total of 198 cases comprising 140 boys (70.71%) and 58 girls (29.29%) were included, and the average age of participants was 3.40 ± 1.06 years, with 3.33 ± 1.18 years in the typical development (TD) children group and 3.46 ± 0.95 years in the ASD group. The social adaptability of 107 ASD children was abnormal, including 37 children (34.5%) with marginal, 48 children (44.9%) with mild, 17 children (15.9%) with moderate, and 5 children (4.7%) with severe. In 91 TD children, there were 51 children (56.04%) with normal social adaptability, 38 children (41.75%) with marginal, 2 children (2.19%) with mild, and nobody with moderate or severe. The ASD children had lower levels of developmental behavior than those of TD children, and the difference was statistically significant. The results of logistic regression showed that fine motor increased by 1 unit, and the OR value of one level decreased in social adaptability was 2.24 times (OR = $e^{0.807}$ = 2.24).

Conclusion: In children with ASD, not only motor development is delayed, but also social adaptability is affected, and fine motor skill may be important for social adaptability.

KEYWORDS

autism, motor development, gross motor, fine motor, social adaptability

Introduction

Autism spectrum disorder (ASD) comprises a group of neurodevelopmental disorders characterized by persistent deficits in social communication and interaction and the presence of restricted, repetitive behaviors (1). Its population has dramatically grown worldwide (2) with 78 million people diagnosed with ASD (3), entailing remarkably medical costs and social hardships. As a result, autism is now a major public health issue that seriously affects the health of children.

In the 1980s, the concept of cerebellar dysfunction was introduced to explain the link between movement disorders and other neurodevelopmental disorders (4, 5). In the last four decades of research, in addition to typical ASD behaviors, children with ASD show varying degrees of impairment in motor development (6–8). Compared with typically developing (TD) children, children with ASD often have difficulties with motor development (9), such as coordination disorders in gross and fine activities, poor balance, and movement posture instability (10–12). Motor is an individual's "somatic-psychological" response to the environment under the multi-level regulation of the brain. It is not only the basic means of effective interaction between the individual and the environment, but also an important window to observe and detect the physical and mental development of the individual (13). Motor development occurs throughout the course of a person's life and is closely related to the development of cognitive abilities, language, emotions, and social adaptability (10). Good motor development in early childhood will have positive effects on cognitive, language, emotional and social development, and provide favorable conditions for the overall development of individuals in the future. On the other hand, if the motor development is obstacle, the individual development will also be hindered (14–17). Motor development disorder is a non-verbal neuropsychological dysfunction that brings difficulties to the individual's daily life and causes cognitive deficits and social interaction limitations (18).

Social adaptability refers to an individual's ability to independently handle daily life and take social responsibility to the extent expected by his age and social and cultural conditions (19), including self-care, labor skills, language development, social responsibility, and so on. The social dysfunction of autistic patients leads to low social adaptability. Several studies have demonstrated that motor performance plays a significant role in cognitive and social functioning (20–23). When a child is able to crawl or walk, he or she can explore the environment more in novel ways, which contributes to their cognitive and social functioning. Motor development and social functioning are linked at the neurobiological level. Poor action ability makes children unable to participate in peer games and even weaken their social adaptability in the long run. Amygdala and prefrontal cortex (PFC) share a reciprocal connection and both play a crucial role in social behavior and motor planning (24). In autism spectrum disorders, this close relationship between motor, cognitive, and social development is also evident (25). At present, there are many studies on the social problems of autism. At the same time, many studies have found that children with autism have poor motor development. However, is there a relationship between the motor domain and social adaptability, and which type of motor skill is more closely related to social adaptability? Therefore, this study aimed to understand the characteristics of motor development and social adaptability in children with ASD, explore the relationship between motor development and social adaptability in children with ASD, in order to provide reference for early intervention of ASD.

Materials and methods

Participants

The case data of children's health care were selected in 2021. The case group was composed of 107 children who were clearly diagnosed with autism in the outpatient department. ASD diagnosis was performed according to DSM-5 clinical criteria. Meanwhile, 97 TD children were chosen from daily physical examination. Inclusion criteria: (1) diagnosed by a health care physician of our hospital; (2) complete the developmental behavior and social adaptability assessment; And (3) without training intervention. Exclusion criteria: (1) other severe psychiatric and neurological diseases, known chromosomal diseases, inherited metabolic diseases, autoimmune diseases, other major physical diseases, such as heart, liver, renal insufficiency, epilepsy, audiovisual disorders, severe traumatic brain injury. (2) incomplete data. If the same child was measured multiple times, the first test data was selected. This study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (IEC-C-008-A08-V.05.2).

Measurements

Developmental behavior was evaluated by the Developmental Behavior Assessment Scale for Children Aged 0–6 years which released by the National Health and Family Planning Commission, PRC in 2017. The scale includes 211 items on several areas. This technique was used to evaluate the children's (1) language, (2) adaptability, (3) fine motor skills, (4) social ability, (5) gross motor skills, and (6) developmental quotient (DQ). The gross motor refers to the basic movement skills related to walk, run, and jump shot. The fine motor refers to the basic motor abilities related to hand function. The developmental quotient reference range is 130 as excellent, 100–129 as good, 99–80 as moderate, and 70–79 as critically low. Scores under 70 indicate mental retardation. The *test-retest* reliability and criterion validity of the scale were 0.73–0.81 and 0.95 respectively (26).

Social adaptability was measured using the Normal Development of Social Skills from Infant to Junior High School Children(S-M). The scale includes 132 items on several areas and evaluates from two aspects: the degree of individual independence, the degree of meeting personal and social obligations and requirements. The scale was filled out by parents or daily caregivers according to the children's corresponding ages. Higher scores on this scale indicate less social adjustment, and lower scores indicate greater social adjustment. Standard score $\geq$ 10 is considered as normal, 9 as marginal, 8 as mild, 7 as moderate and under 6 as severe. The scale is the Chinese adaptation and revision of the original test: the validity and *test-retest* reliability have been validated (validity: 0.95, *test-retest* reliability: 0.98) (26).

In the actual evaluation, all of the evaluation personnel are hospital staff who underwent professional training to obtain the corresponding qualifications.

Statistical methods

Statistical analysis was conducted with SPSS 22.0 software package. Continuous data consistent with normal distribution were demonstrated by mean ± standard deviation (SD). Categorical data will be presented in terms of frequencies or percentages. An independent samples *t*-test was used to compare the developmental behavior of ASD and TD children. Logistic regression analysis was conducted to analyze the relationship between motor development of ASD children and social adaptability. $P < 0.05$ was considered statistically significant.

Results

General information of the research objects

A total of 198 cases comprising 140 boys (70.71%) and 58 girls (29.29%) were included, and the average age of participants was 3.40 ± 1.06 years, with 3.33 ± 1.18 years in the TD group and 3.46 ± 0.95 years in the ASD group. The social adaptability of 107 ASD children was abnormal, including 37 children (34.5%) with marginal, 48 children (44.9%) with mild, 17 children (15.9%) with moderate, and 5 children (4.7%) with severe. In 91 TD children, there were 51 children (56.04%) with normal social adaptability, 38 children (41.75%) with marginal, 2 children (2.19%) with mild, and nobody with moderate or severe (Table 1).

Comparison of developmental levels between children with autism spectrum disorders and typical development children

Compared with typically developing children, the ASD children had lower levels of gross motor, fine motor, language, adaptability, social ability, and developmental quotient than those of TD children, and the difference was statistically significant (Table 2).

Association between motor development and social adaptability in children with autism spectrum disorders

In logistic regression, the dependent variable(Y) was the level of social adaptability. Due to the small sample size of children with severe social adaptability (five cases), this category was excluded from the regression. The "marginal" was used as the control group in the regression analysis. The logistic regression showed that after controlling for other variables, the regression coefficient value of fine motor was 0.807, $P < 0.001$, which means that fine motor has a significant positive relationship with social adaptability (Table 3). Parallel line test $\chi^2 = 3.083$, $P = 0.687 > 0.05$, which indicated that the parallel hypothesis was valid, that is, the regression equations were parallel to each other and could be analyzed by the ordered logistic process. So, the results of logistic regression showed that fine motor increased by 1 unit, and the OR value of one level decreased in social adaptability was 2.24 times ($OR = e^{0.807} = 2.24$).

Discussion

In 1968, Kanner (27) first described the abnormal motor behaviors of infants with ASD, including clumsy gait and gross movement. Nearly 20 years, a growing number of studies confirmed that children with ASD have lesser action ability than TD children; show bulky action, fine motor and related action coordination. These abnormal behaviors can appear in the infant period (before the age of 2) (18), and obstacles in action ability development become more apparent as children with ASD grow (28). In this study, the movement scores of children with ASD were considerably lower than those of normal children. This finding is consistent with the results of Sally (29) on the motor skills of children with ASD aged 4–5 years. The development of fine motor and gross motor skills is the basis of children's physical activity and daily learning life in growth. Motor development delay in children with ASD is less severe than that caused by simple motor development

TABLE 1 General information of the research objects.

Group	Age	Sex		Social adaptability				
		Male	Female	Normal	Marginal	Mild	Moderate	Severe
	(Mean ± SD)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
TD(*n* = 91)	3.33 ± 1.18	60 (65.93)	31 (34.07)	51 (56.04)	38 (41.75)	2 (2.19)	0 (0.00)	0 (0.00)
ASD(*n* = 107)	3.47 ± 0.96	80 (74.77)	27 (25.23)	0 (0.00)	37 (34.58)	48 (44.86)	17 (15.89)	5 (4.67)

TABLE 2 Results of comparison of developmental levels between autism spectrum disorders (ASD) and typical development (TD).

Group	DQ	Gross motor	Fine motor	Adaptability	Language	Social ability
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)
TD(*n* = 91)	89.20 ± 11.20	91.30 ± 12.70	82.23 ± 14.40	95.74 ± 11.90	90.52 ± 18.10	86.00 ± 17.01
ASD(*n* = 107)	58.42 ± 13.87	72.70 ± 14.89	52.52 ± 14.75	62.45 ± 17.17	48.71 ± 18.04	53.32 ± 15.94
P-value	< 0.001**	<0.001**	< 0.001**	<0.001**	< 0.001**	<0.001**

**$P < 0.001$.

TABLE 3 Regression analysis of motor development and social adaptability in children with autism spectrum disorders (ASD).

Model		Variable	Estimate	Std.Error	Wald	df	Sig.	95% Confidence interval	
								Lower bound	Upper bound
1	Threshold	Mild social adaptability	27.782	6.55	17.992	1	0.000*	14.945	40.619
		Moderate social adaptability	39.96	9.182	18.941	1	0.000*	21.964	57.957
	Location	Gross motor	0.027	0.03	0.792	1	0.373	−0.032	0.085
		Fine motor	0.66	0.151	19.066	1	0.000∗	0.364	0.956
2	Threshold	Mild social adaptability	34.815	9.177	14.394	1	0.000*	16.829	52.801
		Moderate social adaptability	49.7	12.72	15.266	1	0.000*	24.769	74.631
	Location	Gross motor	0.09	0.065	1.935	1	0.164	−0.037	0.218
		Fine motor	0.807	0.211	14.628	1	0.000*	0.393	1.221
		Age	0.167	0.626	0.071	1	0.79	−1.059	1.393
		DQ	-0.183	0.205	0.797	1	0.372	−0.584	0.218
		Adaptability	0.12	0.087	1.933	1	0.164	−0.049	0.29
		Language	0.106	0.066	2.614	1	0.106	−0.023	0.235
		Social ability	−0.118	0.069	2.887	1	0.089	−0.254	0.018
		[Female = 0]	0.898	1.076	0.698	1	0.404	−1.21	3.007
		[Male = 1]	0[a]			0			

Link function: Logit. [a]This parameter is set to zero because it is redundant. *$P < 0.05$.

or common diseases. Moreover, the gross and fine motor skills of children with ASD may show temporary delay, and the children can eventually acquire the corresponding skills. Therefore, improvement in motor skills is also important in the intervention treatment of children with ASD.

Motor development defects are common in children with ASD and may further hinder the social adaptability of these children (29). The early motor development of children can be regarded as the early explicit intelligence of individuals, and the physical and mental development of individuals is mainly through the adaptation of motor to the environment (30). Because of motor development disorders, autistic children are less likely to participate in group activities, which limits their contact with peers and further affects the development of their social adaptability (31). Sipes (32) found a positive correlation between motor ability and social adaptation in children with ASD. This finding is consistent with the findings of the present study that children with low score on motor ability had similarly low scores on social adaptability, and vice versa. As far as current neuroscience is concerned, the cerebellum is believed to play important roles in controlling skilled movements and interacting with others in social environments (33). During exercise, in addition to the information from proprioceptors and visual and auditory organs transmitted to the cerebellum, the happy atmosphere of peer communication and group activities also stimulated the cerebellum and promoted the function of the cerebellum (34), which in turn led to the joint development of children's motor ability and social adaptability. Mac Donald (35) found that children's early activities and communication are supported by actions. Poor action ability makes children unable to participate in peer games and even weaken their social adaptability in the long run. Therefore, the improvement of children's motor skills should also be the focus of early ASD intervention in addition to the improvement of children's social adaptability.

In this study, as compared to gross motor skills, fine motor skills were found to be more strongly related to some social adaptability, which supports previous studies t in typically developing children (24, 36). As compared to gross motor skills, fine motor skills were found to be more strongly related to some social skills, which involve smaller muscles such as the hands and fingers, and are involved in activities like eating with utensils, finger-painting, cutting with scissors, and writing. Our motor skills play an important role in developing our cognition and social functioning, according to the theory of embodied cognition (37). Hellendoorn (38) found that fine motor functioning in children with ASD was related to visuospatial cognition, object exploration, and social orientation, as well as to language development, and fine motor functioning aids preschool students in interacting with both the physical and social environment and improves visuospatial cognition, which in turn increases language development. Fine motor skills are also important because they are highly correlated with social skills, and hand motor skills directly affect living ability. Difficulty fine motor skill affects the ability to take care of themselves, such as eating and dressing. In addition, children with low fine motor skills may not be able to participate in many social activities due to their inability to carry out motor functions necessary for play, which can lead to social estrangement (39). Furthermore, also found in the study of fine motor development in infants and children with ASD that fine motor is related to language development and that a worse fine motor development corresponds to a worse language development (40, 41). Evidence suggests that motor and social skills are interconnected at the neurophysiological level (24, 42). Early fine motor skills development and brain cognitive development overlap in time and space. Cognitive and motor skills are acquired in a basically similar way, and they are highly similar in the learning rate, learning effect, and learning stage. The smooth and effective development of early fine motor skills may be conducive to the maturation of early brain structure and function, and then promote the development of the cognitive system. The association between motor and social development in children with ASD may be explained by these transactions between brain structures. There may be consequences for multiple skill sets if there is dysfunction in one area of the brain (43). Furthermore, strengthening one or more of these skills early on might have positive effects elsewhere (44).

At present, the focus of intervention for children with autism is mainly on language and social interaction. And all interventions are aimed at improving the functional communication skills of children with ASD, such as opportunity learning, critical response training, TEACCH program and SCERTS mode (45). However, early motor skill intervention is often neglected. In fact, for any child, gross motor skill is more favorable for their own body control, and fine motor skill will be of great help to improve children's cognition and social skills. Infants' motor and cognitive development cannot be completely separated, especially the hand-eye coordination ability, which is an important indicator of cognitive development (46). The influence of fine motor is not only limited to social adaptation ability, but also has a great impact on learning ability and memory ability. As a special group, autistic children have their own characteristics in social adaptability and self-care. Strengthening the hand-eye coordination ability of autistic children through hand function training may play a certain role in improving the self-care ability of autistic children. Therefore, an early assessment and intervention of fine motor skills may be useful in improving the multiple abilities of children with ASD.

Conclusion

This study found that in children with ASD, not only motor development is delayed, but also social adaptability is affected, and fine motor skill may be important for social adaptability. Motor problems can pose an additional burden on a child, affecting child's quality of life and ability to interact socially.

Thus, in future research, we can further clarify the possible role of fine motor development in improving social adaptability may help identify motor skills for early intervention, which may reduce the burden of ASD and may also help to provide optimal rehabilitation programs for these children and help them reach their full potential.

Data availability statement

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

Author contributions

YC, XF, HW, and AL conceived the study. YC and TW analyzed the data. XF wrote the manuscript. HL revised and refined the manuscript. NX, RS, and YW contributed to the collection of data. YC and XF was responsible for the integrity of the work as a whole. All authors critically reviewed various drafts of the manuscript and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect of different types of physical activity on cognitive reaction time in older adults in China

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Introduction: Aging is not only reflected in the degeneration of physiological functions but is also embodied in the decline of psychological and cognitive functions. The decline of cognitive function can reduce the quality of life in older adults, and even potentially cause Alzheimer's disease, which may lead to a heavy burden on patients, families, and society. The purpose of this study was to investigate the effects of physical activity (PA) on cognitive reaction time in older adults.

Methods: A cross-sectional survey design was used in this study. A total of 839 elderly subjects were recruited from Beijing and Shanghai. In total, 792 subjects met the inclusion criteria (age $>$ 60 years, without disability, speech, and hearing impairment), including 384 men (age:67.7 $\pm$ 5.7 years) and 408 women (age: 68.2 $\pm$ 5.8 years). The PA was assessed by the Physical Activity Scale for the Elderly (PASE). All kinds of PA were divided into three levels: "Low" ($<$ 50% average score), "Moderate" (50–150% average score), and "High" ($>$150% average score). The reaction time of subjects was measured by the selective reaction tester (Model: CSTF-XF, TFHT, Beijing, China).

Results: For leisure-time PA, the results showed that the cognitive reaction time of older adults in the "Low" group (1.11 $\pm$ 0.32 s) was significantly longer than that in the "Moderate" group (1.05 $\pm$ 0.30 s, $p < 0.01$) and the "High" group (0.99 $\pm$ 0.28 s, $p < 0.01$). For housework PA, there was no significant difference in the cognitive reaction time among the three groups ("Low": 1.09 $\pm$ 0.31 s; "Moderate": 1.07 $\pm$ 0.31 s; "High": 1.05 $\pm$ 0.28 s, $p > 0.05$). For work-related PA, the results showed that the cognitive reaction time of older adults in the "Low" group (1.09 $\pm$ 0.30 s) was significantly longer than that in the "High" group (0.99 $\pm$ 0.28 s) and the "Moderate" group (1.03 $\pm$ 0.32 s, $p < 0.01$).

Conclusion: The PA has a positive effect on reducing cognitive reaction time in older adults. It is recommended that older adults maintain a moderate level of leisure PA and work-related PA to delay the decline in cognitive reaction time.

KEYWORDS

reaction time, cognitive function, physical activity, old adults, aging

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Introduction

Population aging is a major issue facing human society in the twentifirst century, and it is also one of the more serious social problems in China. The WHO states that by 2025, there will be 1.2 billion people over the age of 60, 75% of whom will be in developing countries (1). The latest survey shows that the proportion of China's population aged 60 years and above has reached 18.70%, with the proportion of people aged 65 years and above reaching 13.50%, which is close to the standard share of a deeply aging society (14%) (2). Faced with the reality that China's elderly population is large, and the aging process is significantly accelerating, it is especially important to maintain the physical and mental health of the elderly.

Cognitive function in older adults is one of the key indicators of physical and mental health and is closely related to their quality of life. On the one hand, with aging, the elderly experience varying degrees of decline in organismal function and a consequent increase in health problems, leading to a decline in physiological and immune function (3). On the other hand, during the aging process, nerve cells in the elderly gradually atrophy or even apoptosis, leading to a decrease in neurophysiological reserve and causing a decline in cognitive function in the elderly. Neuroscience studies have shown that dopamine is an important neurotransmitter in the hippocampus that regulates the excitability of the cerebral cortex, but as we age, the concentration of dopamine decreases, impairing cognitive function in humans (4), and those who are severe enough develop diseases, such as Alzheimer's disease. In addition, cognitive decline is more strongly correlated with poor health outcomes, such as basic activities of daily living impairment (5), low quality of life (6), and death (7). Therefore, it is important to improve the level of cognitive function in older adults to maintain their health and quality of life.

Physical activity (PA) is a human activity that is highly directional, subjective, and consciously produced by skeletal muscle contraction. Since the 1970s, research on the benefits of PA for cognitive function in older adults has received increasing attention. PA has become the focus of research to slow cognitive decline, improve executive function, promote neural growth in the brain, and reduce the risk of dementia in older adults. Previous studies have found that older adults who regularly participate in a variety of physical activities have a 30–46% lower risk of cognitive decline and a 28–45% lower likelihood of developing Alzheimer's disease compared to those who are sedentary and less active (8). An organized, individualized, high-intensity, long-term, and multi-element exercise program maintains cognitive performance in older adults (9). Studies have also found negative effects of reduced PA levels on cognitive function. Rogers et al. (10) did a follow-up analysis of changes in PA levels and cognitive function in 90 older adults over 4 years and found that those subjects with reduced PA levels had reduced cerebral blood flow and reduced cognitive function.

Maintaining PA as an important means of preventing and controlling various chronic diseases provides new directions for improving cognitive function in older adults. PA can improve a variety of cognitive functions in older adults by increasing cardiorespiratory fitness (11), such as cognitive processing speed (12), memory (13, 14), executive function (12, 15), and basic perceptual function (16). However, the overall concept of PA is broad and includes a variety of activities of different natures, such as leisure PA, housework, and work-related PA (17). The effect of different categories of PA on cognitive improvement may not be the same. Most of the current studies are limited to the effects of total PA or leisure PA on cognitive function(10, 18–21). The effects of housework and work-related PA on cognitive function are rarely studied (22). Therefore, this study aims to investigate the effects of different types of PA on cognitive function in older adults to provide a reference for achieving active aging.

Methods

Subjects

A cross-sectional health survey design was used in this study. A total of 839 subjects were recruited from the community in the Beijing and Shanghai areas. Inclusion criteria are as follows: age > 60 years, clear consciousness, basic reading and writing ability, and no significant speech or hearing impairment. All tests were completed in 1 day, and subjects were asked to fill out a questionnaire about their illness and physical condition to ensure they met the inclusion criteria for this study. The final number of elderly subjects included in the study was 792, of whom 384 were men (age: 67.7 ± 5.7 years) and 408 were women (age: 68.2 ± 5.8 years).

All subjects were informed of the detailed procedures and signed the informed consent documents before participating in the study. Additionally, subjects were clearly informed that they could withdraw from the study at any time for any reason, and all information would be kept anonymous and confidential. The study was approved by the Medical Ethics Committee of Tsinghua University.

PA assessment

Physical activity was measured by the internationally classic Physical Activity Scale for the Elderly (PASE). The PASE questionnaire was developed by Washburn at Illinois at Urbana-Champaign University in 1993 (17), which consists of leisure PA, housework, and work-related PA. Leisure PA includes walking, light sport and recreational activities (such as Tai Chi, yoga, golf, and fishing), moderate sport and recreational activities (such as doubles tennis, table tennis, and dancing), strenuous sport and recreational activities (such as jogging, swimming, and cycling), and muscle strength exercise, and each PA is assessed on a 4-point scale of "days of activity per week" (never, 1–2, 3–4, and 5–7 days) and "time of activity per day" (<1, 1–2, 2–4 h, and more than 4 h). Housework includes cleaning, gardening, repairing electrical appliances, and taking care of others. Work-related PA mainly includes paid work and volunteer work. The items of housework activity and work-related PA were presented by asking the subjects whether they had performed any activity in the past week, and the subjects answered "yes/no."

The PASE involves 13 questions with a total score of 0–360. The final score was calculated by adding the weighted scores of the 12 items (the first item "sedentary activity" was excluded), with higher scores indicating greater PA. The PASE is widely used in many countries, and it has good reliability and acceptable levels of validity (reliability: 0.897 and validity: 0.442) among the elderly in China (23). The questionnaire-based survey process had strict quality control.

Reaction time assessment

The reaction time can reflect the information processing speed and evaluate the cognitive function (24). The reaction times of subjects were measured by the selective reaction tester (Model: CSTF-XF, TFHT, Beijing, China). During the test, the subject pressed the red "start" button with the middle finger of the dominant hand and waited for the signal to be issued, and then pressed the signal key as fast as possible. After the signal disappeared, the subject pressed and held the "start" button again with the middle finger and waited for the next signal to be given, a total of 5 times. After the subject had answered the signal five times, all the signal keys would emit "light" and "sound" signals at the same time, indicating the end of the test. The instrument automatically recorded the average reaction time of five times, and the record was in seconds, retaining two decimal places. All subjects should be clear about the test process before the test and the best scores were chosen between the two tests.

Statistical analysis

According to the average score of each part of the PASE, all kinds of PA were divided into three levels: "Low" (< 50% average score), "Moderate" (50–150% average score), and "High" (>150% average score). Results were expressed as mean ± SD for continuous variables or frequencies (percentages) for categorical variables. An independent-samples Test was used for comparison between the two groups. PASE scores did not conform to a normal distribution, and the Mann–Whitney *U*-test was used for comparison between groups. The one-way ANOVA and Tukey's *post hoc* tests were conducted to compare the difference in cognitive reaction time among older adults with different PA levels of a certain PA type and to identify the optimal PA level in the specific PA type for improving cognitive reaction time. The level of significance was set at $p < 0.05$. In this study, we also indicated the significance level at $p < 0.01$. The statistical analyses were implemented by using SPSS 26.0.

Results

Demographic analysis

The descriptive characteristics and PA levels of the 792 subjects are shown in Table 1. More than half of the older adults had insufficient levels of leisure PA, 70% had low levels of work-related PA, and most of the older adults had moderate to high levels of housework.

Intergroup comparison of PASE scores and cognitive reaction time in older adults

Table 2 shows the differences between the PASE scores and reaction time of older adults in different age groups. There was a significant difference in the scores of leisure PA between the younger and the older elderly ($p < 0.01$), and there was no significant difference in the scores of housework and work-related PA. In addition, there was no significant difference in cognitive reaction time between the younger and the older elderly (60–74 years: 1.07 ± 0.30 s, ≥75 years: 1.08 ± 0.32 s).

The results of the comparison of PASE scores and reaction time of older adults by gender are shown in Table 3. There was a significant difference in the scores of housework between men and women ($p < 0.01$), while the scores of leisure PA and work-related PA did not have a significant difference. Additionally, there was no statistically significant difference in cognitive reaction time between male and female older adults (male: 1.06 ± 0.29 s and female: 1.09 ± 0.32 s).

The difference in cognitive reaction time in older adults with different types of PA

The cognitive reaction times of elderly subjects with different levels of leisure PA, housework, and work-related PA are shown in Table 4. Using multi-level one-way ANOVA analysis, we could find that there was a significant difference in the reaction time of the elderly with different leisure PA levels, and there was also a significant difference in the reaction time of the elderly with different work-related PA levels. Additionally, after Turkey's

TABLE 1 Descriptive characteristics and physical activity ($n = 792$).

Characteristic	Participants	Leisure PA Level			Housework PA Level			Occupational PA Level		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Participants	792	436 (55.1)	220 (27.8)	136 (17.2)	193 (24.4)	449 (56.7)	150 (18.9)	565 (71.3)	135 (17.0)	92 (11.6)
Gender										
male	384	216 (56.3)	107 (27.9)	61 (15.9)	80 (20.8)	206 (53.6)	98 (25.5)	271 (70.6)	72 (18.8)	41 (10.7)
female	408	220 (53.9)	113 (27.7)	75 (18.4)	113 (27.7)	243 (59.6)	52 (12.7)	294 (72.1)	63 (15.4)	51 (12.5)
Age (years)										
60∼74	692	406 (58.7)	186 (26.9)	100 (14.5)	167 (24.1)	393 (56.8)	132 (19.1)	486 (70.2)	121 (17.5)	85 (12.3)
≥75	100	30 (30.0)	34 (34.0)	36 (36.0)	26 (26.0)	56 (56.0)	18 (18.0)	79 (79.0)	14 (14.0)	7 (7.0)
Education level										
Primary school or below	57	40 (70.2)	11 (19.3)	6 (10.5)	17 (29.8)	32 (56.2)	8 (14.0)	44 (77.2)	7 (12.3)	6 (10.5)
Junior high school	365	220 (60.3)	102 (27.9)	43 (11.8)	86 (23.6)	220 (60.3)	59 (16.2)	258 (70.7)	64 (17.5)	43 (11.8)
Senior high school	208	120 (57.7)	57 (27.4)	31 (14.9)	56 (26.9)	110 (52.9)	42 (20.2)	148 (71.2)	37 (17.8)	23 (11.1)
Vocational colleges	76	30 (39.5)	21 (27.6)	25 (32.9)	16 (21.1)	39 (51.3)	21 (27.6)	50 (65.8)	17 (22.4)	9 (11.8)
University	86	26 (30.2)	29 (33.7)	31 (36.0)	18 (20.9)	48 (55.8)	20 (23.3)	65 (75.6)	10 (11.6)	11 (12.8)
Occupation										
Mental worker	238	98 (41.2)	75 (31.5)	65 (27.3)	59 (24.8)	125 (52.5)	54 (22.7)	171 (71.8)	37 (15.5)	30 (12.6)
Light worker	430	266 (61.9)	112 (26.0)	52 (12.1)	105 (24.4)	259 (60.2)	66 (15.3)	307 (71.4)	78 (18.1)	45 (10.5)
Heavy worker	106	60 (56.6)	30 (28.3)	16 (15.1)	23 (21.7)	57 (53.8)	26 (24.5)	71 (67.0)	19 (17.9)	16 (15.1)
Others	18	12 (66.7)	3 (16.7)	3 (16.7)	6 (33.3)	8 (44.4)	4 (22.2)	16 (88.9)	1 (5.6)	1 (5.6)
Smoking										
Never	568	305 (53.7)	160 (28.2)	103 (18.1)	153 (26.9)	329 (57.9)	86 (15.1)	407 (71.7)	97 (17.1)	64 (11.3)
Yes	224	131 (58.5)	60 (26.8)	33 (14.7)	40 (17.8)	120 (53.6)	64 (28.6)	158 (70.5)	38 (17.0)	28 (12.5)
Drinking										
Never	619	338 (54.6)	169 (27.3)	112 (18.1)	160 (25.8)	360 (58.2)	99 (16.0)	454 (73.3)	92 (14.9)	73 (11.8)
Yes	173	98 (56.6)	51 (29.5)	24 (13.9)	33 (19.1)	89 (51.4)	51 (29.5)	111 (64.2)	43 (24.8)	19 (11.0)

PA, physical activity.

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TABLE 2 Comparison of PASE score and reaction time in participants of different ages.

	60∼74 years ($n = 692$)	≥75 years ($n = 100$)	Z	T	*P*-value
Leisure PA Score	8.57 (0.00,171.00)	25.71 (0.00,91.57)	5.63		0
Housework PA Score	45.00 (0.00,141.00)	45.00 (0.00,101.00)	−0.27		0.79
Work-related PA Score	0.00 (0.00,120.00)	0.00 (0.00,30.00)	−1.91		0.06
Reaction Time (s)	1.07 ± 0.30	1.08 ± 0.32		−0.59	0.95

PA, physical activity.

TABLE 3 Comparison of PASE score and reaction time in participants of different genders.

	Male ($n = 384$)	Female ($n = 408$)	Z	T	*P*-value
Leisure PA Score	8.57 (0.00,171.00)	8.57 (0.00,171.00)	−0.19		0.85
Housework PA Score	50.00 (0.00,141.00)	35.00 (0.00,121.00)	−2.84		0
Work-related PA Score	0.00 (0.00,21.00)	0.00 (0.00,120.00)	−0.11		0.91
Reaction Time (s)	1.06 ± 0.29	1.09 ± 0.32		−1.27	0.2

PA, physical activity.

post hoc analysis, we could distinguish the specific significant differences between these groups.

For leisure PA, the results showed that the cognitive reaction time of older adults in the "Low" level leisure PA group (1.11 ± 0.32 s) was significantly longer than that in the "Moderate" (1.05 ± 0.30 s, $p < 0.01$) and the "High" level leisure PA groups (0.99 ± 0.28 s, $p < 0.01$). There was no significant difference between the "Moderate" and the "High" level leisure PA groups.

For housework PA, although the average cognitive reaction time of the elderly with a "Moderate" level (1.07 ± 0.31 s) and "High" level (1.05 ± 0.28 s) was less than that of the "Low" level (1.09 ± 0.31 s), there was no significant difference among the three groups after using the *post hoc* analysis.

For work-related PA, the results showed that the cognitive reaction time of old adults in the "Low" work-related group (1.09 ± 0.30 s) was significantly longer than that in the "High" (0.99 ± 0.28 s) and the "Moderate" work-related PA groups (1.03 ± 0.32 s, $p < 0.01$). There was no significant difference between the "Moderate" and the "High" level work-related PA groups.

Discussion

The study categorized PA and explored the effect of the level of each type of PA on cognitive reaction time in older adults providing an important reference for PA to delay cognitive decline in older adults. Not only leisure PA but also active participation in work-related PA can shorten the reaction time of older adults. Moreover, there is no significant difference in the effect of moderate and high levels of PA on the improvement of cognitive reaction time in older adults. To avoid the negative effects of higher levels of PA, older adults are encouraged to maintain a moderate level of leisure PA and work-related PA daily as much as possible according to their abilities.

The descriptive statistics of the demographic and PA of the subjects in this study suggested that older adults are not physically active enough in their leisure time, and more than 50% of them are at a low level of leisure PA. This indicates that most older adults are less physically active and still spend most of their time in a sedentary and less active state, which is also consistent with other studies. Only half of older Australians are physically active enough (25), and only 20% of older Americans are even more physically active (26), while in South Korea, a neighboring country to China, 80% of 60- to 70-year-olds and 90% of those aged 70 years and older do not engage in moderate to high PA (27). This study showed that 55% of Chinese older adults do not engage in moderate to high levels of leisure PA, a lower percentage than in developed countries, but this percentage is likely to increase further as the economy develops, so we need to pay more attention to the phenomenon of insufficient PA among older adults. At the same time, work-related PA accounts for a relatively small proportion of PA among older adults, with more than 70% of older adults having no or little involvement in work-related PA, which is in line with the current reality in China. Older adults have retired after the age of 60 years, and few continue to work, more often taking on household tasks, such as childcare, cleaning, grocery shopping, and cooking. Additionally, this study shows that most older adults have a high level of housework, with only 24% doing little housework in general.

The level of PA in older adults decreases with age (28). However, the present study showed that the level of leisure PA increased in the older elderly compared to the younger elderly, and the older elderly did not reduce leisure PA due to

TABLE 4 The reaction time of participants with different levels of physical activity.

		Reaction Time (s)	*P*-value	*F*
Leisure PA Level	Low	1.11 ± 0.32	0.00	8.1
	Moderate	1.05 ± 0.30*		
	High	0.99 ± 0.28*		
Housework PA Level	Low	1.09 ± 0.31	0.11	0.65
	Moderate	1.07 ± 0.31		
	High	1.05 ± 0.28		
Work-related PA Level	Low	1.09 ± 0.30	0.00	6.48
	Moderate	1.03 ± 0.32#		
	High	0.99 ± 0.28#		

PA, physical activity; *Compared with "Low" Leisure PA Level, significant difference on reaction time ($p < 0.01$); #Compared with "Low" Work-related PA Level, significant difference on reaction time ($P < 0.01$).

declining physical function. This may be related to the higher education level of the older elderly subjects in this study, who generally attach more importance to physical health and actively participate in various types of physical activities on a daily basis. The reaction times of older adults in this study also did not increase with age, which is different from previous studies that considered age as a risk factor for cognitive function (29), presumably also due to the higher level of education in the older age group, which is a protective factor for cognitive function (30), offsetting the negative effect of age. In addition, there was no significant difference in the cognitive reaction time between men and women in this study, indicating that gender did not affect cognitive function in older adults. However, the level of housework was higher in men than in women, probably because the PASE used in this study only answered "yes/no" participation in housework, while items with higher weight, such as carrying things, cleaning the yard, and repairing, were often performed by men.

The positive effect of leisure PA on cognitive function in older adults was also verified in this study. Spirduso conducted pioneering research on the relationship between PA and cognitive function in older adults. The difference in the cognitive processing speed between the subjects was determined by comparing the reaction time and it was found that older adults with exercise routines had faster reaction times than the average older adults (24). Several subsequent studies have also found that older adults who are physically active have better cognitive performance than those who are sedentary and less active (10, 20, 21). Older adults in this study who usually maintained moderate-to-high levels of leisure PA also had significantly faster reaction speeds than those with low levels of leisure PA. Frequent participation in leisure PA can exercise balance and physical function, reshape the brain, and strengthen synaptic connections in neural networks, thereby delaying the decline of cognitive function in older adults.

This study did not find any improvement in cognitive function in older adults from housework, but a study has found that gardening can improve memory, logical thinking, and communication skills in older adults (31). This study did not separately analyze the effect of flower gardening and watering on the reaction time of older adults. Moreover, in the Chinese revised version of the PASE used in the study, some of the entries are still not suitable for Chinese older adults, such as cleaning the yard (most older adults live in buildings and do not have a yard), which may cause a decrease in the validity of the assessment of housework.

In the PASE, the work-related PA of older adults was mainly participation in jobs that required sitting, standing, walking, or running. The main work-related PA of older adults was participation in street and community volunteer activities, such as patrols. This study found that moderate to high levels of work-related PA can be good for improving cognitive function in older adults. Work-related physical activities involve not only physical activities but also cognitive and social activities. Cognitive (32, 33) and social activities (22) can also benefit cognitive function in older adults. Some studies have also shown that participation in volunteer activities contributes to the development of cognitive reserve in older adults and can slow down the rate of cognitive aging (22). Participation of older adults in volunteer work, in which walking or standing PA improves cardiorespiratory fitness, improves cerebrovascular function, and prevents neuropathological changes (33). In addition, the need of the elderly to communicate with others contributes to the maintenance of their verbal and memory skills.

These findings suggest that older adults should be encouraged to participate in voluntary activities organized by the street or community after retirement, which can reflect their self-worth and slow down cognitive decline. If the elderly are usually burdened with household chores, they can choose to temporarily put aside their chores, such as child care, grocery shopping, and cooking on weekends, to participate in some volunteer activities of interest and get out of the house to communicate more with the outside world. Instead of letting simple and repetitive chores take up most of the time and energy of the elderly, they should make full use of their leisure time for physical exercise, reduce the time spent on watching television (TV), reading newspapers, and other sedentary activities, and do active physical activities in the morning or after dinner every day.

This is a cross-sectional study, and it is difficult to clarify the causal relationship between PA and cognitive reaction time, which has certain limitations. In addition, measuring PA by questionnaires is not precise enough, although it is suitable for large-scale population surveys. In addition, cognitive reaction time is a common index to assess cognitive function, but its assessment of cognitive function is not comprehensive enough.

In future studies, we hope to conduct longitudinal surveys to clarify the effects of PA on cognitive reaction time in older adults through dynamic and long-term observations. The recommended amount of PA to delay cognitive decline in older adults can also be given through more accurate PA measurements. In addition, cognitive function in older adults is a multidimensional indicator, and the effects of PA on cognitive function in older adults should be explored in terms of attention, memory, and responsiveness.

Conclusion

Leisure PA and work-related PA have positive implications for improving cognitive reaction time in older adults. Cognitive reaction times were significantly shorter in older adults who maintained moderate and high levels of leisure PA and work-related PA. The effect of high levels of leisure PA and work-related PA on improving cognitive reaction time in older adults was not significantly different from that of moderate levels. To avoid other negative effects of high levels of PA, moderate levels of leisure PA and work-related PA are recommended for older adults to slow down the decline of cognitive function.

Data availability statement

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

Ethics statement

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

Author contributions

JL: conceptualization, resources, and supervision. YL and XH: methodology and writing—original draft preparation. YL: formal analysis and visualization. ZT and HZ: investigation. YL and JL: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1051308/full#supplementary-material

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Effect of resistance training on heart rate variability of anxious female college students

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Introduction: Female college students are a group with high incidence of anxiety, and anxiety will lead to the disorder of autonomic nervous system (ANS), which will adversely affect their study and life. Resistance training plays a positive role in improving anxiety, but there is little evidence on whether resistance training can improve ANS of anxious female college students. Heart rate variability (HRV) has gained widespread acceptance in assessing ANS modulation. Therefore, the objective of this study aimed to investigate the effects of resistance training on heart rate variability (HRV) in anxious female college student.

Methods: A randomized controlled study of resistance training intervention was conducted in 27 anxious female college students that assigned randomly into an intervention group ($n = 14$) and a control group ($n = 13$). The intervention group was intervened by cluster training for 8 weeks. Self-rating anxiety scale (SAS) was used. ANS is evaluated by short-term HRV. Muscle strength was assessed by 1 RM indirect method. Independent-sample *t*-test was used to test post-test–pre-test scores between the intervention and control groups.

Results: After the intervention, SAS score of the intervention group was significantly decreased ($P < 0.05$), SDNN of the intervention group was significantly increased ($P < 0.05$) and LF/HF was significantly decreased ($P < 0.05$).

Conclusion: The resistance training intervention adopted in this study significantly increased the HRV of anxious female college students and improved their autonomic nervous disorder.

KEYWORDS

resistance training, anxious female college students, heart rate variability, autonomic nervous function, randomized controlled trial

Introduction

With the continuous development of society and increasingly fierce social competition, college students are facing great pressure of study and life, and have become a high-risk group of anxiety. The incidence of anxiety among college students is as high as 54.4%, which is one of the common psychological problems faced by college students (1). Evidence-based research proves that female college students are more likely to be anxious (2, 3). However, anxiety is not a simple psychological problem, especially it will lead to the disorder of autonomic nervous system (ANS) that generally involves failure of sympathetic and parasympathetic nervous system. Heart rate variability (HRV) has gained widespread acceptance in assessing ANS modulation. Adolescent females with anxiety show a decrease HRV compared with healthy controls (4–6). Prospective studies have found that HRV reduction is an independent risk factor for cardiovascular disease risk and increased all-cause mortality (7). Moreover, the decrease of HRV is also an independent risk factor for metabolic diseases such as diabetes (8). Therefore, if the autonomic nervous dysfunction of anxious female college students is not corrected and intervened. Then, it will not only bring adverse effects to the current study and life, but also increase the risk of cardiovascular disease.

Medicine and cognitive behavioral therapy are effective methods to improve anxiety, but medicine usually has obvious side effects and is easy to cause excessive mental dependence (9). Cognitive intervention usually needs trained experts to complete (10). In contrast, exercise, as a safe and low-cost intervention method, can also improve anxiety (11), and at the same time, it can bring more health benefits, such as the improvement of cardiopulmonary endurance and muscle strength, etc. Evidence-based studies have shown that both aerobic exercise and resistance training can effectively improve HRV (12, 13). Compared with aerobic exercise, resistance training is more flexible and less dependent on training places. Resistance training intervention should be more acceptable to improve ANS. Interestingly, recent studies found that resistance training leads to improvement in cardiac autonomic control of patients with chronic metabolic diseases rather than healthy individuals (13). However, there is still a lack of evidence that resistance training intervention can improve ANS of anxious individuals. Therefore, the purpose of this study was to explore the influence of resistance training on the HRV of anxious female college students.

Materials and methods

Subjects

A total of 27 anxious female college students (18–25 years old) from non-training majors in Beijing Sport University were enrolled in the randomized controlled trial (Table 1). The included criteria were: (1) SAS score ≥ 50, (2) no cardiovascular diseases and other contraindications to exercise, (3) no exercise habits. The experiment was approved by the Ethics Committee of Beijing Sport University and followed the principles of the last revised Declaration of Helsinki (7^{th} revision of October 2013). All participants volunteered to participate in the experiment. Before the experiment started, they fully understood the content and process of the experiment and signed the informed consent form.

TABLE 1 Baseline characteristics of participants in intervention and control groups.

Characteristic	Intervention	Control
n	13	14
Age (years)	22.6 ± 2.5	22.5 ± 2.0
Height (cm)	163.5 ± 4.6	164.8 ± 3.6
Weight (kg)	58.3 ± 8.0	56.3 ± 5.9
BMI (kg/m^2)	21.8 ± 2.7	20.7 ± 2.0
SAS	58.2 ± 6.2	54.7 ± 6.5

BMI, body mass index; SAS, Zung's self-rating anxiety scale.

Study design

In this randomized controlled trial, the sample size was estimated based on the measurement data of HRV indices in previous study (14, 15). When Type I error was 5% ($\alpha = 0.05$), Type II error was 80% ($\beta = 0.20$), respectively, to detect a 25% mean difference at end of intervention. The sample size required was calculated according to the formula $n1 = n2 = 2(Z_{\alpha/2} + Z_{\beta})^2\delta^2/\sigma^2$. Therefore, the intervention group and the control group had about 13 subjects, respectively.

We conducted an 8-week randomized controlled trial. After completing the baseline measurements, the participants were randomly divided into intervention group ($N = 13$) and control group ($n = 14$) using a computer-generated simple randomization software. All participants were instructed to maintain their usual lifestyle habits and not to be engaged in other structured exercise interventions.

Training intervention

The intervention group was intervened by cluster training for 8 weeks. Cluster training is a special resistance training method, which is different from the traditional resistance training in the intermittent arrangement between work and rest. Under the same amount and intensity of training, the degree of autonomic nervous fatigue caused by cluster training is lower (16). The intermittent arrangement adopted in this experiment is to rest for 90 s between groups and rest for 30 s within groups. The training frequency is about twice a week, and the interval between two trainings is about 72 h. Each training session consists of three movements, including barbell bench press (pectoralis major), Lat pull-down machine; (latissimus dorsi) and leg lift machine (quadriceps femoris), with five groups of exercises for each movement. Training intensity is 70% 1 RM. Each training session starts with a 5-min warm-up exercise (low-intensity aerobic exercise), about 40 min of resistance training, and relaxation training for 5 min.

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Measurements

In the intervention, HRV indicator was the primary outcome. Muscle strength and anxiety level were the secondary outcomes.

HRV indicator evaluation

Subjects came to our laboratory, avoiding any physical activity since they woke up, between 7.00 and 9.00 a.m. following study pre-conditions: (1) fasting conditions; (2) not altered sleep pattern the night before; (3) to be abstained from alcohol intake and drugs or stimulant consumption, including coffee and other stimulants 24 h before; and (4) to avoid moderate-intensity physical activity within 24 h and vigorous-intensity physical activity within 48 h before the test. After the subjects arrived at the test site, they sat comfortable chair and rested for 5 min, then wore the heart rate meter in their left hand and the heart rate belt to the xiphoid process of sternum, and collected the R-R interval signals for 10 min in a quiet environment at thermo-neutral conditions (22–24°C and 40–60% relative humidity). The Polar heart rate (V800, Finland) was used to collect the R-R interval signals. Kubios HRV Standard 3.4 software (University of Eastern Finland, Kuopio, Finland) was used to calculate the HRV time domain and frequency domain indicators. Time domain indexes include SDNN (standard deviation of all RR intervals, ms) and RMSSD (square root of the sum of the mean of the difference between adjacent RR intervals, ms). Frequency domain indicators include low frequency power (LF, 0.04–0.15 Hz; sympathetic activity index) and high frequency power (HF, 0.15–0.40 Hz; vagus nerve activity level index) and LF/HF ratio (sympatheticvagus nerve balance index). The corrections to be made on the RR series are displayed on the RR interval axis. When the corrections are applied, detected artifact beats are replaced using cubic spline interpolation (17). HRV analyses were conducted by the same trained researcher to obtain reproducible and valid data.

One repetition maximum prediction

The 1 RM indirect test was used to evaluate the muscle strength of the subjects. Before the test starts, the subjects completed 8–12 lifts with light weight to get familiar with the movements and warm up fully, then chose a weight that can enable the subjects to complete 3 repetitions. If the repetitions exceeded 3 times, the subjects should have a rest for 2 min, and then increased the weight by 5% for the next set. This was repeated until the subject could finish exactly 3 repetitions, and the lifted weight and the number of repetitions were recorded and substituted into the formula: 1 RM = [lifted weight× (1 + 0.025× repetitions)] to estimate 1RM (18).

Measurement of anxiety level

Zung's Self-rating Anxiety Scale (SAS) was used to measure the anxiety degree of the subjects. The Chinese version of SAS has good reliability and validity (19). There are 20 questions in SAS. Each question is divided into 4 grades according to its severity, with scores of 1, 2, 3, and 4. The higher the score, the higher the degree of anxiety. The total score was multiplied by 1.25 and converted into a standard score. SAS standard score ≥50 was rated as anxiety.

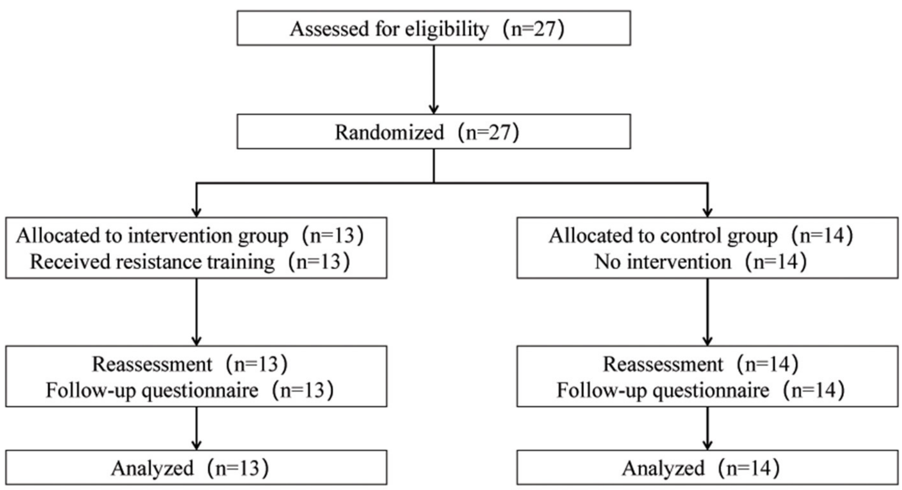

FIGURE 1
The flow of participants through the trial.

Statistical analysis

All experimental data were expressed as mean ± standard deviation and statistically analyzed by SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The differences in HRV parameters, 1 RM and SAS score before and after the experiment were calculated, respectively, and independent samples *t*-test was used to test post-test–pre-test scores between intervention group and control group. In all cases, values of $P < 0.05$ were considered statistically significant.

Results

Figure 1 shows the flow of participants through the study. The baseline primary and secondary outcomes of all participants are described in Table 2. No differences were observed in the baseline values between intervention group and control group.

Effect of resistance training on HRV in anxious female college students

Table 3 shows changes in HRV parameters as the primary outcomes after 8 weeks of resistance training. Compared with the control group, SDNN increased significantly ($P < 0.05$) and LF/HF decreased significantly ($P < 0.05$) in the intervention group. RMSSD, PNN50, LF, and HF showed an increasing trend in the intervention group, but there was no statistical difference compared to the control group.

TABLE 2 Baseline primary and secondary outcomes of participants in intervention and control groups.

Outcomes	Intervention	Control	*T*-value	*P*-value
Primary outcomes				
SDNN (ms)	33.9 ± 9.2	36.5 ± 9.2	−0.725	0.475
RMSSD (ms)	32.1 ± 10.9	31.3 ± 12.0	0.167	0.868
PNN50 (%)	12.1 ± 10.6	13.8 ± 12.5	−0.385	0.704
LF (log)	6.2 ± 0.6	6.3 ± 0.6	0.062	0.951
HF (log)	5.7 ± 0.6	5.9 ± 0.8	0.392	0.698
LF/HF	2.2 ± 1.8	2.0 ± 1.5	0.369	0.715
Secondary outcomes				
BMI (kg/m^2)	21.8 ± 2.7	20.7 ± 2.0	1.15	0.262
SAS	58.2 ± 6.2	54.7 ± 6.5	1.406	0.172
Barbell bench press (kg)	23.8 ± 5.8	22.5 ± 5.7	0.603	0.552
Lat pull-down (kg)	37.0 ± 15.5	39.4 ± 8.5	−0.484	0.633
Leg lift (kg)	89.7 ± 43.1	101.4 ± 28.0	−0.839	0.409

BMI, body mass index; SAS, Zung's Self-rating Anxiety Scale; SDNN, standard deviation of all R-R intervals; RMSSD, square root of the sum of the mean of the difference between adjacent RR intervals; LF, low frequency power; HF, high frequency power.

Effect of resistance training on BMI, muscle strength, and anxiety level in anxious female college students

The changes of secondary outcomes were shown in Table 4, after 8 weeks of resistance training, compared with the control group, BMI did not change significantly ($P > 0.05$), SAS score of intervention group decreased significantly ($P < 0.05$), and the 1RM of barbell bench press, Lat pull-down and leg lift were significantly increased ($P < 0.05$) in the intervention group.

Discussion

This study shows that resistance training interventions improved HRV parameters (i.e., increments of SDNN and LF/HF ratio) during resting conditions in anxious female college students. These findings have important clinical implications to improve the autonomic nervous disorder of adolescent females with anxiety.

Resistance training and HRV

HRV has been recognized as an effective non-invasive index reflecting autonomic nerve function. The time domain parameter SDNN of HRV mainly reflects the overall activity of autonomic nerve function. Frequency domain parameter LF is mainly mediated by sympathetic activity. RMSSD, PNN50, and HF are associated with parasympathetic activity (6). Cardiac autonomic control is an important indicator of cardiovascular health (20). Prospective longitudinal cohort studies have shown that impaired cardiac autonomic control is a strong predictor of all-cause and cardiovascular disease mortality and can be diagnosed clinically by HRV (21). Physical exercise has been proved to modulate the autonomic control of the heart (13, 22). Especially, the majority of studies on clinical populations demonstrated significant positive changes in cardiac autonomic control after resistance training (13). However, there is still a lack of such evidence-based research exploring the resistance training intervention to improve the autonomic nervous disorder of adolescent females with anxiety disorders. Our study explored that the time-domain parameter SDNN is significantly increased and the frequency-domain parameter LF/HF is significantly decreased, which indicates that resistance training can reduce the sympathetic activity and improve sympatho-vagal balance after resistance training intervention in anxious female college students.

Based on the position statements published by the American College of Sports Medicine (ACSM) and American Heart Association (AHA) (23), 70% 1RM was used as the training intensity in this study. An acute resistance training temporarily increases the sympathetic activity and temporarily decrease

TABLE 3 Differences of mean HRV indices compared with the control group.

Primary outcomes	Intervention		Control		Post-test–pre-test				
	Pre-test	Post-test	Pre-test	Post-test	Intervention-control				
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	95% CI	*T*-value	*P*-value	Cohen's d
SDNN (ms)	33.9 ± 9.2	39.6 ± 12.1	36.5 ± 9.2	33.9 ± 10.8	9.4 ± 3.5	2.3,16.6	2.718	0.012	1.09
RMSSD (ms)	32.1 ± 10.9	40.5 ± 16.0	31.3 ± 12.0	30.1 ± 15.1	10.5 ± 5.8	−1.6,22.5	1.8	0.085	0.73
PNN50 (%)	12.1 ± 10.6	20.9 ± 15.3	13.8 ± 12.5	13.8 ± 16.1	9.9 ± 6.3	−3.2,22.9	1.566	0.131	0.63
LF (log)	6.2 ± 0.6	6.1 ± 0.7	6.3 ± 0.6	6.2 ± 0.8	0.01 ± 0.3	−0.6,0.6	−0.027	0.979	0.00
HF (log)	5.7 ± 0.6	6.2 ± 0.7	5.9 ± 0.8	5.5 ± 1.2	0.9 ± 0.4	−1.7, −0.2	−2.545	0.018	1.08
LF/HF	2.2 ± 1.8	1.3 ± 1.1	2.0 ± 1.5	3.2 ± 2.8	−2.2 ± 1.0	−4.3, −0.03	−2.096	0.047	0.84

BMI, body mass index; SAS, Zung's Self-rating Anxiety Scale; SDNN, standard deviation of all R-R intervals; RMSSD, square root of the sum of the mean of the difference between adjacent RR intervals; LF, low frequency power; HF, high frequency power.

TABLE 4 Differences of mean BMI, muscle strength, and anxiety level compared with the control group.

Secondary outcomes	Intervention		Control		Post-test–pre-test				
	Pre-test	Post-test	Pre-test	Post-test	Intervention-control				
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	95% CI	*T*-value	*P*-value	Cohen's d
BMI (kg/m^2)	21.8 ± 2.7	21.6 ± 2.6	20.7 ± 2.0	20.4 ± 1.8	−0.2 ± 0.2	−0.5, 0.2	−0.859	0.399	0.09
SAS	58.1 ± 6.2	39.0 ± 4.2	54.7 ± 6.5	46.3 ± 9.5	−10.1 ± 3.2	−16.7, −3.4	−3.12	0.005	1.26
Barbell bench press (kg)	23.8 ± 5.8	29.6 ± 7.0	22.5 ± 5.7	23.1 ± 6.7	4.4 ± 1.1	2.1, 6.8	4.006	0.001	1.70
Lat pull-down (kg)	37.0 ± 15.5	44.7 ± 12.1	39.4 ± 8.5	37.8 ± 7.9	10.5 ± 4.0	2.2, 18.7	2.638	0.015	1.09
Leg lift (kg)	89.7 ± 43.1	147.6 ± 68.3	101.4 ± 28.0	105.3 ± 31.2	54.2 ± 8.5	35.6, 72.9	6.412	0.000	2.75

BMI, body mass index; SAS, Zung's Self-rating Anxiety Scale.

the parasympathetic activity; Chen, et al. found that HF drop significantly within 24 h of post-training recovery and return to baseline values by 72 h, and LF is marginally elevated in 24 h and return to normal values within 48 h (24). Therefore, in order to avoid the fatigue accumulation of autonomic nerves, we chose 72 h as the interval between the two training sessions, and resistance training twice a week as the appropriate exercise frequency in the resistance training intervention.

Resistance training and anxiety

Resistance training has been postulated as an effective strategy to improve anxiety, especially for young patients with anxiety, and 6–8 weeks of resistance training can significantly improve anxiety (25). Gordon et al. conducted resistance training for young anxiety patients with an average age of 26.0 ± 6.2 years, twice a week, for 8 weeks, and found that their anxiety was significantly reduced (26). They also conducted resistance training intervention for obese adolescents aged 14–18 for 22 weeks, 4 times a week, and 8–15 RM, and found that their anxiety was significantly improved (27). Consistent with previous studies, we found that 8-week resistance training intervention significantly reduced the anxiety level of anxious female college students. At the same time, resistance training can bring more health benefits, such as the improvement of body composition and muscle strength (25–27). In our study, we also founded the significant increase of muscle strength, such as barbell bench press, Lat pull-down and leg lift. There was no significant change in BMI, which may be because BMI of all subjects was almost normal.

Limitations of research

There are still some limitations in this study. The subjects of this study are female college students with anxiety, so we should be cautious when extending the results of this study to others. First of all, there are gender differences in HRV. The average heart rate of women is higher, the R-R interval is shorter, and the HRV is lower than that of men of the same age, and this difference is more obvious in young people (28). The results of this study only prove that resistance training can improve the HRV of anxious female college students, and whether the anxious male college students can get similar results by regular resistance training needs further verification. In addition, HRV is also affected by age, and it will gradually decrease with the increase of age (29). The intervention effect of resistance training is related to the basic value of HRV before intervention (13). The intervention of resistance training for anxious middle-aged and elderly women may make the HRV more improved, but it still needs to be proved by further experiments. In addition, the results of this study support the hypothesis that resistance training can have beneficial effects on HRV, it is necessary to explore the biological mechanism of resistance training affecting HRV and further clarify the intervention effect of resistance training on HRV.

In conclusion, resistance training intervention can significantly improve the anxiety level, muscle strength and HRV during resting conditions in anxious female college students. The training program in this study can be used as an exercise prescription to improve the autonomic nervous system disorder in anxious female college students.

Data availability statement

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

Ethics statement

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

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RL, RY, WC, and HR. The first draft of the manuscript was written by RL. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The after-school sedentary behavior status among children and adolescents with intellectual disabilities

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Background: There is evidence that the after-school period plays an essential role in accumulating sedentary behavior (SB) among children and adolescents, as well as implementing potential interventions. However, relatively little is known regarding SB status of children and adolescents with intellectual disabilities (ID) during the after-school period. The purpose of this study was to investigate the total level and specific pattern of the after-school SB among children and adolescents with ID.

Methods: The after-school SB status among 325 children and adolescents with ID was evaluated by the parent-reported Children's Leisure Activities Study Survey-Chinese edition questionnaire.

Results: Parents of children and adolescents with ID reported approximately 204 min/day of after-school SB. Specifically, the longest time of the after-school period was spent performing the screen-based SB (84 mins/d). This was followed by recreational SB and educational SB (50 and 30 mins/d, respectively). The children aged 6–12 years old engaged more time in recreational SB than adolescents aged 16–18 years old ($p < 0.05$) during the after-school period. Further, the data indicated that 37.5% of children and adolescents with ID achieved the guideline limitation of 2-h-maximum screen-based SB during the after-school hour.

Conclusion: Children and adolescents with ID spent a large portion of the after-school period in SB, particularly engaged in more time on after-school screen-based SB. Future efforts should focus on developing and implementing period-specific interventions designed to reduce after-school SB in the segment of this population.

KEYWORDS

after-school, sedentary behavior, intellectual disabilities, children and adolescents, health promotion (HP)

Introduction

The review by Carson et al. showed that it was crucial and beneficial for children and adolescents to engage in moderate-to-vigorous physical activity (MVPA) for 60 min every day (1). However, research focusing on other health-related behavior for the remaining 23 h of the day has traditionally been scarce, although it is fast increasing. Sedentary behavior (SB) is one of the particular critical behaviors, which is defined as any waking behavior (e.g., in a seating, reclining, or lying down posture) with an energy expenditure $\leq$ 1.5 METs (metabolic equivalents) (2).

It has been demonstrated in numerous studies that SB is increasingly linked to all-cause mortality, overweight/obesity, type II diabetes, lower physical fitness, cardiovascular disease, and some cancers, independent of physical activity (PA) (3–5). Furthermore, the findings from Carson et al.'s review have also revealed that different types of SB (e.g., watching TV, using the computer, or doing homework) may have various impacts on health (1).

More recently, SB has been common among children and adolescents worldwide (6). Based on solid evidence from two national-level datasets in Canada and the United States, SB was found to account for a substantial proportion of waking times (50–60%) of the day in children and adolescents (7, 8). To reduce the adverse health impacts of SB, the World Health Organization (WHO) suggests that 5–17-year-old children and adolescents should limit screen-based SB to under 2 h per day (9). The 24-Hour Movement Guideline also recommends that children and adolescents minimize time spent in SB (10). These recommendations apply to most children and adolescents, including those peers with ID.

Prior studies have found that children and adolescents with ID spent more time sedentary than their counterparts without ID (11–13). Esposito et al. and Phillips et al. also pointed out that the high prevalences of obesity, poor fitness, and functional limitations experienced by children and adolescents with ID, possibly be related to their high levels of SB (11, 12). A high level of SB may, in turn, lead to a further increase in adverse health outcomes among children and adolescents with ID. Under such circumstances, children and adolescents with ID may not be able to avoid the negative health effect of long-term SB engagement, even though they could follow the MVPA recommendations. In addition, it is essential to note that in the general population, SB appears to increase from childhood to adulthood (6, 8). The existing data indicate that, from the life-cycle perspective, individuals with ID often experience premature aging issues (14). These early onset aging may affect the pattern of SB development throughout the lifespan of children and adolescents with ID. Thus, there is a great need for a more comprehensive and detailed look at the characteristics of SB among children and adolescents with ID.

A range of research has revealed that the specific time of the day that can potentially make a significant contribution to children and adolescents' daily SB is the after-school period (15, 16). Children and adolescents are often not bound by school schedules during this period. They have more choices about their behavior than during the school day. However, to our knowledge, there was only one study that focused on the field of after-school SB among children with ID (17). Foley and McCubbin found that 7–12 year-old children with ID spent time on watching TV or on the computer was no different than their peers without ID, but it was encouraging that the majority of the children did not exceed the limitation of 2 h/d. It is worth noting that the study was published more than 10 years ago, and given the small sample size, it is uncertain whether its findings are still valid in terms of reflecting the after-school SB of children with ID today. In this context, our study was conducted to understand the overall level SB and detailed information on different types of SB during the after-school period among children and adolescents with ID aged 6–18 years through a relatively large sample sampling, as a step toward establishing and collecting baseline data to provide targeted period-specific strategies for health promotion in this population.

Materials and methods

Study design

A cross-sectional descriptive design assessed the after-school SB status among children and adolescents with ID by using parent-reported surveys. The survey was completed between

September 13 and December 24, 2021. All parents involved in this study, as well as their children, were explicitly advised that participation was entirely voluntary. All the data were centrally analyzed anonymously. The study was conducted in accordance with the Declaration of Helsinki Principles, and approved by the ethics committee of the university.

Participants

A convenience sampling strategy focusing on the parents of children and adolescents with ID was utilized among special education schools in Shandong Province. The following were inclusion criteria for the parents: (1) their child came from day school; (2) their child was between the ages of 6 and 18; (3) their child could walk without any help; and (4) their child did not experience coexisting cerebral palsy, autism, and other sensory impairments. The ID level was categorized as profound [intelligence quotient (IQ) < 25], severe (IQ of 25–39), moderate (IQ of 40–54), and mild (IQ of 55–70) (18). Additionally, children and adolescents with ID were divided into three age subgroups, 6–12, 13–15, and 16–18 years old, which matched the Chinese school education system's definition of the age range for the primary, junior middle, and junior high schools (19).

Procedures

Based on the most recent data, 33 special education schools primarily recruit children and adolescents with ID in Shandong Province of China (20). The school-keepers from 16 special education schools were contacted through the help of the China Disabled Persons' Federation. Finally, 10 special education schools accepted the invitation and consented to participate in the study. Invitations containing the purpose and content of this study were sent out by headmasters to the legal guardians of children and adolescents with ID. In the meantime, the objective of the present study was explained briefly to children and adolescents with ID. Verbal permission was also obtained in their schools prior to data collection. Once the caregivers gave written informed consent, the teachers contacted them to come to school to complete the questionnaire. The parents were given step-by-step instructions by trained teachers and researchers through the parents' meeting on how to complete the questionnaire. They were also given plenty of time for questions.

Sedentary behavior assessment

After-school SB of children and adolescents with ID was assessed using reliable items from the Children's Leisure Activities Study Survey-Chinese edition (CLASS-C) questionnaire, which is widely used in China and has good reliability and validity (21). Li et al. also stressed that no statistically significant difference was observed in measurement between the CLASS-C questionnaire and accelerometry (21). In this study, prior to data collection, a pretest CLASS-C questionnaire was completed by a sample of 30 parents from one special education school in the Jinan City of Shandong Province. The pretest showed that the CLASS-C questionnaire possessed sound reliability (Cronbach's $a = 0.752$). The CLASS-C questionnaire contained a list of twelve common after-school SB in addition to demographic information that consisted of gender, age, height, weight, and ID level. Based on the manifestation of behavior, these common after-school SB can be classified into four categories: screen-based SB (watch TV, play video/computer games, and surf the Internet), educational SB (do homework and read books), recreational SB (play with toys, listen to music, play musical instruments, play card games, and art activities) and social SB (chat while sitting stationary and make phone calls). In addition, as this study only focused on the after-school period, parents were requested to provide the amount of time their child spent on the specific after-school SB pattern from Monday to Friday (five consecutive days). After-school hours, in this study, were defined as the period between the end of school bell time and bedtime.

The parent-reported survey was chosen in the current study for the following three reasons. First, children and adolescents with ID may not completely understand the content of the questionnaire, and hard to finish the questionnaire independently. In documenting their child's activities, Burdette et al. found that parents were able to give accurate estimates (22). Second, the questionnaire measurement could gather information about the type of SB–a capability not provided by device-based assessments, such as accelerometers. Further, large-scale epidemiological studies often consider questionnaires as a cost-effective alternative to accelerometers.

Statistical analyses

All data analyses were conducted on SPSS version 25.0 for Mac (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated for all study variables (gender, age, weight status, and ID level). All variables were examined whether they were normally distributed by means of the Kolmogorov–Smirnov test. Due to the non-normal distribution of SB variables, the Mann–Whitney U test was utilized to compare the SB differences between gender and weight status. The Kruskal–Wallis test was applied to analyze differences in SB between age and ID level. For prevalence, estimates were calculated as the percentage of children and adolescents with ID who achieved the 2-h-maximum screen-based SB time limitation in the guideline. Differences in the prevalence of screen-based SB time limitation by gender, age, weight status, and ID level were tested using a binary logistic regression model. Prevalence estimates, odds ratio (OR), and corresponding 95% confidence interval (CI) were calculated from the logistic regression. P-values < 0.05 were considered statistically significant for all analyses.

Results

Demographic analysis

Data in relation to after-school SB from 325 children and adolescents with ID were provided from parents' reports. A total of 220 (67.7%) children and adolescents with ID were boys, aged 12.4 ± 3.3, and 105 (32.3%) were girls, aged 12.7 ± 3.8. In addition, 104 (32.0%) of them were moderate ID, 167 (51.4%) were severe ID, and 54 (16.6%) were profound ID.

After-school sedentary behavior level among children and adolescents with intellectual disabilities

The daily time of total after-school SB and specific types of after-school SB among children and adolescents with ID are presented in Table 1. Children and adolescents with ID engaged in approximately 204 min of total after-school SB per day. In detail, they spent approximately 84 mins/d during the after-school period in the screen-based SB. Furthermore, after-school children and adolescents with ID performed about 50 mins/d of recreational SB and 30 mins/d of educational SB, respectively. Additionally, no significant differences were observed in total after-school SB or particular after-school SB for children and adolescents with ID by gender, weight status, and level of ID ($p > 0.05$). An exception, however, was seen during the after-school period where the youngest-aged (6–12 years old) group engaged more time in recreational SB than the oldest-aged (16–18 years old) group ($p < 0.05$).

Table 2 displays the detailed prevalence estimates of screen-based SB during the after-school period by gender, age, weight status, and ID level of children and adolescents with ID. Overall, 37.5% of them achieved the 2-h-maximum screen-based SB time limited in the guideline during the after-school time. No statistically significant differences were found in the prevalence estimates of screen-based SB by gender, age, weight status, and ID level during the after-school period from the logistic regression model results (Table 3).

Discussion

This study described the overall level and specific pattern of the after-school SB in children and adolescents with ID, derived from parent-reported data. Based on the daily routine of school days, we deduce that children and adolescents with ID leave school at 4:00 p.m. and sleep at 10:00 p.m. After removing approximately 1 h of time needed to get home and have dinner, there are approximately 5 h left during this period. The results of this study indicated that during the after-school time, present children and adolescents with ID had 204 mins/d of SB, which was equivalent to 3.4 h every day. Excessive after-school SB is a serious problem for children and adolescents with ID. It was evident that they spent approximately 70% of their after-school time in SB, which was relatively higher than the findings of Arundell et al.'s systematic review focused on after-school

TABLE 1 Daily minutes of total after-school SB and specific types of after-school SB among children and adolescents with ID [M (P25–P75), min/days].

	Total SB	Educational SB	Screen-based SB	Recreational SB	Social SB
Both gender	204 (96–252)	30 (0–60)	84 (48–120)	50 (0–60)	0 (0–18)
Gender					
Boys	216 (117–252)	45 (0–60)	84 (48–120)	50 (0–60)	0 (0–17)
Girls	195 (84–252)	27 (0–68)	60 (48–120)	48 (6–60)	0 (0–24)
Age					
6–12	228 (98–278)	36 (0–60)	84 (36–120)	50 (12–84)	0 (0–24)
13–15	195 (108–240)	30 (0–60)	96 (50–120)	50 (4–60)	0 (0–10)
16–18	180 (96–240)	30 (0–84)	60 (60–120)	12 (0–60)	0 (0–48)
ID level					
Moderate	228 (120–254)	46 (0–72)	72 (60–130)	50 (5–84)	0 (0–12)
Severe	195 (110–246)	30 (0–60)	90 (48–120)	50 (6–60)	6 (0–24)
Profound	157 (50–264)	18 (0–72)	66 (21–120)	24 (0–60)	0 (0–30)
Weight status					
Normal weight	192 (96–264)	30 (0–60)	72 (36–120)	50 (12–60)	2 (0–24)
Overweight/Obesity	216 (105–245)	45 (0–60)	120 (60–120)	36 (0–72)	0 (0–17)

TABLE 2 Prevalence estimates of after-school screen-based SB time limitation among children and adolescents with ID by gender, age, weight status, and ID level.

	Achieving the screen-based SB time limitation (95% CI)
Both gender	37.5 (32.2–42.8)
Boys	39.1 (32.6–45.6)
Girls	34.3 (25.1–43.5)
Age	
6–12	35.2 (27.3–43.2)
13–15	39.7 (30.6–48.7)
16–18	38.8 (26.8–50.8)
Weight status	
Normal weight	37.8 (30.6–44.9)
Overweight/Obesity	37.2 (29.3–45.2)
ID level	
Moderate	37.5 (28.0–47.0)
Severe	38.9 (31.5–46.4)
Profound	33.3 (20.3–46.3)

TABLE 3 Differences in prevalence of achieving the after-school screen-based SB time limitation among children and adolescents with ID by gender, age, weight status, and ID level.

	Achieving the screen-based SB time limitation OR (95% CI)
Both gender	
Girls	Referent
Boys	1.225 (0.747–2.011)
Age	
6–12	Referent
13–15	1.234 (0.734–2.074)
16–18	1.242 (0.674–2.291)
Weight status	
Normal weight	Referent
Overweight/Obese	0.951 (0.598–1.510)
ID level	
Moderate	Referent
Severe	1.066 (0.641–1.773)
Profound	0.820 (0.403–1.669)

SB among typically developing (TD) children and adolescents (15). Arundell et al.'s study revealed that TD children spent between 41 and 51% of the after-school period sedentary, and TD adolescents engaged 57% of the after-school time in SB (15). The earlier reports of poor health conditions associated with SB in children and adolescents with ID may explain part of the higher level of their after-school SB (11, 12). However, it is hard to confidently conclude whether the after-school SB of children and adolescents with ID differs from TD peers due to the fact that difference in the after-school period definitions and the measurement tools between the present study and the systematic review study. Additionally, existing data focusing on the overall SB level appear conflicting in the literature. Foley et al., Whitt–Glover et al., and Pitchford et al. concluded that no significant difference was found in the overall SB between children and adolescents with ID and TD peers (17, 23, 24). In contrast, a study from Poland based on a large sample showed that children and adolescents with ID had significantly longer SB than their counterparts (25). The reasons for this may be related to the choice of SB measurement tools, the size and type of sample with ID, and the use of SB cut-off points between studies. Therefore, caution is needed when making comparisons across different studies.

A key finding of this study was that screen-based SB was the most common form of after-school SB for children and adolescents with ID. The results found that the amount of time spent on screen-based SB after school was approximately 84 mins/day, which made up 41.2% of the total after-school SB level. This finding is similar to that reported in a previous study by Foley et al. In Foley et al.'s study, children with ID spent the majority of their after-school time watching television and computers for a combined 82 ± 64 mins/d (17). The findings of Adelantado–Renau et al. (26) highlighted that screen-based SB was the most prevalent behavior for TD children and adolescents in their daily lives. According to the review study by Carson et al., prolonged screen-based SB time was linked with adverse health effects (1). In detail, higher screen time/frequency was associated with unfavorable body composition, lower fitness performance, lower self-esteem, and higher risk of clustered cardiometabolism (1). A gradient was also observed across the different health indicators, showing that less SB, particularly screen time, was related to better health (1). In addition to the screen-based SB, the present study found that the recreational and educational SB comprise 39.2% of the total after-school SB level. Of note, it is possible several of these particular SB occur concurrently during the after-school period. For example, some learning and leisure activities are screen-based devices, such as reading books on pads, doing homework on the computer, listening to music on phones, and drawing pictures on the laptop. Therefore, screen-based devices usage should be limited, except for essential learning or leisure activities during the after-school period. It is also recommended to choose non-screen learning and entertainment activities instead of screen-based learning and entertainment activities. Moreover, from the point of view of the type of after-school SB, although the time accumulation and energy expenditure of SB are similar between educational SB and recreational SB, there may be specificity in the determinants and biological effects of health consequences of positive and negative SB. It is therefore challenging to effectively distinguish between different particular SB pattern and their health benefits in future studies.

In the present study, one unanticipated finding was that children and adolescents with ID in the youngest-age group

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engaged in more recreational SB compared to those in the oldest-age group during the after-school period, which indicated that there might be different after-school SB patterns among children and adolescents with different age ranges. This result, therefore, needs to be interpreted with some caution because the sample size across age groups in this study was uneven, as well as investigating SB status only during the after-school period. In addition, it is clear that the evidence from the present stage of the study does not establish whether age is an influential factor in the SB of children and adolescents with ID. Esposito et al. highlighted that the time of SB per week for adolescents with ID usually increased with age (11). One study from Japan also noted that children with ID aged 11–12 years old engaged significantly more time in SB than those aged 7–8 years old (27). However, Foerste et al.'s study outlined that there was no correlation between SB and age in adolescents with ID (28). It is worthy to mention that the above-mentioned studies recruited samples with Down's syndrome (DS). Phillips and Holland found that individuals with DS are significantly more sedentary than those with ID without DS. Furthermore, it has been noted that individuals with DS engaged in lower PA and fitness levels, leading to cardiac chronotropic incompetence, impaired autonomic function, low muscular strength, and muscle hypotonia compared to individuals with ID without DS (12). Therefore, more research is needed to provide an in-depth analysis of the relationship between age factors and SB level/specific SB pattern at different periods of the day (e.g., at school or after school) based on a clear sampling (e.g., recruitment of samples with ID without DS or samples with ID only) type.

Several theories have been applied to facilitate the investigation of behaviors and their correlates. The ecological model theory suggests that behavior is influenced by intrapersonal factors as well as social/cultural and physical/policy environment (29). In this study, personal, family, and environmental factors could contribute to excessive after-school SB among children and adolescents with ID. As far as personal factors are concerned, on the one hand, children and adolescents with ID may have skeletal development and motor development issues that limit their activities (30). On the other hand, because of their cognitive deficits, they have difficulty recognizing the adverse health effects of SB and planning/organizing their after-school activities. Furthermore, a lack of interest in sports activities and social difficulties may also be factors contributing to higher levels of after-school SB among children and adolescents with ID. Regarding family factors, Izquierdo–Gomez et al.'s pointed out that the mother's education, work status, and socio-economic status were associated with total SB time and watching TV time among adolescents with DS (31). Additionally, overprotective or worried parents could restrict their children's range of activities or deny them the opportunity to participate in sports activities, making them more anxious and vulnerable (30). Therefore, parents' understanding of the harmful effects of SB and their behavioral habits may influence their children's behavior. To reduce the after-school SB of children and adolescents with ID, parents' awareness of the value of after-school sports activities should be raised, their role in the healthy development of their children should be clearly defined, and their role as role models should be fully explored. The environment in the community and the facilities at home can also impact the after-school SB of children and adolescents with ID. According to Izquierdo–Gomez et al.'s study, total SB levels were positively correlated with the number of bedrooms, the presence of a garden, and a walkable neighborhood (31), which give direction to the identification of factors relevant for family or community-based interventions. Hence, in summary, children and adolescents with ID may experience high levels of after-school SB because of a combination of individual, family, and environmental factors.

One situation that cannot be ignored is that children and adolescents with ID spend half of their waking hours at school on weekdays. Traditionally, the classroom environment has been related to children and adolescents with ID spending long periods of time sitting. Consequently, the after-school period represents a vital part of the day for them. In general, they are not restricted by school schedules after school, and they may have some choices between active and sedentary options during these discretionary periods of the day. Furthermore, after-school SB may also contribute to daily SB level and affect the health of children and adolescents with ID. Hence, the targeted period-specific interventions given may be effective. For example, outdoor plays may provide a feasible opportunity for children and adolescents with ID to take some exercise or participate in sports activities and subsequently reduce SB during the after-school period. Also, Robinson et al. offered after-school dance classes to TD children, which had been shown to successfully reduce their screen-based SB (32). These directed at after-school interventions may be adapted to children and adolescents with ID and have the potential to change their after-school SB status. Further, two previous studies took different approaches to intervene on SB status in children and adolescents with DS or ID at the community level and school level, respectively. Ulrich et al. conducted a 7-week bicycle intervention for children and adolescents with DS in the community setting, with the results indicating that children and adolescents with DS who learned to ride engaged significantly less time in SB compared to their peers in the control group (33). A study from Hong Kong, China examined the effectiveness of active video games intervention strategy on PA level, motor proficiency, and body composition. The result of the study showed that, compared to the control group, children with ID in the intervention group had a decrease in SB after a 12-week intervention (34). However, the long-term effectiveness of these interventions in reducing SB and whether they are also applicable to the period after school need to be further investigated.

There are some limitations to this study. First, data were collected from special education schools in the fall semester. Previous studies showed that children were found to be more sedentary in the winter than in the spring or summer (35, 36). Therefore, this surveillance data may only represent after-school SB at a specific period of the year and may not be generalizable throughout the entire school year due to the after-school SB may be associated with the seasonal variation. Second, the convenience sample used from northern China may not be representative of the entire children and adolescents with ID in China. Additionally, the unbalanced sample size of each ID severity may have some influence on the interpretation of the results of the present study. Thus, a more complete sampling strategy is necessary for future research. Third, due to the cross-sectional study's design, no causal relationship can be established. Therefore, in order to clarify and understand the trend and patterns of change in after-school SB over time, this requires future prospective analysis in further large longitudinal studies focusing on investigating the prevalences, trajectories, and determining factors of the after-school SB. Finally, notwithstanding these limitations, this investigation provides invaluable information to understand the pattern and distribution of after-school SB among children and adolescents with ID.

Conclusion

Overall, the findings of this study highlighted that children and adolescents with ID spent a high level of SB during the after-school period. Among varieties of types of after-school SB, children and adolescents with ID particularly engaged in more time on after-school screen-based SB. A certain number of them exceeded the 2-h-maximum limit for screen-based SB time during the after-school period. Thus, it is necessary to implement period-specific strategies to reduce SB among the vulnerable population.

Data availability statement

The data are not publicly available due to privacy or ethical restrictions. Requests to access these datasets should be directed to YY, crystal_267@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Shandong Sport University, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

YL and JL contributed to conception and design of the study. CW and JD organized the database. SZ and YW performed the statistical analysis. YY and YL wrote the first draft of the manuscript. JD wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Physical activity levels associated with insomnia and depressive symptoms in middle-aged and elderly patients with chronic schizophrenia

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Background: Previous evidence suggested that physical activity had beneficial effects on psychopathological symptoms, insomnia, or depressive symptoms in people with schizophrenia. This study investigated the association between physical activity levels and insomnia and depressive symptoms in middle-aged and elderly hospitalized patients with chronic schizophrenia (CS).

Methods: 179 participants were enrolled. We used the 30-item Positive and Negative Syndrome Scale ($PANSS_{-30}$) to assess the psychopathological symptoms. We used the Insomnia Severity Index scale (ISI) and 17-item Hamilton Depression Scale (HAMD-17) to evaluate insomnia and depressive symptoms. Daily physical activity time less than 30 min, within 30–60 min, and more than 60 min were defined as physical inactivity, moderate physical activity, and vigorous physical activity, respectively. The Chi-square test, analysis of variance (ANOVA), and Mann–Whitney *U*-test were applied for categorical, continuous, and non-normal distribution variables, respectively. The Pearson or Spearman's correlation analyses were utilized to examine the association between physical activity levels, ISI total scores, HAMD total scores, and socio-demographic and clinical variables. Finally, socio-demographic variables with a *P*-value < 0.05 in the comparison between insomnia/depressive group and non-insomnia/depressive group were considered for inclusion in binary logistic regression analysis to determine the relationship between physical activity levels and insomnia or depressive symptoms.

Results: The ISI total scores ($r = -0.247$, $P = 0.001$) and HAMD total scores ($r = -0.312$, $P < 0.001$) were negatively correlated with physical activity levels. Logistic regression analysis revealed that older age, higher depressive factor scores, and lower physical activity level were influential factors of insomnia symptoms in CS patients ($P < 0.05$). In addition, vigorous physical activity (compared with physical inactivity) and higher negative and depressive factor scores were independently associated with depressive symptoms in CS patients ($P < 0.05$).

Conclusion: Physical activity levels were influential factors in comorbid insomnia and depressive symptoms in CS patients. Given the benefits of physical activity, it should be strengthened as a routine adjunct to clinical treatment or psychiatric care so as to improve the physical and mental health of patients with psychiatric symptoms.

KEYWORDS

physical activity, insomnia, depressive, middle-aged, elderly, schizophrenia

Introduction

World Health Organization (WHO) statistics reported that approximately 15% of older adults aged 60 years and older suffer from mental disorders, such as depression, anxiety, and dementia, making it a category of public health challenges that seriously affects the elderly population (1). The results of the Global Burden of Disease Study (GBD) showed that mental disorders accounted for a significantly increasing proportion of global disability-adjusted life years (DALYs) and 14.6% of global disability life lost years (YLDs), making it one of the top 10 global burdens of disease (2). The latest, the most authoritative the national epidemiological survey of mental disorders in China indicated that the lifetime prevalence of mental illness in adults was 16.57% (3), with alone accounting for approximately 17% of the global burden of mental disorders (4), creating a heavy long-term burden at the individual, societal, and national levels.

Schizophrenia is a group of severe mental disorders of unknown etiology. Patients suffer from serious abnormalities in cognition, thinking, and behavior (5), with a lifetime prevalence of approximately 1% worldwide (6). Previous literature stated that the population with mental disorders suffered poorer sleep quality than the general population, and about 20–40% of patients with chronic schizophrenia (CS) were comorbid insomnia symptoms (7–9). Furthermore, research suggested that worse sleep quality was strongly related to more severe psychotic symptoms (10) and that insomnia symptoms could even exacerbate psychiatric symptoms and lead to increased somatic comorbidity. In contrast, healthy sleep hygiene significantly improved the severity of psychopathological symptoms (11). Strong evidence suggested that regular physical activity enhanced mental health (12) and could predict a better global and social quality of life in schizophrenic patients (13). Furthermore, higher physical activity levels were strongly related to fewer insomnia symptoms, better cognitive functioning, social functioning, and life satisfaction compared to lower levels of physical activity (14).

Comorbid depressive symptoms were more frequent in patients with schizophrenia, with an estimated prevalence of 18.8–80% (15–17). One study noted that depressive symptoms were negatively associated with the severity of psychotic symptoms (16). Compared to patients with mildly depressed schizophrenia, patients with major depressive symptoms had more serious psychiatric symptoms and poorer quality of life (15). Furthermore, a cross-sectional survey showed that more severe depressive symptoms in patients with schizophrenia were strongly related to less daily physical activity (18). Strong evidence suggests that regular physical activity may reduce depressive symptoms and improve social functioning in schizophrenic patients significantly (19, 20).

Physical activity, or physical exercise, sports, etc., is considered to be an important factor related to mental health. The latest meta-analysis shows that participation in sports can significantly reduce the body fat content and improve the physical function and mental health of elderly people over 60 years old (21). Another meta-analysis suggests that aerobic exercise may have a significant effect on mood and anxiety symptoms (22). In addition, clinical study indicates that a combination of high sedentary behavior and low moderate-to-vigorous intensity physical activity (MVPA) is strongly associated with higher levels of depression and anxiety symptoms compared with populations with less sedentary behavior and with sufficient MVPA (23). According to a national survey, higher PA frequency was associated with lower levels of depression, anxiety in Chinese physicians (24). A systematic review of 31 studies found that reducing sedentary behavior and increasing MVPA were significantly associated with better mental health and quality of life (25). Meanwhile, physical activity has also proven to be a promising adjunctive intervention for mood disorders.

Although growing literature evidence reported the correlation between physical activity levels, insomnia symptoms, depressive symptoms and psychopathology, studies on middle-aged and elderly Chinese hospitalized schizophrenic patients are still lacking. This research investigated the association between physical activity levels, insomnia and depressive symptoms in middle-aged and elderly hospitalized patients with schizophrenia. Further, we analyzed the influencing factors of comorbidities of insomnia or depressive symptoms in schizophrenia.

Materials and methods

Subjects

The subjects were psychiatric inpatients from May to December 2018 from three tertiary hospitals (Chaohu Hospital of Anhui Medical University, Hefei Fourth People's Hospital, and Ma'anshan Fourth People's Hospital) in Anhui Province, China. This cross-sectional study was a secondary analysis of the physiological and psychological conditions of inpatients with CS. Please refer to our previous manuscripts for sample size calculation (26). Inclusion criteria: (1) age $\geq$ 45 years; (2) it met the diagnostic criteria of schizophrenia according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V); (3) disease duration $\geq$ 5 years; and (4) able to complete clinical scale assessment. Exclusion criteria: (1) the presence of other serious mental retardation or neurological diseases; (2) unable to complete the assessment of clinical symptoms scales; (3) women who are pregnant or breastfeeding; (4) complicated with serious physical diseases (such as cardiovascular diseases, digestive system diseases, respiratory diseases, etc.).

The enrolled patients and their guardians agreed to participate in the project after knowing the study process and the related advantages and disadvantages and signed the paper informed consent. This research was approved by the Ethics Committee of Chaohu Hospital of Anhui Medical University (No. 201805-kyxm-03) and obtained registration number (No. ChiCTR1800017044) from the China Clinical Trials Registry.

Socio-demographic and clinical data

Demographic variables (age, gender, education, etc.) and clinical information of each patient were collected by questionnaire and the electronic medical record. Antipsychotic dose in chlorpromazine equivalents was calculated using the defined daily dose method (27).

Blood indicators

Ten milliliters of fasting venous blood was collected on the second morning after enrollment. The fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and other blood lipid indexes were detected by a specialized laboratory technician.

Physical activity levels

According to the dietary guidelines for Chinese residents, it is recommended that middle-aged and older people exercise outdoors one to two times a day for 30–60 min each time (28). In addition, WHO suggested that adults complete 150–300 min of moderate physical activity per week (29). In this study, the daily physical activities included walking, rhythmic exercises, etc., and the activity time was comprehensively judged by patients' self-reported and medical care records. All subjects were measured by three simple questions and answered the questions "yes" or "no": (1) Did you participate in any form of physical activity during hospitalization, such as rhythmic exercises, jogging, walking, etc. (2) The amount of physical activity you did each day: less than 30 min, 30–60 min, or more than 60 min. (3) Did you have any physical discomfort when you participate in physical activity? Less than 30 min per day was considered physical inactivity, 30–60 min per day was considered moderate physical activity, and more than 60 min per day was considered vigorous physical activity.

Assessment of psychiatric symptoms

30-item Positive and Negative Syndrome Scale ($PANSS_{-30}$) was utilized to assess the psychiatric symptoms of each inpatient. The five-factor model consists of positive, negative, cognitive, depressive, and excited factor scores were used for the statistical scoring, respectively (30).

Insomnia Severity Index scale (ISI) was used to assess insomnia symptoms with good reliability and validity (31, 32). The ISI total scores range from 0 to 28. We defined ISI total scores $\geq$ 8 as comorbid insomnia symptoms (31).

17-Item Hamilton Depression Scale ($HAMD_{-17}$) was used to assess depressive symptoms. Higher scores of HAMD indicate the different degrees of depression. We defined HAMD total scores $\geq$ 8 as comorbid depressive symptoms (33). The three clinical assessment scales' intraclass correlation coefficient (ICC) exceeded 0.8.

Statistical analysis

The SPSS 23.0 software package (*IBM, Chicago, IL, USA*) was used for data analysis. First, Chi-square test, analysis of variance (ANOVA), and Mann–Whitney *U*-test were applied for categorical, continuous, and non-normal distribution variables, respectively. Second, Pearson or Spearman's correlation analyses were utilized to examine the association between physical activity levels, ISI total scores, HAMD total scores, and socio-demographic and clinical variables. Finally, socio-demographic variables with a *P*-value < 0.05 in the comparison between insomnia/depressive group and non-insomnia/depressive group were considered for inclusion in binary logistic regression analysis to determine the relationship between physical activity levels and insomnia or depressive symptoms. The significance level was set as $\alpha = 0.05$ (2-tailed).

Results

Comparisons between groups with and without insomnia or depressive symptoms

179 inpatients with CS were included, and the prevalence of insomnia or depressive symptoms was 22.9% (41/179) and 71.5% (128/179). Compared to patients without insomnia symptoms, the comorbid insomnia symptoms patients had older age, lower physical activity level, higher proportion of antipsychotic polypharmacy, higher FBG levels, and higher psychopathology symptoms such as positive/depressive factor scores, PANSS, ISI, and HAMD total scores. Compared to patients without depressive symptoms, the patients with depressive symptoms had lower physical activity levels, fewer hospitalizations, higher positive, negative, cognitive, and depressive factor scores, PANSS, ISI and HAMD total scores (see **Table 1**).

Correlation analysis between ISI total scores, HAMD total scores, and demographic and clinical variables

ISI total scores were positively related to age ($r = 0.206$), FBG ($r = 0.169$), positive ($r = 0.234$), negative ($r = 0.181$), depressive factor scores ($r = 0.261$), PANSS total scores ($r = 0.167$), and were negatively correlated with physical activity levels ($r = -0.247$), significantly. After controlling for other variables related to ISI total scores, ISI total scores were still negatively correlated with physical activity levels ($r = -0.168$, $P = 0.027$) (see **Table 2**).

HAMD total scores were positively correlated with negative ($r = 0.316$), cognitive ($r = 0.251$), depressive ($r = 0.506$), PANSS total scores ($r = 0.314$), and were negatively correlated with number of admissions ($r = -0.177$) and physical activity levels ($r = -0.312$), significantly. After controlling for other variables related to HAMD total scores, HAMD total scores were still negatively correlated with physical activity levels ($r = -0.188$, $P = 0.013$) (see **Table 2**).

Influencing factors associated with insomnia symptoms in CS patients

The results showed that older age (*OR* = 1.07, *95% CI*: 1.02–1.14, $P = 0.013$),vigorous physical activity (compared to physical inactivity) (*OR* = 0.22, *95% CI*: 0.06–0.88, $P = 0.032$), and higher depressive factor scores (*OR* = 1.22, *95% CI*: 1.02–1.46, $P = 0.030$) were independently correlated with insomnia symptoms in CS patients (see **Table 3**).

Influencing factors associated with depressive symptoms in CS patients

The results found that vigorous physical activity (compared to physical inactivity) (*OR* = 0.19, *95% CI*: 0.07–0.48, $P = 0.001$), higher negative factor scores (*OR* = 1.10, *95% CI*: 1.02–1.19, $P = 0.019$) and depressive factor scores (*OR* = 1.52, *95% CI*: 1.21–1.91, $P < 0.001$) were related to depressive symptoms in CS patients (see **Table 4**).

Discussion

This study revealed that (1) insomnia and depressive symptoms in middle-aged and elderly CS inpatients were 22.9 and 71.5%. Patients with insomnia symptoms tend to be older, have lower levels of physical activity, higher rates of antipsychotic medication combination, higher FBG levels, and higher psychopathological symptoms such as positive, depressive factor scores, PANSS, ISI, and HAMD total scores. Patients with depressive symptoms tended to have fewer hospitalizations, lower levels of physical activity, higher positive, negative, cognitive, and depressive factor scores, PANSS, ISI, and HAMD total scores. (2) After controlling for potential confounders, the ISI total scores and HAMD total scores were still negatively correlated with physical activity levels. (3) Logistic regression analysis revealed that older age, higher depressive factor scores, and lower physical activity level were influential factors of insomnia symptoms in CS patients. In addition, vigorous physical activity (compared with physical inactivity) and higher negative and depressive factor scores were independently related to depressive symptoms in CS patients.

Our research noted that 22.9% of middle-aged and elderly CS patients had insomnia symptoms, which was more consistent with previous studies (7, 8). In addition, older age, higher

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TABLE 1 Comparison of clinical and biological indicators between insomnia group and non-insomnia group, depressive group, and non-depressive group.

Variables	Insomnia group (*n* = 41)	Non-insomnia group (*n* = 138)	X^2/F	*P*	Depressive group (*n* = 128)	Non-depressive group (*n* = 51)	X^2/F	*P*
Age (years, $\bar{x} \pm s$)	55.71 ± 7.49	52.94 ± 5.97	−2.449	**0.015**[a]	52 (49.25, 57)	52.45 ± 5.92	−1.385	0.166[b]
Gender								
Male (%)	21 (51.2)	78 (56.5)	0.360	0.549[c]	69 (53.9)	30 (58.8)	0.357	0.550[c]
Female (%)	20 (48.8)	60 (43.5)			59 (46.1)	21 (41.2)		
Education (years)	7.68 ± 3.73	8 (5, 11)	−0.454	0.650[b]	8 (5, 11)	8 (8, 11)	−1.154	0.249[b]
Onset age (years)	29.12 ± 8.67	29.32 ± 8.62	0.128	0.898[a]	29.41 ± 8.56	28.92 ± 8.78	−0.345	0.731[a]
Illness duration (years)	26.39 ± 11.64	23.75 ± 9.78	−1.449	0.149[a]	24.67 ± 10.31	23.57 ± 10.20	−0.648	0.518[a]
Number of admissions	5 (3, 8.5)	5 (3, 9)	−0.017	0.986[b]	5 (3, 8)	8.25 ± 5.82	−2.274	**0.023**[b]
BMI	24.03 ± 3.48	23.96 ± 3.90	−0.107	0.915[a]	24.05 ± 3.60	23.77 ± 4.27	−0.442	0.659[a]
Antipsychotic category (%)								
Monotherapy	9 (22.0)	67 (48.6)	9.154	**0.002**[c]	50 (39.1)	26 (51.0)	2.120	0.145[c]
Polypharmacy	32 (78.0)	71 (51.4)			78 (60.9)	25 (49.0)		
Hematological index								
FBG (mmol/L)	5.30 ± 1.09	4.80 (4.40, 5.40)	−2.008	**0.045**[b]	4.90 (4.50, 5.40)	5.20 ± 1.24	−0.005	0.996[b]
TC (mmol/L)	5.08 ± 2.03	4.69 (4.03, 5.50)	−0.757	0.449[b]	4.74 (4.09, 5.49)	4.86 ± 1.65	−0.413	0.680[b]
TG (mmol/L)	2.30 ± 1.75	1.82 (1.35, 2.59)	−0.326	0.744[b]	1.82 (1.36, 2.52)	1.96 (1.28, 2.93)	−0.272	0.786[b]
HDL-C (mmol/L)	1.06 ± 0.31	0.98 (0.87, 1.19)	−0.888	0.375[b]	1.04 ± 0.27	1.06 ± 0.26	0.422	0.674[a]
LDL-C (mmol/L)	2.54 ± 0.64	2.45 ± 0.65	−0.823	0.412[a]	2.48 ± 0.62	2.45 ± 0.73	−0.267	0.790[a]
Physical activity levels								
Physical inactivity	18 (43.9)	38 (27.6)	9.756	**0.008**[c]	48 (37.5)	8 (15.7)	12.846	**0.002**[c]
Moderate physical activity	20 (48.8)	58 (42.0)			56 (43.8)	22 (43.1)		
Vigorous physical activity	3 (7.3)	42 (30.4)			24 (18.7)	21 (41.2)		
PANSS								
Positive factor scores	11.8 ± 4.94	9 (6.75, 14)	−2.019	**0.044**[b]	10.5 (7, 15)	9.47 ± 5.40	−2.509	**0.012**[b]
Negative factor scores	19.66 ± 7.35	17.64 ± 6.61	−1.668	0.097[a]	19.33 ± 6.35	15.04 ± 7.05	−3.951	**<0.001**[a]
Cognitive factor scores	9.46 ± 3.23	9.12 ± 2.84	−0.666	0.506[a]	9.57 ± 2.77	8.25 ± 3.14	−2.761	**0.006**[a]
Depressive factor scores	7.90 ± 2.91	6 (4, 8)	−2.732	**0.006**[b]	7.48 ± 2.84	5.16 ± 1.90	−5.365	**<0.001**[a]
Excited factors scores	8.10 ± 3.27	6 (5, 9)	−1.538	0.124[b]	7 (5, 9)	6 (4, 10)	−1.500	0.134[b]
PANSS total scores	84.95 ± 24.45	76.73 ± 22.78	−1.995	**0.048**[a]	82.97 ± 21.57	67.69 ± 24.30	−4.125	**<0.001**[a]
ISI total scores	11.61 ± 3.29	1.82 ± 1.54	−26.596	**<0.001**[a]	3 (1, 8)	1 (0, 2)	−6.012	**<0.001**[b]
HAMD total scores	14.49 ± 4.31	8.91 ± 4.45	−7.100	**<0.001**[a]	12 (9, 15)	5 (3, 7)	−10.458	**<0.001**[b]
Chlorpromazine equivalent (mg/d)	468.23 ± 221.92	360 (227.5, 600)	−1.682	0.093[b]	428.02 ± 223.05	300 (240, 540)	−0.848	0.397[b]
Hypnotics prescription (yes,%)	9 (22.0)	30 (21.7)	0.001	0.977[c]	29 (22.7)	10 (19.6)	0.199	0.656[c]
Antidepressants prescription (yes,%)	2 (4.9)	10 (7.2)	0.283	0.594[c]	10 (7.8)	2 (3.9)	0.883	0.347[c]

[a]Independent samples *t*-test.
[b]Mann-Whitney *U*-test.
[c]Pearson chi-square. Bold value means $P < 0.05$.

TABLE 2 Correlation analysis of clinical and biological indicators with ISI total scores and HAMD total scores.

Variables	ISI total scores		HAMD total scores	
	r	*P*	*r*	*P*
Age (years)	0.206	**0.006**	0.145	0.052
Gender	0.084	0.262	0.050	0.504
Education (years)	−0.076	0.311	−0.147	0.050
Illness duration (years)	0.062	0.413	0.063	0.402
Number of admissions	−0.082	0.273	−0.177	**0.018**
BMI	0.060	0.427	−0.045	0.552
Monotherapy/ Polypharmacy	0.111	0.138	0.118	0.117
FBG (*mmol/L*)	0.169	**0.024**	0.048	0.527
TC(mmol/L)	0.098	0.191	0.013	0.862
TG (mmol/L)	−0.011	0.884	−0.049	0.514
HDL-C (mmol/L)	0.129	0.087	0.000	0.996
LDL-C (mmol/L)	0.109	0.149	−0.020	0.791
Physical activity levels	−0.247	**0.001**	−0.312	**<0.001**
Positive factor scores	0.234	**0.002**	0.203	0.006
Negative factor scores	0.181	**0.016**	0.316	**<0.001**
Cognitive factor scores	0.077	0.305	0.251	**0.001**
Excited factor scores	0.085	0.259	0.116	0.122
Depressive factor scores	0.261	**<0.001**	0.506	**<0.001**
PANSS total scores	0.167	**0.026**	0.314	**<0.001**
Chlorpromazine equivalent (mg/d)	0.117	0.118	0.112	0.134
Hypnotics prescription	0.000	0.996	0.058	0.440
Antidepressants prescription	−0.014	0.852	0.025	0.741

Bold value means $P < 0.05$.

TABLE 3 Demographic and clinical variables independently associated with insomnia symptoms by binary logistic regression analysis.

Variables	*B*	*P*	*OR*	*95% CI*
Age	0.072	**0.013**	1.07	1.02–1.14
FBG (mmol/L)	0.095	0.535	1.10	0.82–1.48
Physical activity levels (ref. physical inactivity)		0.098		
Moderate physical activity	−0.264	0.547	0.77	0.33–1.81
Vigorous physical activity	−1.517	**0.032**	0.22	0.06–0.88
Positive factor scores	0.071	0.297	1.07	0.94–1.23
Negative factor scores	0.038	0.421	1.04	0.95–1.14
Depressive factor scores	0.200	**0.030**	1.22	1.02–1.46
PANSS total scores	−0.025	0.241	0.98	0.94–1.02

Bold value means $P < 0.05$.

TABLE 4 Demographic and clinical variables independently associated with depressive symptoms by binary logistic regression analysis.

Variables	*B*	*P*	*OR*	*95% CI*
Number of admissions	−0.038	0.216	0.96	0.91–1.02
Physical activity levels(ref. physical inactivity)		0.002		
Moderate physical activity	−0.873	0.057	0.42	0.17–1.03
Vigorous physical activity	−1.679	**0.001**	0.19	0.07–0.48
Negative factor scores	0.096	**0.019**	1.10	1.02–1.19
Cognitive factor scores	0.002	0.983	1.00	0.82–1.22
Depressive factor scores	0.418	**<0.001**	1.52	1.21–1.91
PANSS	−0.017	0.344	0.98	0.95–1.02

Bold value means $P < 0.05$.

depressive factor scores, and lower physical activity were related factors of insomnia symptoms. Previous studies pointed out that compared to the general population, schizophrenic patients had less sleep, and the prevalence of sleep-related problems was significantly higher. In contrast, patients with sleep problems had significantly lower life satisfaction and happiness (34). In a study of outpatients with schizophrenia, a high prevalence of sleep disorders was strongly associated with older age, physical inactivity, and severe psychopathological symptoms (9).

Historical literature suggested that physical inactivity was strongly correlated with poorer psychosomatic health in patients with schizophrenia (18). In contrast, regular physical activity significantly improved patients' insomnia symptoms and their subjective sleep quality to a consistent degree (14, 35). A randomized controlled study in Germany noted that patients with regular physical activity had significantly better sleep quality than psychiatric patients with physical inactivity (36). Second, patients with adequate physical activity had lower rates of insomnia symptoms than those with physical inactivity (37, 38). In addition, schizophrenic patients who underwent weekly physical activity had less overall symptom severity and a higher quality of life than conventional treatment modalities without physical activity (39). A systematic review also indicated that higher levels of physical activity predicted a moderate increase in patients' motor activity (40) and that increased motor activity improved patients' insomnia symptoms and cognitive-related impairments (41) and was strongly associated with fewer negative symptoms and depressive symptoms (42). Furthermore, analysis of studies has shown that the beneficial effects of physical activity on sleep quality in psychiatric patients were attributed to its improvement of the overall health status of patients (43). The adjunctive use of physical activity interventions in schizophrenic populations has clear efficacy and no associated side effects (44).

In this study, we found that 71.5% of middle-aged and elderly CS patients had depressive symptoms, and depressive symptoms were independently correlated with severe psychopathological symptoms such as (negative, cognitive, depressive factor scores, PANSS total scores), fewer hospital admissions, and lower physical activity levels. In addition, vigorous physical activity (compared to physical inactivity) and higher negative or depressive factor scores were related to depressive symptoms in CS patients. A study noted that the prevalence of depressive symptoms as a usual comorbidity of schizophrenia in the elderly ranged from 44 to 75% (45). Two studies of older Chinese patients with schizophrenia noted the incidence of depressive symptoms of 48.5% (patients aged: above 65 years old) (46) and 32.8% (patients aged: above 60 years old) (47), both using the Geriatric Depression Scale (GDS) to evaluate depressive symptoms. In addition, a Tunisian study assessed by Depression Anxiety and Stress scales ($DASS_{-21}$) noted that older patients with schizophrenia (age: 66.9 ± 3.8 years old) had a prevalence of comorbid moderate-to-severe depressive symptoms of only about 25% (48). A French study that used the Center of Epidemiologic Studies Depression (CESD) scale to assess depressive symptoms in patients found that 78.1% presented with subsyndromes or syndromes depressive symptoms which were positively related to psychotic symptoms and were not associated with psychotropic medication use, or with the use of antidepressants (49). The results of our research were consistent with those of previous studies by using the $HAMD_{-17}$ scale to assess depressive symptoms. Previous studies have shown that weekly physical activity levels were negatively related to depressive symptoms in schizophrenic patients (50). Furthermore, evidence indicated that regular physical activity significantly reduced depressive symptoms in older adults (51), mainly because patients who engaged in regular physical activity had significantly reduced psychiatric symptoms and fewer physical complaints (52). Physical activity improved the prognosis of quality of schizophrenic patients, resulting in fewer accompanying depressive symptoms (53). According to a national survey in China, compared to population on physical activity in the last 1 year, people who sometimes or often participated in physical activity had significantly lower symptoms of depression and anxiety (24). Moreover, a systematic review indicated that compared to adults engaged in lower level of physical activity, MVPA was associated with better mental health and higher quality of life (25). The previous solid conclusions suggested that physical activity could be routinely incorporated into the regular treatment and daily care of patients with mental disorders because of its clear benefits (54).

Although current evidence pointed to a beneficial role of physical activity on psychopathological symptoms, insomnia, or depressive symptoms in CS patients, schizophrenic patients spend significantly less time physically active than the general population (10, 55), with only about one-fifth of patients meeting the minimum required level of physical activity (56). In contrast, physical inactivity associated with sedentary behavior in schizophrenic patients was closely related to a higher prevalence of depressive symptoms (57). Furthermore, due to their negative and depressive symptoms and lack of internal drive, patients with severe mental disorders obtained a lower level of physical activity (58). The relationship between depressive symptoms and physical activity levels is a two-way process (59). Moreover, the high rate of sleep disturbance in schizophrenic patients, resulting in reduced energy and deficits, was also associated with physical inactivity (60).

The Study on Global Ageing and Adult Health (SAGE) demonstrated that meeting physical activity guidelines (≥ 150 min of MVPA/week) was significantly associated with more happiness (61). A systematic review of 31 studies found that reducing sedentary behavior and increasing MVPA were significantly associated with better mental health and quality of life (25). Our study indicated that the prevalence of insomnia and depressive symptoms was high in CS patients. Furthermore, higher level of physical activity correlated to fewer insomnia and depressive symptoms. In clinical treatment, in addition to conventional pharmacotherapy or psychotherapy, physical activity can also be used to relieve the emotional symptoms of patients with mental disorders.

This study has the following limitations. First of all, this study was a cross-sectional study, which only explored the correlation between physical activity levels and insomnia and depressive symptoms of the enrolled patients, and could not be determined the causality. Second, the enrolled subjects were middle-aged and older adults, and the prevalence of depressive symptoms was slightly higher than that of the elderly reported in previous studies, which might be due to the differences in the age of the subjects or the assessment tools, which was also the innovation of this study. Third, although combined with electronic medical records as an objective reference, the physical activity level of the subjects in this study was assessed using subjective questions. Using objective methods like accelerometers will give stronger corroborating evidence than subjective description of the physical activity by patients. Moreover, the small sample size included in this study could lead to the bias of the study results, and further large-sample controlled studies are needed.

Conclusion

This study investigated the association between physical activity levels, insomnia, and depressive symptoms in middle-aged and elderly patients with CS. The results pointed out that lower physical activity levels were influential factors in comorbid insomnia and depressive symptoms in CS patients. Due to the advantages of physical activity on psychotic symptoms, we should enhance the use of physical activity as a regular adjunct in clinical treatment or psychiatric care to improve the psychosomatic health and quality of life of patients with psychiatric symptoms.

Data availability statement

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

Ethics statement

This study was reviewed and approved by the Biomedical Ethics Committee of Chaohu Hospital of Anhui Medical University (Grant no. 201805-kyxm-03). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZL, YZ, LS, JW, and HL collected and statistically analyzed the data and wrote the first draft. All authors revised and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Personalized individual-based exercise prescriptions are effective in treating depressive symptoms of college students during the COVID-19: A randomized controlled trial in China

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Background: The COVID-19 pandemic has seriously increased depression prevalence among the public, including Chinese college students. However, many exercise cannot be performed as usual under the stay-at-home order. This study was a 12-week three-arm randomized controlled trial using the intention-to-treat principle, aiming to explore and compare the feasibility and effect of individual-based personalized aerobic-exercise and resistance-training prescriptions on depressive symptoms in college students, and conclude with some recommendations for individual-based exercise prescriptions.

Methods: Eighty-six college students with depressive symptoms were randomized into aerobic-exercise (AE), resistance-training (RT), and wait-list control (WLC) groups. Participants in two experimental groups received 12-week personalized AE and RT prescriptions on their individual situations, respectively. No intervention was implemented on participants in the WLC group. Depressive symptoms and physical activity (PA) were measured by Zung Self-Rating Depression Scale (SDS) and International Physical Activity Questionnaire-Short Form (IPAQ-SF), respectively. All data were collected at the baseline, 4, 8, and 12 weeks, and 4-week post-intervention.

Results: At 12 weeks, 72.09% of depressive participants improved to "normal." Participants exhibited a statistical reduction in SDS in all 3 groups ($p < 0.05$) at 12 weeks compared to baseline. Follow-up assessments showed no significant increase in SDS at 4-week post-intervention compared to 12 weeks ($p > 0.05$). The independent *t*-test revealed significantly lower SDS in AE and RT group than in WLC group ($p_{AE} < 0.001$ and $p_{RT} < 0.05$) at 4, 8, and 12 weeks, and 4-week post-intervention. Furthermore, the PA of participants (including total PA and intensities) in both experimental groups represented a significant improvement at 4-week post-intervention compared to baseline ($p < 0.05$), while no differences were observed in the PA of participants in the WLC group ($p > 0.05$).

Conclusion: Personalized exercise prescriptions have good feasibility as they can increase adherence to intervention and reduce serious adverse events. Besides, individual-based personalized aerobic-exercise and resistance-training prescriptions result in a similar effect in relieving depressive symptoms and improving physical activity in college students. The individual-based exercise programs performed in 45- to 60- min with progressive moderate-to-vigorous intensity, 3 times/week for at least 12 weeks, may reduce depressive symptoms in college students during the COVID-19.

KEYWORDS

personalized medicine, aerobic exercise, resistance training, COVID-19, depressive symptoms, College student

1. Introduction

The ongoing pandemic of SARS-CoV-2 (COVID-19) has affected millions of people worldwide and further increased depression prevalence among the public (1, 2). The widespread and high mortality nature of COVID-19 has seriously affected individuals' mental health and well-being in China, including college students (3, 4). Higher levels of stress response during such special circumstance could lead to a higher prevalence and incidence of depression (5–7). Identified risk factors for depression during the COVID-19 pandemic included having family members being diagnosed, low level of social support, prior diagnosis of mental health disorders (5). A national survey in 33 universities found the pre-epidemic prevalence of depressive disorders was about 19.9% in China (7). A recent large-scale survey revealed that the prevalence of depression state was 21.1% among Chinese college students during the pandemic (5), and there is growing evidence showing that the COVID-19 pandemic has increased the incidence of depression by approximately 30% in Chinese college students (8, 9). Therefore, preventative strategies are needed to prevent the current trend of the increasing incidence rate of depression (10).

Recent studies found that the increased rate of depression in college students was correlated with decreased physical activity due to the COVID-19 stay-at-home order (11, 12). As there is a general belief that physical activity and exercise have positive effects on depression (13), many researches have confirmed that a bidirectional relationship exists between physical activity, exercise and depression (14, 15). Existing studies explained this relationship from biological and psychosocial mechanisms (16–18), including changes in neuroplasticity, the endocrine system, self-esteem, exercise satisfaction, etc. Exercise intervention has been proven to be effective in improving physical activity and relieving depressive symptoms comparable to common psychological and medical treatments (19). Specifically, long-term, group-based aerobic exercise intervention has been widely acknowledged as an effective approach to reducing depression in college students (20), but under the stay-at-home order, a home-based exercise program which can be performed individually is more preferred than group-based programs. Moreover, resistance training with own body weight and/or small household appliance-assisted resistance training are more convenient than aerobic training, most of which needs to be performed outdoors. In recent years, researchers gradually recognized the potential positive effects of resistance training on depression (21). Resistance training is an essential part of exercise and has numerous health benefits (22). However, few randomized controlled trials compared the effect of aerobic exercise and resistance training on the depressive symptoms of college students. Therefore, this study used aerobic exercise and resistance training as the exercise type. Besides, extroversion and neuroticism in personality traits can affect the susceptibility of individuals to depression (23, 24), so that influence the effect of exercise in treating depression. In order to ensure the effect of exercise on depressive symptoms can be clearly confirmed, controlling participants to have no significant differences in these two factors is necessary.

Compared to pre-designed exercise programs, personalized adjusted exercise prescriptions after the evidence-based program can decrease the rate of adverse and/or extreme responders (25). Furthermore, personalized exercise prescriptions paid more attention to personal preferences and willingness of participants. The content of this exercise is more targeted and flexible than that of the ordinary pre-designed exercise in terms of exercise types, intensity and progression. Evidence has shown that prescribing exercise as an alternative therapy can have a positive effect for multiple chronic diseases, including depression (26). However, researches on prescribing exercise programs for depression mainly focused on disease-induced depression in older adults, such as Parkinson (27) or stroke (28). Considering the high prevalence and incidence rate of depressive symptoms among college students during the COVID-19, personalized home-based individual exercise prescriptions are needed.

The main purpose of this 12-week randomized controlled trial was to compare the effect of personalized individual-based aerobic exercise and resistance training prescriptions on depressive symptoms and physical activity level. We also concluded with some recommendations for individual-based exercise prescriptions which can be performed at home for college students with depressive symptoms during the COVID-19.

We hypothesized that personalized individual-based exercise prescriptions are effective in treating depressive symptoms of college students during the COVID-19. Furthermore, personalized aerobic exercise and resistance training would achieve a similar improvement in depressive symptoms and physical activity.

2. Materials and methods

2.1. Study design and study participants

This is a 12-week, three-arm, single-blinded, parallel-group, randomized controlled trial (RCT) comparing the effect of aerobic exercise and resistance training prescriptions on depressive symptoms in college students. This study was approved by the Sport Science Experiment Ethics Committee of Beijing Sport University (No. 2020128H), from October 10, 2020, to August 01, 2021, and followed the ethical guidelines set out in the Declaration of Helsinki. The research was conducted at Beijing Sport University, China.

Participants were 157 depressive college students, recruited primarily through campus and online advertisements. The inclusion criteria were as follows: (1) being full-time undergraduate or graduate students aged between 18 and 25 years old; (2) standard score of Zung Self-Rating Depression Scale (SDS) $\geq$ 53, but not meeting the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) for depression (29); (3) being inactive (exercise less than 3 times/week and the total time not exceeding 150 min); (4) not participating in other interventions of similar type. The exclusion criteria included: (1) undergoing depression treatment during the prior year; (2) having a psychiatric history or somatic disease history; and (3) having diseases that may affect exercise. Following an online questionnaire (age, gender, SDS, and regular exercise habits) and telephone screening (DSM-IV, other participation interventions), potential participants attended an introductory meeting during which they would provide written informed consent and complete a medical history checklist. Finally, 86 participants (males: $n = 25$; females: $n = 61$) were enrolled in this trail.

2.2. Randomization

All eligible participants were randomly allocated to one of the three different groups (aerobic-exercise, resistance training, and wait-list control groups) at a 1:1:1 ratio through computer-based block randomization. The allocation sequence is automatically generated by applying a permuted block design with random blocks of varying length stratified by depressive symptoms and sex. As shown in **Figure 1**, participants in 2 experimental groups followed 12-week progressive aerobic exercise (AE) or resistance training (RT), respectively, and participants in the wait-list control (WLC) group would receive the exercise intervention after the completion of all assessments. In this research, raters are not allowed to know the randomization process of each participant and conduct intervention sessions, while therapists are not involved in assessing outcomes. Thus, the study strictly adhered to a single-blinded (rater-blinded) design by completely separating intervention and assessment.

2.3. Phase I: Exercise interventions prescribing

According to these previous studies, including aerobic-exercise and resistance-training ones (20, 27, 30–32), and *ACSM's Guidelines for Exercise Testing and Prescription, tenth edition* (33), both AE and RT were performed in 40- to 60-min supervised sessions (including 30- to 40- main exercise), 3 times per week for 12 weeks. The specific content of exercise programs was finally structured and revised based on previous evidence, suggestions of sports medicine experts and results of relevant pre-experiments.

2.3.1. Aerobic exercise prescribing

AE was performed as brisk walking and jogging using treadmills. Each AE session consisted of four parts: warm-up, main exercise, cool-down, and stretching (**Table 1**). The percentage of heart rate reserve (%HRR) was used to measure the exercise intensity. Average prior-intervention resting heart

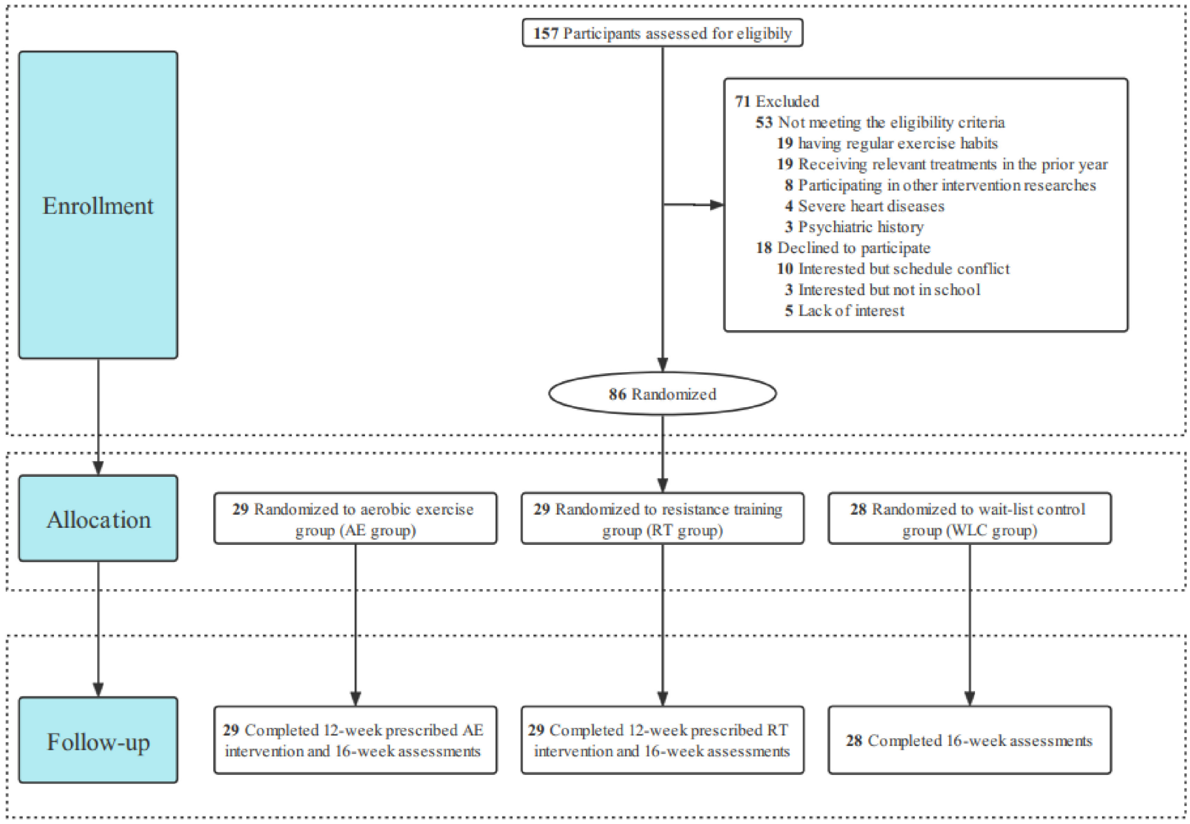

FIGURE 1
Flowchart.

rate (RHR) for 3 consecutive days, assessed by carotid artery measurement (10-s × 6-s), was used to compute %HRR. Following the principle of progressive physical activity, AE intensity was initially set at 50 ∼ 60% of HRR and gradually progressed up to 60 ∼ 75% and 75 ∼ 90% of HRR (33). To assess whether participants met the target exercise intensity, post-exercise heart rate (HR) was measured immediately after performing Main Exercise. The target post-exercise heart rate (PEHR) was calculated using the %HRR formula: %HRR = (HR exercise − RHR)/(HR max − RHR) × 100%, where HR max = 216.6 − 0.84 × age (34). In addition, participants self-reported the RPE using BORG SCALE (35) after the completion of the main exercise completed. After each AE session, participants were also instructed to measure RHR on the following day to determine if there was a fatigue accumulation (no fatigue accumulation: the increase of RHR < 5 beats/min) (36).

We used ratings of perceived exertion (RPE), HR and RH to assess whether participants had adapted to exercise intensity. Specifically, if an individual's PEHR and RPE were below the target range for 3 consecutive sessions, and there was no fatigue accumulation, the individual would progress to the next exercise intensity stage.

2.3.2. Resistance training prescribing

The RT was performed with dumbbells and elastic bands. Similar to the AE group, each RT session consisted of warm-up, main exercise, cool-down and stretching (**Table 2**). The finalized RT exercise consisted of six upper-limb (bicep curl, lateral raise, shoulder outward rotation, triceps kickback, and bent Y- and TW-shaped stretch) and six lower-limb plus core exercises (X-band walks, clam-like opening and closing, kneeling hip extension, dynamic glute bridge, and wall squat and plank). The initial intensity was set at 20 repetitions

TABLE 1 Stage I aerobic exercise program.

Program part	Specific content	Target RPE
Warm-up	3-min dynamic stretching and 3-min accelerating brisk walking.	9 ∼ 11
Main exercise	30-min continuous brisk walking or jogging at 50 ∼ 60% of HRR.	12 ∼ 14
Cool-down	4-min gradually decelerating walking combined with a breathing exercise.	9 ∼ 11
Stretching	Stretching exercises of all parts of the body for at least 10 min.	≤8

TABLE 2 Stage I resistance training program.

Program part	Specific contents and training loads	Target RPE
Warm-up	(1) 3-min dynamic stretching. (2) Alternately perform 15-s high leg lifts and 15-s jumping jacks. Three groups with a 10-s interval between each group.	9 ∼ 11
Main exercise	Alternately perform upper-limb and lower-limb plus core exercises. Three groups × 6 exercise actions × 20 repetitions. 30-s intervals between each action and 2-min intervals between each group.	12 ∼ 14
Cool-down	4-min gradually decelerating walking combined with a breathing exercise.	9 ∼ 11
Stretching	Stretching exercises of training parts for at least 10 min.	≤8

maximum (RM). In order to compare the intensity of 2 experimental groups, the RPE was also used for participants in RT group to assess the post-exercise fatigue. To avoid muscle fatigue accumulation, participants were instructed to alternate between upper-limb and lower-limb plus core exercises during the intervention. The total duration of each repetition, which included both concentric and eccentric phases, was approximately 2-4 s. In addition, participants were instructed to exhale on the concentric phase and inhale on the eccentric phase.

Prior to intervention implementation, the researchers conducted a pre-experiment to determine the optimal exercise modalities and training load of the RT session (see **Supplementary Appendix** for the procedure of pre-experiments for resistance training prescribing). According to the results of the pre-experiment, we can find the relatively weak aspects of participants and increase targeted resistance exercises.

As mentioned above, the RT was progressive in terms of training load or repetitions. If a participant could complete the standard action of the last group for more than two repetitions in two consecutive sessions (37), the RPE remained unchanged or even decreased and there was no exercise fatigue, the participant would progress to the next stage. The criterion of fatigue accumulation was the same as that of AT group.

2.4. Phase II: Intervention implementation

For 12 weeks, participants in AE group received a 30-min session of aerobic exercise three times per week, while participants in RT group received resistance training at the same time and frequency. To ensure intervention fidelity, participants from AE and RT groups were invited for in-person supervised exercise sessions. Participants in WLC group did not receive any exercise intervention.

2.4.1. Intervention monitoring

During the first week, participants completed the training session under the demonstration and guidance of the professionals to avoid incorrect action modes. They were also asked to self-report their RPE and measure their post-exercise HR. Professionals would adapt their exercise prescription to achieve the pre-setting target HR and RPE according to participants' feedback. If there was a conflict between the HR and RPE, RPE was used. After prescribing exercise programs, participants should complete each session independently. In order to simulate the situation of independent home-based exercise during the COVID-19, the researchers only provided necessary exercise guidance to participants. Each exercise session had a maximum of two participants.

To monitor the exercise adaptability of each participant and progress the exercise stage, training logs were used during the intervention. Participants in both experimental groups were required to fill in the training log, including HR and RPE after the main exercises and RHR in the next morning. In addition, researchers would measure the post-exercise HR in the last session of each week. Participants with at least an 80% attendance rate were included in the final sample.

2.5. Outcome measures

The primary outcome, depressive symptoms of participants, was measured using the Zung Self-Rating Depression Scale (SDS), which is a self-report questionnaire. The SDS has been widely adopted in clinical research and has reported good reliability and validity in various populations (38–42), including college students (9, 43, 44). This scale consists of 20 items, of which 10 are reverse scoring. Each item is rated on a 4-point scale. The standard score of the SDS ranges from 25 to 100, and a high score represents a high level of depressive symptoms. In the Chinese norm, a score from 53 to 62 indicates mild depression, while a score from 63 to 72 indicates moderate depression and more than 73 indicates severe depression. In this study, the Cronbach's alpha is 0.829.

Secondary outcomes included (1) sensitivity to intervention and the possibility of exercise adherence as measured by the neuroticism and extraversion subgroups of Neuroticism Extraversion Openness Five Factor Inventory (NEO-FFI) (45, 46); (2) physical activity (PA) as measured by the International Physical Activity Questionnaire-Short Form (IPAQ-SF) (47–49).

The SDS was administered at each time point during the study: baseline (T_0), 4 weeks (T_1), 8 weeks (T_2), 12 weeks (immediately after the intervention) (T_3), and 16 weeks (4 weeks post-intervention) (T_4). The IPAQ-SF was assessed at T_0 and T_4, while the NEO-FFI was only assessed at T_0.

2.6. Sample size

The prior sample size for this research was calculated by G*Power version 3.1.9.7 (*F*-tests; ANOVA, Repeated measures, within-between interaction) using the following equation:

$$\sqrt{N\sum_{i=1}^{k} c_i^2/n_i} = \frac{\left|\sum_{i=1}^{k} \mu_i c_i\right|}{f \times \sigma}$$

where N, n_i denote total sample size and sample size in group i, respectively, and k is the number of levels, f is the effect size, σ and c represents the standard deviation and weights.

According to a meta-analysis on the effect of aerobic exercise on depression, the effect size of 0.66 was used (32). The other meta-analysis showed the effect size of 0.42 on the effect of resistance training on depression (21). After averaging the 2 effect sizes and assuming an attrition rate of 25%, a sample size of 18 participants with 6 participants per group was required to provide a three-arm trial with 95% power to detect an effect size of at least 0.54 at a 5% level of significance. In this study, a total of 86 samples with depressive symptoms were finally recruited in Beijing Sport University, China.

2.7. Statistical analysis

Descriptive statistics were used to summarize the demographics, physical activity and depressive symptoms of the participants at each time point. According to the data type, all values are expressed as mean ± SD, quartile or constituent ratio. The analysis of variance (ANOVA) and Chi-square (χ^2) test were used to analyze the differences of baseline characteristics, personality traits, PA and depressive symptoms. All participants were examined at each time point for changes in depressive symptoms. The intention-to-treat procedure was used in this research. A two-way analysis of variance with repeated measures (time point as within-subject factor and intervention group as a between-subject factor) was run to examine whether depressive symptoms changed over time in participants across experimental and control groups. A partial eta-squared (η_p^2) value was calculated to estimate effect size. Besides, differences in PA between 3 groups from T_0 to T_4 were tested by ANOVA, and differences between different time points in three groups were tested by paired *t*-test. The statistical results would be corrected by the Greenhouse—Geisser method for the degree of freedom and *p*-value. To confirm the data validation, two raters separately input the data and checked it jointly. Statistical analysis was performed using SPSS statistical software, version 18.0 (IBM Corporation). All statistical tests were 2-tailed with a 5% level of statistical significance.

3. Results

3.1. Baseline characteristics of participants

Experimental and control groups were similar in baseline characteristics (Table 3). The mean (SD) age of participants was 21.20 (2.10) years, and 61 of 86 were females (70.9%). For educational level, masters and doctors were seen in 27 and 3 participants (31.4% and 3.5%), and most participants were undergraduates (65.1%). Of the participants, the mean (SD) of PA was 1370.65 (1410.02) and most individuals (33.72%) preferred to walking. The means (SD) of neuroticism and extraversion scores were 38.19 (7.18) and 24.43 (4.47). For depressive symptoms, the mean (SD) of SDS was 62.48 (6.62). No significant heterogeneity of demographic and clinical baseline characteristics among participants of 3 groups (Table 4, p: 0.061 ∼ 0.957 > 0.05).

3.2. The implementation of exercise intervention

Of 157 potential participants screened, 53 participants did not meet the eligibility criteria and 18 declined to participate. The enrollment rate of this study was 54.78% (Figure 1). Of 86 participants randomized, 2 experimental groups were randomly assigned to 29 participants and the WLC group was assigned to 28. Participants randomized to 2 experimental groups were asked to attend at least 29 sessions (total of 36), while participants randomized to the control group did not attend any exercise interventions. After completing all exercise interventions (Table 4), the mean (SD) attendance rates were 92.58% (6.61%) for all experimental participants, 93.00% (6.24%) for participants in AE group and 92.15% (7.04%) for participants in RT group. Besides, 9 of 29 participants (31.03%) in each group attended all sessions. All the 86 participants completed 16-week measurements with none dropout.

For experimental groups, the average duration of stage I was 3.24 (0.95) weeks for AE group and 3.93 (1.00) weeks for RT group. The independent *t*-test showed a significant difference of durations of stage I between groups. Stage II took the longest durations in both AE [3.90 (1.52) weeks] and RT groups [3.34 (2.54) weeks].

During the intervention, 5 participants (8.47%) of experimental groups self-reported mild knee or ankle pain with exercises (1 from AE and 4 from RT), which resolved with the use of a thick towel or reduce speed. Another common adverse event in the intervention was delayed muscle soreness. Thirty-seven participants (62.71%) reported this event after the first two sessions (17 from AE and 20 from RT). The rates of delayed muscle soreness decreased to 6.78% (1 from AE and 3

TABLE 3 Baseline characteristics of the participants ($N = 86$).

Characteristic	All ($N = 86$)	Participants, no. (%)			*P*-value
		AE group ($n = 29$)	RT group ($n = 29$)	WLC group ($n = 28$)	
Age, years	21.20 (2.10)	20.72 (2.05)	21.66 (1.97)	21.21 (2.25)	0.243
Sex					
Male	25 (29.1)	8 (27.6)	9 (31.0)	8 (28.6)	0.957
Female	61 (70.9)	21 (72.4)	20 (69.0)	20 (71.4)	
Educational level					
Undergraduates	56 (65.1)	21 (72.4)	17 (58.6)	18 (64.3)	0.859
Masters	27 (31.4)	7 (24.1)	11 (37.9)	9 (32.1)	
Doctors	3 (3.5)	1 (3.4)	1 (3.4)	1 (3.6)	
Physical activity, MET-min/week					
Total	1370.65 (1410.02)	1405.93 (1280.64)	1591.31 (1623.99)	1105.55 (1302.56)	0.429
Walking	561.58 (864.44)	687.31 (824.34)	518.90 (857.32)	475.55 (926.80)	0.624
Moderate intensity	321.16 (534.84)	227.59 (418.31)	374.48 (423.49)	362.86 (720.30)	0.516
Vigorous intensity	487.91 (814.18)	491.03 (704.83)	697.93 (1097.25)	269.14 (474.54)	0.136
NEO-FFI					
Neuroticism scores	38.19 (7.18)	38.55 (7.73)	36.59 (7.49)	39.61 (5.94)	0.320
Extraversion scores	24.43 (4.47)	25.38 (3.10)	24.96 (4.47)	22.61 (5.47)	0.061
Depression state-SDS	62.67 (6.43)	62.55 (6.44)	64.48 (5.72)	60.93 (6.81)	0.112

For continuous variables, an analysis of variance was used, and for categorical variables, a χ^2 test was used to compare differences between three groups.
Data are presented as mean (SD).

TABLE 4 The implementation of exercise intervention of the participants.

Variables	AE group ($n = 29$)	RT group ($n = 29$)	WLC group ($n = 28$)	*P*-value
Duration of stages, weeks				
Stage I	3.24 (0.95)	3.93 (1.00)	–	0.009**
Stage II	4.86 (1.16)	4.66 (0.90)	–	0.450
Stage III	3.90 (1.52)	3.34 (1.62)	–	0.191
Attendance of exercise interventions, times/%	33.48 (2.25)/93.00 (6.24)	33.17 (2.54)/92.15 (7.04)	–	0.624

For all the variables, an independent *t*-test was used.
**Represents a significant difference between AE group and RT group in time point, $^{**}p < 0.01$.
Data are presented as mean (SD).

from RT) after 2 weeks and 1.69% (1 from RT) after stage I. No other serious adverse events were reported.

3.3. Efficacy of interventions on depressive symptoms and PA in college students

The outcome of analysis of SDS was presented in Table 5 and Figure 2. The 3 × 5 RM-ANOVA revealed a significant time × group interaction for SDS [$F(5.593,151.012) = 9.569$, $p < 0.001$, $\eta_p^2 = 0.262$]. Both time and group showed significant main effects for SDS [time: $F(2.331,62.943) = 104.387$, $p < 0.001$, $\eta_p^2 = 0.795$; group: $F(2,54) = 29.270$, $p < 0.001$, $\eta_p^2 = 0.520$]. The contribution of each factor to SDS was that time > group > interaction [$\eta^2_{ptime} > \eta^2_{pgroup} > \eta^2_{pinteraction}$). In experimental groups, followed-up analysis for simple effects showed that compared with the previous point, SDS was significantly lower following AE and RT interventions ($p_{AE} < 0.05$, $p_{RT} < 0.05$). Furthermore, no significant difference was found in SDS at T_4 compared to T_3. In WLC group, simple effects analysis revealed that the SDS was significantly decreased at T_1 and T_3 compared to the previous time-point ($p < 0.05$). Besides, significant differences were found in SDS of AE and RT group compared with WCL group ($p_{AE} < 0.001$, $p_{RT} < 0.05$) at all time-points, but no significant differences were revealed between AE and RT group during the study ($p > 0.05$).

Table 5 also revealed the outcome of pairwise comparison of PA. A paired *t*-test to compare PA of participants revealed that the total of PA and different intensities ($p < 0.05$), except

TABLE 5 Comparison of within-group changes in outcomes variables (continuous) for AE, RT, and WLC groups.

Variables	AE group		RT group		WLC group	
	Mean (SD)	*P*-value	Mean (SD)	*P*-value	Mean (SD)	*P*-value
SDS						
Baseline (T_0)	62.55 (6.44)		64.48 (5.72)		60.93 (6.81)	
4 weeks (T_1)	49.38 (8.08)	0.000***	52.45 (8.89)	0.000***	57.36 (5.83)	0.016*
8 weeks (T_2)	45.90 (9.73)	0.046*	48.29 (9.22)	0.003**	55.61 (7.59)	0.152
12 weeks (T_3)	41.72 (7.22)	0.002**	45.54 (9.39)	0.016*	52.79 (6.87)	0.028*
16 weeks (T_4)	41.97 (6.65)	0.812	43.82 (9.62)	0.125	51.04 (7.57)	0.070
IPAQ – PA (total), MET-min/week						
Baseline (T_0)	1402.93 (1280.64)	0.001**	1591.31 (1623.99)	0.001**	1146.50 (1308.88)	0.625
16 weeks (T_4)	3119.17 (2343.46)		2554.02 (2057.66)		1061.52 (1155.04)	
IPAQ – walking, MET-min/week						
Baseline (T_0)	687.31 (824.34)	0.087	518.90 (857.32)	0.186	493.17 (939.67)	0.232
16 weeks (T_4)	1128.83 (1107.50)		762.98 (983.12)		631.89 (871.11)	
IPAQ – moderate, MET-min/week						
Baseline (T_0)	227.59 (418.31)	0.017*	374.48 (423.49)	0.014*	376.30 (730.44)	0.066
16 weeks (T_4)	713.10 (1057.39)		618.62 (651.46)		240.00 (674.46)	
IPAQ – vigorous, MET-min/week						
Baseline (T_0)	491.03 (704.83)	0.005**	697.93 (1097.25)	0.047*	277.04 (480.63)	0.430
16 weeks (T_4)	1277.24 (1450.51)		1172.41 (1591.84)		189.63 (371.37)	

*Represents a significant difference between this point and the previous point.
Data are presented as mean (SD).
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

walking in 2 experimental groups increased significantly at T_4 compared to baseline: ($p > 0.05$). However, no significant increase of PA was showed in WLC group ($p > 0.05$).

As shown in **Figure 2**, the independent *t*-test to compare PA of different groups at T_0 and T_4 revealed that there was no significant difference among groups at T_0 ($p > 0.05$), while significant differences were found in the total and vigorous-intensity of PA between the WLC group and two experimental groups at T_4 ($p < 0.01$). There was also a significant difference of moderate-intensity of PA between RT group and WLC group ($p < 0.05$). No significant difference between AE group and RT group was found at both T_0 and T_4 ($p > 0.05$).

At baseline, moderate depression was seen in 27 of 87 participants (31.4%), and most had mild depression (53, 61.63%). The depression level of participants relieved over time, and 62 participants (72.09%) showed no depressive symptoms after the intervention (AE: 26, 89.66%; RT: 21, 72.41%; and WLC: 15, 53.57%). Furthermore, the rates of individuals with no depressive symptoms in WLC group continued to increase during the 4 weeks after intervention, while the rates of other experimental groups remained unchanged (WLC: 19, 67.86%). The Chi-test revealed that there was a significant difference of rates of moderate depression among three groups at different time points ($\chi^2 = 20.880$, $p < 0.01$) (**Table 6**).

4. Discussion

We found a statistically and clinically significant reduction in depressive symptoms and improvement in PA among all groups. AE and RT prescriptions achieved an effective reduction in depressive symptoms. Our findings also complemented previous evidence by showing that prescribed AE and RT had a similar effect on depressive symptoms in college students. Prescribed exercise programs can be effectively used on relieving depressive symptoms in college students. For PA, our results showed that AE and RT prescriptions were effective to improve PA, including moderate-, vigorous-intensity of PA and total PA.

We achieved a higher program adherence rate than previous studies as all participants completed the 12-week intervention and relevant measurements (27, 50). There is evidence showing a higher adherence rate was associated with a higher level of program satisfaction (51), indicating that our program was not only effective but also satisfying. A strength of our study is that we included multiple individual testing to ensure participants' physical states and subjective feelings were closely monitored and well maintained. As suggested by Wackerhage (25), such testing can avoid adverse events and improve exercise satisfaction.

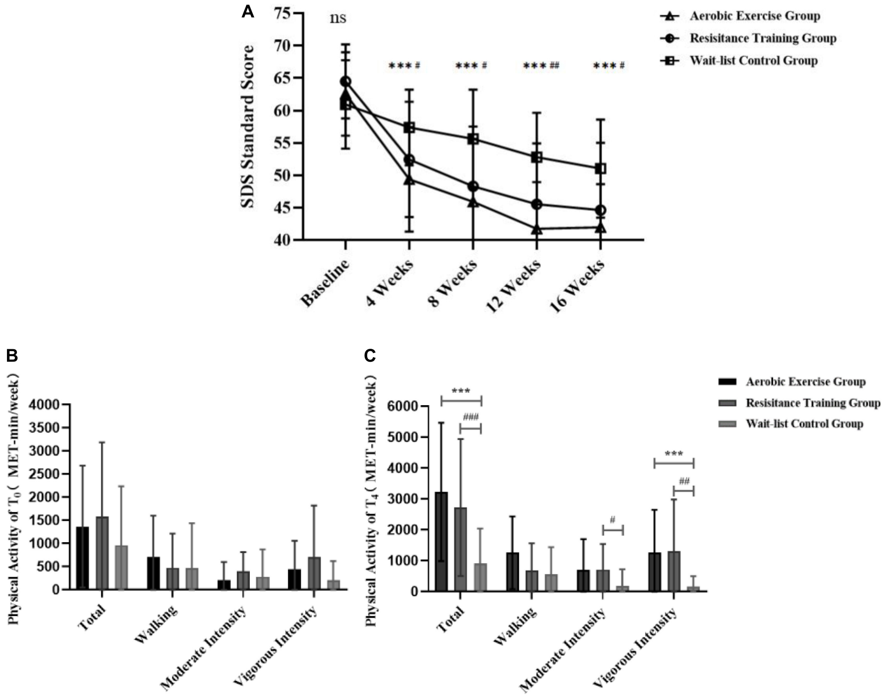

FIGURE 2
Comparison of between-group differences in depression state and physical activity (continuous) for AE, RT, and WLC groups. **(A)** The between-group differences for SDS standard scores. **(B)** Baseline PA differences by intensity. **(C)** PA intensity differences 4 weeks after intervention. ns Represents no significant difference among the three groups in time point. ***Represents a significant difference between the AE group and the WLC group in time point. #Represents a significant difference between the RT group and the WLC group in time point. $^{***}p < 0.001$; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$.

The results of our study found the prescribed aerobic exercise and resistance training have positive effects to relieve depressive symptoms of college students. These findings on the effects of exercise interventions in relieving depressive symptoms are consistent with the conclusion of various previous RCT researches (31, 52, 53) and systematic reviews (20, 21, 32). Besides, such positive effect was well-maintained at 4-week post-intervention in our study, which is consistent with previous studies (54, 55), so it is possible that prescribed exercise continuously contributed to the participants' abilities to deal with depressive stress. For human survival and adaptation, depressive symptoms are very complex psychological activities, and would be affected by many factors, which can be attributed to individual stress. Previous researches believed the specific impact of stress depended on the method individuals deal with it, and the stress itself didn't be distinguished between positive and negative ones (56, 57). As Jackson has confirmed, appropriate stress inoculation training can trigger the (over)compensation mechanism of brain, so that the brain can be more well-prepared to deal with following depressive stress (58). Considering the effect of exercise, we believed that both aerobic exercise and resistance training at a certain intensity can be regarded as one form of the stress inoculation, but this hypothesis needs to be verified by further researches. Many other researchers revealed that through exercise intervention, depression can be relieved due to other changes of physiological, psychological and sociological mechanisms (56, 59). Furthermore, future research with a longer follow-up period is needed to ensure the long-lasting effect of personalized exercise prescription on depressive symptoms.

Previous studies found that depression is associated with physical activity of individuals, especially moderate intensity of PA (60). In this study, prescribed aerobic exercise and resistance training both has positive effects in increasing PA (including the amount and intensity) of college students, and such positive effect was well-maintained at 4-week post-intervention. This result is familiar with the *trans*-theoretical model of stage of change (61)— the process of exercise intervention is the period of action, which is more likely to promote individuals to enter the period of maintenance, especially intervention more than 6 months. Moreover, exercise could enable college students to get more satisfaction and enjoyment, and this process would promote them to exercise regularly (62). As many researchers suggested a correlation between low levels of physical activity and symptoms of depression (63–65), improvement in PA of participants from both exercise groups also proved that the potential mediating role of PA on reliving depressive symptoms. To relieve depressive symptoms in college students,

TABLE 6 Numbers of participants with different depression levels in AE, RT, and WLC groups.

Depression state	Participants, no. (%)				χ^2, *P*-Value
	All (*N* = 86)	AE group (*n* = 29)	RT group (*n* = 29)	WLC group (*n* = 28)	
Normal					
Baseline (T_0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1.220 0.976
12 weeks (T_3)	62 (72.09)	26 (89.66)	21 (72.41)	15 (53.57)	
16 weeks (T_4)	67 (77.91)	26 (89.66)	21 (72.41)	19 (67.86)	
Mild					
Baseline (T_0)	53 (61.63)	18 (62.07)	13 (44.83)	22 (78.57)	6.495 0.592
12 weeks (T_3)	19 (22.09)	3 (10.34)	7 (24.14)	9 (32.14)	
16 weeks (T_4)	14 (16.28)	3 (10.34)	7 (24.14)	5 (17.86)	
Moderate					
Baseline (T_0)	27 (31.40)	9 (31.03)	14 (48.28)	4 (14.29)	20.880 0.007**
12 weeks (T_3)	5 (5.81)	0 (0.00)	1 (3.45)	4 (14.29)	
16 weeks (T_4)	5 (5.81)	0 (0.00)	1 (3.45)	4 (14.29)	
Severe					
Baseline (T_0)	6 (6.98)	2 (6.90)	2 (6.90)	2 (7.14)	–
12 weeks (T_3)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
16 weeks (T_4)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	

**Represents a significant difference of numbers of participants of the same depression state at different time-points among AE, RT, and WLC groups.
$^{**}p < 0.01$.
Data are presented as mean (SD).

we recommend individual-based AE and RT programs, three sessions per week for at least 12 weeks, lasting 45- to 60-min per session. Individuals can self-choose exercise types, such as brisk walking, jogging for aerobic exercise and/or resistance training with household simple exercise equipment. For aerobic exercise, heart rate and RPE can be used to monitor the intensity, and the recommended initial intensity was 50 ∼ 60% HRR and gradually processed to 60 ∼ 90% HRR. RM and RPE can be used to monitor the intensity of resistance training. For college students with no regular exercise habits, some easy-to-learn exercises are recommended. Table 2 presents recommended exercise modes and the corresponding weight of dumbbells and elastic bands. According to the implementation of interventions, the duration of stage I, for both AE and RT programs, could be 4 weeks, and 5 weeks of stage II. Additionally, warm-up, cool-down and stretching exercises are needed in each session. Furthermore, according to the intervention mode and results of this study, we can infer that home-based AE and RT prescriptions are effective in treating depressive symptoms of college students during the COVID-19, but the specific effect still needs further research to confirm.

The strengths of this study include a randomized controlled trial design with personalized exercise program prescribing and training log design to ensure the involvement and adherence of participants, the adaption and safety of exercise intervention for experimental groups, and multiple follow-up time points to elucidate the residual effects of different interventions. However, this research inevitably had limitations which must be considered in interpreting the results. First, expectation bias may exist in this study due to awareness of the treatment allocation. Second, the depressive symptoms was evaluated only by self-reported scales without other objective indexes, such as electroencephalography (EEG) or blood index, to support and analyze the results. Third, this study only simulated the state of home-based exercise, but did not analyze the method that participants can use to keep the exercise routine when they do it themselves. Furthermore, there could be other confounders and covariates, such as unequal numbers of participants of genders and educational levels, that were not included in this study model.

5. Conclusion

Among college students with depressive symptoms, personalized aerobic-exercise and resistance-training prescriptions resulted in an effective and similar reduction in depressive symptoms and improvement in physical activity.

Exercise types did not play a significant role in their effect on depressive symptoms. Our findings suggest that personalized exercise prescriptions have good feasibility in relieving depressive symptoms in college students. We concluded with recommendations for home-based exercise programs for college students during the COVID-19 which can be adapted by future investigators and practitioners.

Data availability statement

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

Ethics statement

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

Author contributions

YZ and WW designed the study, analyzed the data, and wrote the initial manuscript. FG, BC, CH, and WY recruited the participants and supervised the exercise. HR and MW designed the exercise programs and revised the manuscript critically. All authors participated in drafting the manuscript, read, and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Acute electroencephalography responses during incremental exercise in those with mental illness

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Introduction: Depression is a mental illness (MI) characterized by a process of behavioral withdrawal whereby people experience symptoms including sadness, anhedonia, demotivation, sleep and appetite change, and cognitive disturbances. Frontal alpha asymmetry (FAA) differs in depressive populations and may signify affective responses, with left FAA corresponding to such aversive or withdrawal type behavior. On an acute basis, exercise is known to positively alter affect and improve depressive symptoms and this has been measured in conjunction with left FAA as a post-exercise measure. It is not yet known if these affective electroencephalography (EEG) responses to exercise occur during exercise or only after completion of an exercise bout. This study therefore aimed to measure EEG responses during exercise in those with MI.

Materials and methods: Thirty one participants were allocated into one of two groups; those undergoing management of a mental health disorder (MI; $N = 19$); or reporting as apparently healthy (AH; $N = 12$). EEG responses at rest and during incremental exercise were measured at the prefrontal cortex (PFC) and the motor cortex (MC). EEG data at PFC left side (F3, F7, FP1), PFC right side (F4, F8, FP2), and MC (C3, Cz, and C4) were analyzed in line with oxygen uptake at rest, 50% of ventilatory threshold (VT) (50% VT) and at VT.

Results: EEG responses increased with exercise across intensity from rest to 50% VT and to VT in all bandwidths ($P < 0.05$) for both groups. There were no significant differences in alpha activity responses between groups. Gamma responses in the PFC were significantly higher in MI on the left side compared to AH ($P < 0.05$).

Conclusion: Alpha activity responses were no different between groups at rest or any exercise intensity. Therefore the alpha activity response previously shown post-exercise was not found during exercise. However, increased PFC gamma activity in the MI group adds to the body of evidence showing increased gamma can differentiate between those with and without MI.

KEYWORDS
mental illness, EEG, exercise, gamma, frontal alpha asymmetry

Introduction

Depression affects 300 million people worldwide and is the leading cause of disability in populations aged between 15 and 44 years (1). Depression is a mental illness (MI) characterized by a process of behavioral withdrawal whereby people experience symptoms which include sadness, anhedonia, demotivation, sleep and appetite change as well as cognitive disturbances and suicidality in extreme cases (2, 3). The diagnosis of depression can be problematic with the use of subjective questionnaires and symptomology that overlaps with other psychiatric diagnoses, making finding a biomarker for depression an important pursuit. The availability of an objective diagnostic tool could aid in providing more reliable distinction between depression and other mental disorders with overlapping symptoms, ultimately providing better prognosis with earlier treatment.

As a low cost, easy to administer and non-invasive technique, scalp electroencephalography (EEG) has been investigated as a diagnostic tool in depression (4–6). Patients with depression exhibit dysregulated, elevated oscillatory activity, specifically in the alpha frequency band (8–12 Hz) in the prefrontal cortex (PFC) (7, 8). There is currently no clear consensus regarding the functional meaning of alpha wave activity (9), having been shown to be present in cognitive (10), sensorimotor (11), emotional (12), and physiological aspects (13), although historically being an inverse marker of cortical activation (14). These alpha oscillations are also detected by fMRI and have been shown to be positively correlated in a cingulo-insular-thalamic network (15) suggesting alpha synchronization plays a key global role in top down network control (16) and that it is a marker of underlying neural processes (12). Dysfunctional neural processes occurring with depression include the disruption of the serotonin system and increases in alpha activity may reflect low arousal associated with low serotonergic activity (17) which may be related to mitochondrial dysfunction (18). In addition to their potential diagnostic utility, EEG-based biomarkers also have predictive value for patient responses to a variety of depression treatment options (19, 20). This provides scope for the development of personalized medicine in the form of individually tailored treatment options for patients with depression (21). Specifically, alpha power has been shown to reduce following transcranial alternating current stimulation as a therapeutic intervention for treatment of major depressive disorder (22, 23) and to be a predictor of responders to anti-depressant medications (17).

Frontal alpha asymmetry (FAA) is a commonly studied depression biomarker which measures the relative alpha band activity between the brain hemispheres at the frontal electrodes. According to the approach-withdrawal hypothesis, different affective responses are reflected by activity in different sides of the brain. Left sided frontal brain activity is related to approach type behaviors, whereas right sided frontal brain activity (higher alpha activity on the left-hand side) is related to withdrawal behaviors such as those experienced in depression (24, 25). It is the balance in the activation of these systems which is assumed to be reflected in FAA EEG activity. FAA has indeed been reported to be different in those with depression, with depressed patients having higher alpha power in the left hemisphere indicative of withdrawal behaviors (4, 6, 8, 25–27). The presence of abnormal frontal and alpha asymmetries in depressed patients supports the view that they represent state-independent markers of vulnerability to negative affect and depressive disorders (28). Depression symptoms such as anhedonia have also been shown to account for a significant portion of the relationship between FAA and lifetime major depressive disorder (25). Additionally, a decrease in right sided frontal activity has been shown to relate to a decrease in negative affect (29), while an increase in left PFC activity (i.e., less alpha activity) has been associated with positive affect (30).

A positive affective state and improvement in depressive symptoms are well documented following exercise in healthy individuals (31–33) and clinical populations with depression (34, 35). Exercise has been shown to improve symptoms of depression as measured by several validated psychological screening tools (36, 37). This change in affect has been found following a range of exercise intensities which includes low intensity [15–39% oxygen uptake reserve (%VO_2R)], and short durations, from 7 to 35 min. (33). Research examining the change in EEG response to exercise in relation to mood has reported a change in affect post-exercise in conjunction with left FAA or changes in alpha power spectral density (38–40). These EEG responses suggest a link between EEG asymmetry and affective responses to exercise and may explain the mechanism for the positive affect associated with improved mood after an exercise bout.

While there is evidence examining the EEG response following an exercise bout, the EEG responses during exercise in those with MI has not yet been elucidated. There are few studies examining EEG responses during exercise and none yet examining responses in those with MI. Furthermore, it is not yet known if these EEG responses to exercise occur during exercise or only after completion of the exercise bout. One proposed theory, the Transient Hypofrontality theory suggests that changes in brain activity responses during exercise are representative of changes in the PFC which promote the anxiolytic effects of exercise (41). Further work has also shown changes in brain responses to incremental exercise that align with changes in affective responses (42), with higher intensities yielding lower affective responses. This study therefore aimed to measure EEG responses in both the PFC and motor cortex (MC) during exercise in those with MI and healthy controls, utilizing an incremental test to exhaustion which encompasses all exercise intensities. Our hypotheses were that the EEG response at rest would be different between groups with those with MI showing FAA with higher alpha activity in the left PFC. EEG changes during exercise were hypothesized to be similar between groups due to the affective responses previously attributed to exercise, with an increased left sided activity (less alpha activity) indicative of positive affective responses. This study was written in line with the STROBE guidelines for case-control studies (43).

Materials and methods

Participants

For this case-control experiment, the study cohort included 31 participants allocated into one of two groups; those undergoing management of a medically diagnosed mental health disorder (MI; $N = 19$); or reporting as apparently healthy (AH; $N = 12$). Participants were male and female, between 18 and 62 years of age, non-smokers, free from thyroid disease, stroke, head trauma, epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease and other neuromotor disorders or psychotic symptoms and performing <150 min per week of moderate intensity exercise or equivalent. For participants in the MI group who were receiving medication as treatment, a stable dose for 6 months was required with no comorbidities associated with psychiatric illness. Prior to the commencement of the study, all participants were required to provide written and verbal consent following an outline of all procedures and measures. This study conformed to the Declaration of Helsinki and was approved by the Research in Human Ethics Committee at Charles Sturt University.

Prior to commencing exercise, participants were required to undergo a medical screening by their general practitioner (GP) and be deemed eligible for safe participation in the exercise study. Participants completed an adult pre-exercise screening system (APSS, Exercise and Sports Science Australia) and a broader health history questionnaire before commencing testing. Participants also completed the Kessler 10 Psychological Distress Scale (K-10) (44) and the Depression Anxiety and Stress Scale (DASS-21) (45) to ascertain severity of current symptoms. The K-10 provides a measure of psychological distress over the preceding 4 weeks with higher scores indicating greater distress. (46). The DASS-21 measures and discriminates between depression, anxiety and stress with a set of three self-report scales, the scores for each domain calculated by summing the relevant items (47).

Procedures

Resting

Participants reported to the laboratory in allotted time slots across successive mornings in a fasted state. This study was part of a larger study examining inflammatory responses which required fasting blood measures (36). The testing session took approximately 1 h for each participant to complete. Height was measured using a wall-mounted stadiometer (Custom CSU, Bathurst, NSW, Australia) and weight was measured using digital scales (HW 150 K, A & D, Bradford, MA, USA). On arrival participants were instrumented with a 20 channel, 256 Hz, wireless EEG headset (B-Alert, ABM, CA, USA) described subsequently. Following this, participants sat still looking at a blank wall with their eyes open while 2 min of resting data were collected. Following resting measurements, participants were moved to the cycle ergometer for the incremental exercise test.

Incremental exercise

Participants were set up on an electronically braked cycle ergometer (LODE Excalibur sport, LODE BV, Groningen, Netherlands) to ensure they were comfortable and were in an appropriate cycling position. Participants were then fitted with a facemask (Hans Rudolph, Kansas City, MO, USA) connected to a rapid response gas analyzer (AEI Technologies, Pittsburgh, PA, USA) for the measurement of pulmonary gas exchange. The hairnet for the facemask was utilized to prevent the EEG strip from moving thereby reducing artifact. An incremental test to exhaustion was then performed commencing at 25 watts (W) and increasing by 25 W every minute until volitional exhaustion. Participants were asked to keep their cadence as consistent as possible.

Measurements

Electroencephalography

Measurements for EEG strap size were taken; sagittal, coronal plane and circumferential measures were taken for correct strap size and EEG placement using the 10–20 international system (48). Alignment of the EEG strip was ensured by placing the strip at 10% of the coronal measure from the nasion to the inion for placement of FP1 and FP2. The scalp electrode impedance (kΩ) of all electrodes was maintained below 40 kΩ. Paired mastoid references were used and electrode and reference sites were cleaned and abraded prior to fitting. Data were sampled with a bandpass filter from 0.5 and 65 Hz (at 3 dB attenuation) obtained digitally with Sigma-Delta A/D converters as previously reported (49). Data were acquired wirelessly across a R F link *via* an RS232 interface. While EEG signals were recorded at all 20 electrode sites, data produced at the following sites were used for analysis; FP1, FP2, F3, F4, F7, F8, C3, Cz, and C4.

Data analysis

Ventilatory parameters

All gas exchange data were exported into an excel spreadsheet and time averaged over 15 s. Peak oxygen consumption ($\dot{V}O_2$ peak) was determined by the highest 15 s average. The ventilatory threshold (VT) was determined using previously defined methods utilizing increases in ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) (50). The point of 50% VT was computed using linear regression. The EEG data were then aligned to these timespoints by averaging the final 15 s prior to each timespoints: 50% VT and VT.

EEG analysis

The EEG data were processed and analyzed using B-Alert lab (ABM, CA, USA). Each 15 s sample was visually inspected for

TABLE 1 Physical characteristics of participants and incremental exercise test outcomes.

	AH (*n* = 9)		MI (*n* = 12)	
	Mean	SD	Mean	SD
Age (years)	47.78	5.63	39.67*	9.7
Height (m)	1.71	0.1	1.69	0.12
Weight (kg)	74.47	13.5	100.45*	28.82
BMI ($kg \cdot m^{-2}$)	22.87	3.53	35.16**	10.03
$\dot{V}O_2$ peak ($ml \cdot kg \cdot min^{-1}$)	27.59	7.93	20.28*	6.41
VT at % $\dot{V}O_{2\ peak}$	74.31	19.21	82.01	14.2
Test length (s)	406	192	457	168

AH, apparently healthy; MI, mental illness; n, number of subjects; VT, ventilatory threshold. *$P < 0.05$; **$P < 0.01$.

TABLE 2 Mental health characteristics of participants.

	AH (*n* = 9)		MI (*n* = 12)	
	Mean	SD	Mean	SD
K-10	13.9	4.02	18.9*	7.30
DASS-21 scores				
Depression	4	5.5	14.4*	15.5
Anxiety	1.67	2.55	8.00**	4.00
Stress	5.83	6.61	15.2*	11.4

AH, apparently healthy; MI, mental illness; n, number of subjects; K-10, Kessler 10 psychological distress scale; DASS-21, depression anxiety and stress scale. *$P < 0.05$; **$P < 0.01$.

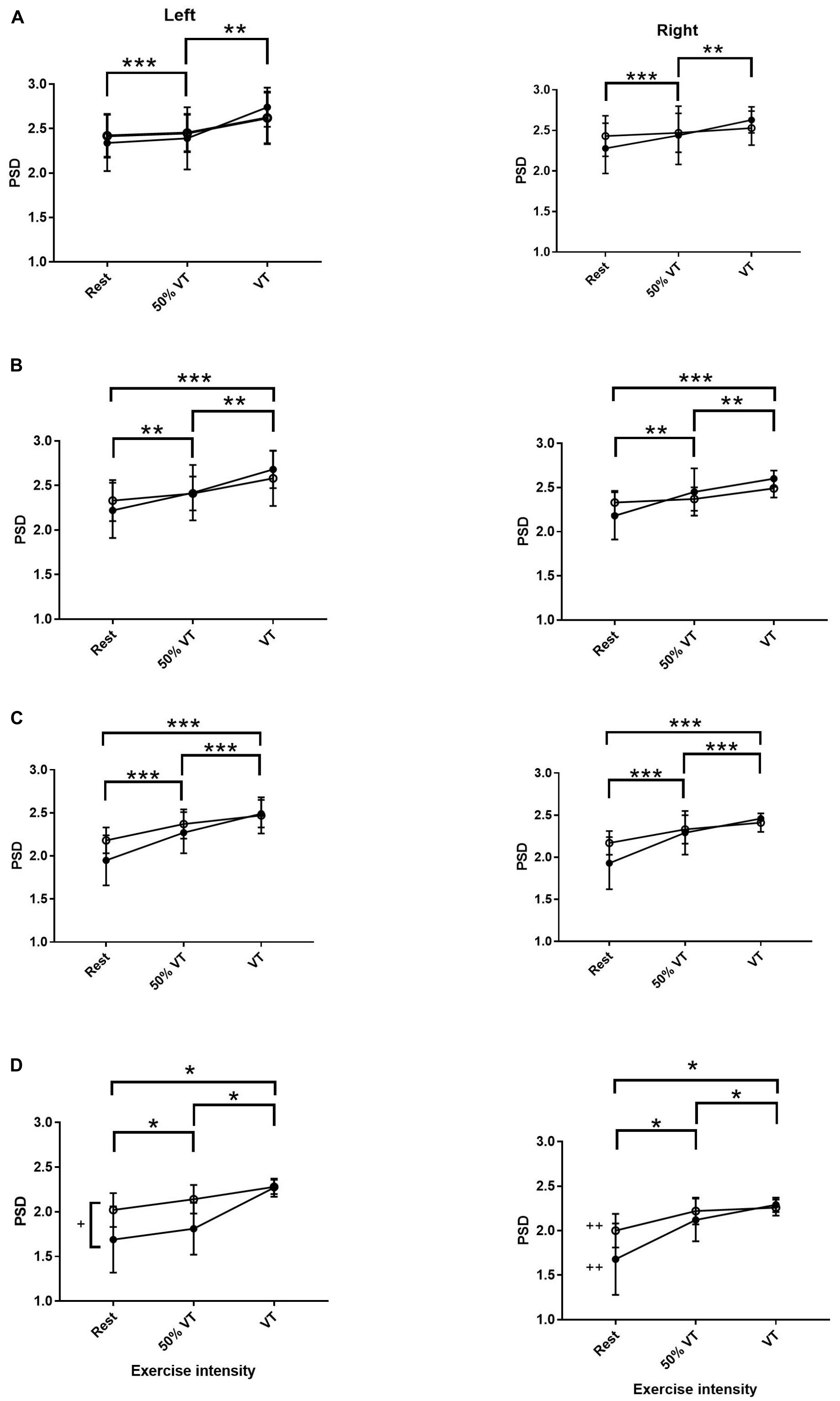

FIGURE 1
Power spectral density (PSD) responses in alpha slow **(A)**, alpha fast **(B)**, beta **(C)**, and gamma **(D)** within the prefrontal cortex in AH (•) and MI (▲) in the left and right hand sides. Significant differences across intensities; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. + significant differences between groups ($P < 0.05$) and ++ significant differences between gamma left AH and MI ($P < 0.05$).

artifact (Polyman, version 1.153.1065) and eye blink and muscle artifact was removed by the B-Alert decontamination algorithms. Decontaminated data were then Fast Fourier Transformed into power spectra and power spectral densities (PSD) were calculated for the following frequency bands; Alpha Slow (αS) (8–10 Hz), Alpha Fast (αF) (10–13 Hz), Beta (β), and Gamma (γ) (30–40 Hz). Prior to statistical analysis EEG channels were divided into regions as follows: PFC left side; FP1, F7, and F3; PFC right side; FP2, F8, and F4; and

MC (C3, Cz, and C4). EEG analysis was undertaken for the 2 min of resting data and the final 15 s of each exercise intensity timespoints.

Statistical analysis

A sample size of 16 was predicted to achieve statistical power based on a large effect size and a *P*-value set at 0.05 (G Power, Germany). Participants with excess artifact were removed from the data analysis leaving a total of 21 (AH; *n* = 9 and MI; *n* = 12). EEG data were analyzed using a mixed effects model (PFC side × intensity × group) with significance set at $P < 0.05$ once residuals were checked for normality [Jamovi, (51)]. EEG data were entered in absolute values rather than by calculating a laterality index. Results are presented as means (±) standard deviation (SD).

Results

Participant characteristics

Participant physical characteristics and incremental exercise test outcomes are provided in Table 1. Compared to AH participants, MI participants were on average significantly younger ($P < 0.05$), had a greater body weight ($P < 0.05$) and body mass index ($P < 0.01$), and had a lower $\dot{V}O_2$ peak ($P < 0.05$). There was no significant difference in VT (as a % of $\dot{V}O_2$ peak) and in test length between groups.

Participant mental health characteristics are provided in Table 2. Compared to AH participants, MI participants had significantly higher K-10 psychological distress scores ($P < 0.05$), DASS-21 depression ($P < 0.05$), anxiety ($P < 0.01$), and stress ($P < 0.05$) scores.

Prefrontal cortex EEG responses

Alpha slow

There was no effect of group or side in αS, however, there was an effect of intensity. Power spectral density in αS increased from rest to VT ($P < 0.001$) and from 50% VT to VT ($P < 0.01$) (see Figure 1 and Table 3). Activity levels at rest were higher in MI compared to AH on both left and right sides (2.43 ± 0.25 vs. 2.34 ± 0.32; 2.47 ± 0.24 vs. 2.29 ± 0.32) respectfully, however, this was not significant ($P > 0.05$).

Alpha fast

There was no effect of group or side in αF, however, PSD in αF showed a significant effect of intensity. There was a significant increase in AF from rest to 50% VT ($P < 0.01$) from 50% VT to VT ($P < 0.01$) and from rest to VT ($P < 0.001$) (see Figure 1 and Table 3).

Beta

There was only a significant effect of intensity in the β EEG response ($P < 0.001$) with β increasing significantly from rest to 50% VT ($P < 0.001$), from 50% VT to VT ($P < 0.001$) and from rest to VT ($P < 0.001$) (see Figure 1 and Table 3).

Gamma

There was a significant effect of group ($P < 0.05$), side ($P < 0.02$), and intensity ($P < 0.001$) in the γ response with both group x intensity and intensity x side interactions ($P < 0.05$). The γ response increased in the MI group from rest to 50% VT ($P < 0.05$) and from rest to VT ($P < 0.001$) and in the AH group from rest to VT ($P = 0.01$), from rest to 50% VT ($P < 0.01$) and from 50% VT to VT (< 0.01) (see Figure 1 and Table 3).

The left side γ activity in the MI group was significantly higher than in the left side AH group ($P < 0.05$). The AH response on the left side was significantly lower than both the AH right side ($P < 0.05$) and the MI right side ($P = 0.001$) (see Figure 1 and Table 3).

Motor cortex EEG responses

Across all bandwidths there was no significant effect of group in the EEG response in the MC. In the bandwidth αS, there were no significant differences across time points from rest, 50% VT and at VT ($P > 0.05$) (see Figure 2). In αF, β, and γ bandwidths, there was a significant effect of time ($P < 0.05$) with power spectral density

TABLE 3 Electroencephalography (EEG) responses (mean ± SD) in AH and MI in the prefrontal cortex on the left and right hand sides at rest, 50% VT and VT.

		AH (*n* = 9)				MI (*n* = 12)			
		Rest	50% VT	VT		Rest	50% VT	VT	
Alpha slow	Left	2.34 (0.32)	2.39 (0.35)	2.74 (0.22)	### &&	2.42 (0.24)	2.45 (0.21)	2.62 (0.29)	### &&
	Right	2.28 (0.24)	2.44 (0.36)	2.63 (0.16)		2.43 (0.25)	2.47 (0.24)	2.53 (0.21)	
Alpha fast	Left	2.22 (0.31)	2.42 (0.31)	2.68 (0.21)	## $$ &&&	2.33 (0.23)	2.41 (0.19)	2.58 (0.31)	## $$ &&&
	Right	2.18 (0.32)	2.45 (0.32)	2.60 (0.11)		2.33 (0.22)	2.41 (0.19)	2.58 (0.31)	
Beta	Left	1.95 (0.29)	2.27 (0.24)	2.49 (0.16)	*** &&& ###	2.18 (0.15)	2.33 (0.17)	2.47 (0.21)	*** &&& ###
	Right	1.93 (0.31)	2.29 (0.26)	2.46 (0.02)		2.17 (0.14)	2.33 (0.17)	2.41 (0.11)	
Gamma	Left	1.69 (0.37)	1.81 (0.29)	2.27 (0.10)$^{\infty}$ α α α	## &&	2.02 (0.19)	2.14 (0.16)	2.28 (0.08)	* ###
	Right	1.68 (0.40)	2.12 (0.24)	2.29 (0.08)		2.00 (0.19)	2.22 (0.15)	2.26 (0.09)	

Symbols denote difference from rest to 50% VT (*), rest to VT ($^{\#}$) and from 50% VT to VT ($^{\&}$) with level of significance set as number of symbols; one, ($P < 0.05$), two ($P < 0.01$), three ($P < 0.001$). Differences between sides denoted as (•) higher than left side, (∞) as lower than AH right side and (α) as lower than MI right side, with number of symbols denoting significance, as above.

increasing from rest to 50% VT ($P < 0.05$) and from rest to VT ($P < 0.01$) (see **Figure 2** and **Table 4**).

Discussion

This study investigated the EEG responses during rest and incremental exercise to exhaustion in both those who were AH and those experiencing a MI. To our knowledge this is the first study to measure EEG responses during exercise in those with MI. Our main findings were that while resting αS and αF were both higher in those with MI compared to AH, this was not significantly so, and there was no difference between the left and right PFC suggesting that no FAA was present. From rest to exercise, each bandwidth increased significantly in both AH and MI (see **Figures 1**, **2**) between at least two of the three intensities. There was a significant difference in the gamma response between groups with gamma being significantly higher on the left PFC in the MI group. The gamma response in the AH left PFC was significantly lower than both the AH right PFC and the MI right PFC. These gamma responses add to the evidence that gamma may be an indicator of differences between AH and those with MI.

Frontal alpha asymmetry

While there is considerable evidence in favor of the alpha asymmetry hypothesis to identify depression (4, 6, 8, 24, 27), there is also building evidence disputing the effectiveness of alpha asymmetry in diagnosis of depression (52). In their meta-analysis the authors highlight some concerns with the FAA literature which may impact interpretations of the findings. They suggest that the conflicting findings across the FAA literature are due to the considerable heterogeneity across study samples (age, gender, symptom severity) impacting the FAA response. This lack of FAA is in line with our results and we note that our MI population were of mixed ages and genders, potential confounding factors. Other potential reasons for the lack of FAA may be due to the combined analysis of channels on the left and right side of the PFC, rather than at individual channel sites. Some previous research has only analyzed one electrode site rather than multiple across one region (4, 6). Although there are others who have combined electrode sites (8) as with our data. There are additional discrepancies depending on the use of eyes closed vs. eyes open measures and if participants are currently utilizing medication (27, 53).

There may, however, be alternating explanations. FAA has been shown to be a predictor of patient responses to the anti-depressant Fluoxetine (Prozac), with non-responders having overall greater resting activation of the right hemisphere asymmetry in the eyes open condition, with this difference being predominantly in the fast alpha range (53). The authors propose that the non-responders resemble patients who have depression with comorbid anxiety disorder, i.e., experiencing different forms of depression. Frontal asymmetry and the degree of activation on each side may therefore be linked to forms of depression, comorbid conditions, or represent a degree of treatment resistance to certain medications. This highlights the importance of EEG asymmetry as a potential marker for clinicians to identify which anti-depressants to use. Further to this, other mechanisms proposed include the relationship between EEG alpha power and brain-derived neurotrophic factor (BDNF) Met/Met polymorphism (54), an indicator of depression severity. A reduced secretion of BDNF may negatively affect functional connectivity in neuronal systems that generate alpha oscillations (54).

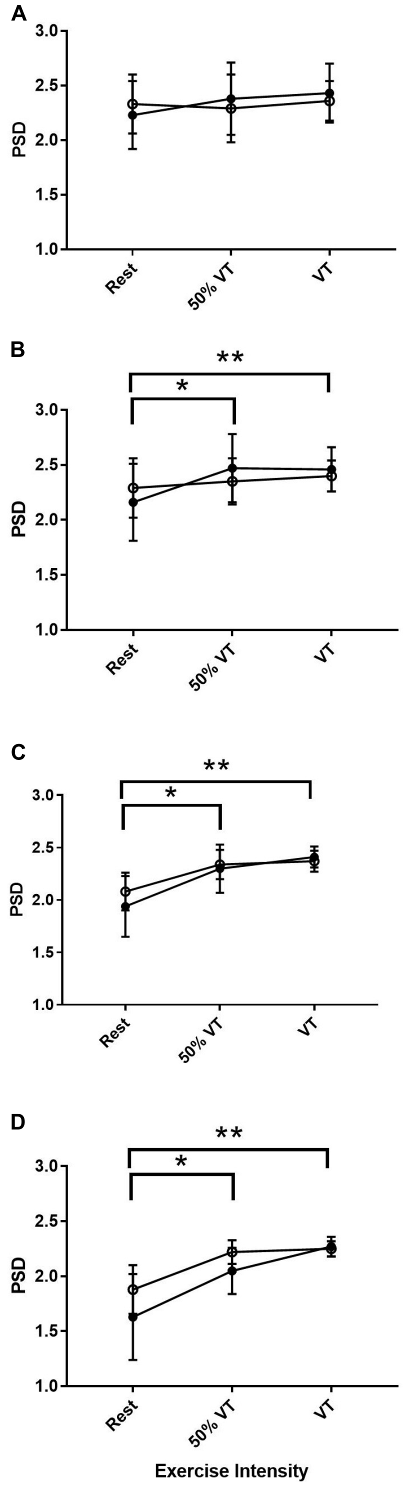

FIGURE 2
Power spectral density (PSD) responses in alpha slow **(A)**, alpha fast **(B)**, beta **(C)**, and gamma **(D)** within the motor cortex in AH (•) and MI (○). Significant differences between rest and intensities; *$P < 0.05$, **$P < 0.01$.

TABLE 4 Electroencephalography (EEG) responses (mean ± SD) in AH and MI in the motor cortex at rest, 50% VT and VT.

	AH (n = 9)				MI (n = 12)			
	Rest	50% VT	VT		Rest	50% VT	VT	
Alpha slow	2.23 (0.31)	2.38 (0.33)	2.43 (0.27)		2.33 (0.24)	2.29 (0.31)	2.36 (0.18)	
Alpha fast	2.16 (0.35)	2.47 (0.31)	2.46 (0.20)	* ##	2.29 (0.27)	2.35 (0.21)	2.40 (0.14)	* ##
Beta	1.94 (0.29)	2.30 (0.23)	2.41 (0.10)	* ##	2.08 (0.18)	2.34 (0.14)	2.37 (0.10)	* ##
Gamma	1.63 (0.39)	2.05 (0.21)	2.27 (0.09)	* ##	1.88 (0.22)	2.22 (0.11)	2.25 (0.07)	* ##

Symbols denote difference from rest to 50% VT (*) and rest to VT (#) with level of significance set as number of symbols; one, ($P < 0.05$), two ($P < 0.01$), three ($P < 0.001$).

Gamma response and depression

The use of gamma oscillations as a biomarker for major depression is an emerging topic (55), with considerable literature examining topics such as gamma responses in treatment resistant depression with ketamine (56), responses to selective attention tasks (57) and as a biomarker for major depressive disorder recurrence (58). Gamma activity is found in a multitude of high level cognitive tasks, such as sensorimotor integration (59), short term or working memory (60) and language tasks (61), however, there is an argument that there is a more elementary explanation for its presence (62). Merker and colleagues (62) propose that Gamma activity instead holds an infrastructural support role whereby it supports neural activity rather than being involved in each cognitive function. As part of their proposal they outline that gamma activity may be contributed to by cortical inhibitory interneurons interacting among themselves to aid in providing inhibitory activity. This activity is necessary for keeping single units from saturating, acting almost like an emergency brake for run-away excitation (62). What role this may play in MI is not yet known.

Changes in gamma responses to depression have been shown to occur in the hippocampus (63) and the anterior cingulate cortex (57) and to be suppressed in various brain sites by serotonin boosting anti-depressants in rats (64, 65). However, there is scarce data examining the PFC. In a comparison between healthy participants and those with major depression, those with major depression were shown to have higher gamma (30–40 Hz) responses in frontal and temporal regions (66) on both sides of the PFC. Further, major depression patients with implanted deep brain simulation showed a significant decrease of frontal gamma, with decreasing depressive symptoms also associated with a decrease in right frontal gamma (67). These data suggest that a depressive state is accompanied by a higher PFC gamma response, similar to our findings. Additionally, work examining non-linear EEG responses to depression have shown an increase in fractal dimensions in the gamma bandwidth in the PFC indicating more complex electrophysiological behavior (68). The authors propose that this pattern of brain activity may represent cognitive dysfunction in depressed patients, a theory supported by the cognitive deficits found within depression (63) that may be modulated by neurotransmitter responses (63). However, as with FAA, findings across gamma activity in those with depression are inconsistent (55).

EEG response and exercise

All bandwidths increased significantly across time with increasing exercise intensity from rest to the point of VT. This increase in EEG activity with incremental exercise has been shown previously in an AH population (49). This finding suggests that without the presence of alpha asymmetry during exercise, that changes in FAA measured previously following exercise (39, 69) do not occur during exercise. However, we found no FAA at rest and therefore this may have confounded a lack of findings in FAA during exercise. Alpha asymmetry and affective responses to exercise have been shown to be influenced by fitness levels (39) with resting frontal asymmetry predicting affect only in a high-fit group, suggesting in order to achieve affective responses that are positive a level of fitness is required. The differences in fitness between the AH and MI groups in our study may therefore be problematic, however, it has also been shown that affective responses are variable in relation to exercise intensity preference (38) thus, potential affective responses and EEG responses may be heterogenous both within and between groups during incremental exercise. Greater relative frontal activation at rest has also been shown to predict a positive affect post-exercise following exercise at 70% $\dot{V}O_2$ max, suggesting that FAA pre-exercise is an important determinant of changes post-exercise in the EEG response (69). As we saw no FAA at rest, this may provide a reason why there were not EEG changes during exercise. Further to this, while there is considerable evidence looking at the affective responses to exercise in those with MI we do not know if individuals with MI have the same affective responses during exercise as AH populations or if they are the same magnitude.

The gamma response to exercise is not well characterized, with most studies exploring changes in alpha and beta bandwidths (70, 71). One study measuring EEG post-exercise found no changes in gamma activity post-exercise and no relation to affective response (38). While there were significant interactions in the gamma response at the group × side level in our data, these did not reach significance at the group × side × intensity level thus it is not possible to say there were differences in gamma responses across groups and sides at each timespoints, although gamma activity was higher in MI at rest and 50% VT. If gamma plays any role in affect is not yet known.

Limitations

It is recognized that the measurement of EEG during exercise is problematic due to muscle artifact (72). Technology for the measurement of EEG has developed rapidly allowing for the use of wireless technologies, significantly reducing artifact. Steps were also taken to ensure that participants kept as still as possible during the trial and that while we measured oxygen uptake, this was done with a mask not a mouthpiece as is often used which can add to muscle artifact. The headset used for attaching the mask to the face of the participants also aided in keeping the EEG strap still. Due to levels of artifact, the EEG response beyond the VT was not reportable. Overall, this is a consideration for this study. However, it should be noted that many studies have been previously published successfully showing EEG responses to exercise (70, 71).

Some considerations for the lack of FAA are that the period of 2 min eyes open resting EEG is a relatively short time, which may explain the discrepancies in resting EEG between AH and MI, however, this time period has been used previously in EEG research (73). While we achieved statistical power as determined by G Power calculations, the presence of artifact meant missing data which reduced our statistical power and therefore may have impacted us finding alpha asymmetry. Other confounding variables consist of the handedness of individuals and the age. Both of these variables have been shown to impact EEG activity. There has previously been reported an association between right hemisphere activity and negative affect *via* an association between EEG activity and non-right handedness (74), as well as a rightward bias in FAA with age (75).

Conclusion

The EEG response to exercise in those with MI and AH controls showed a similar response to what has been shown previously in both the PFC and MC. There were no differences in alpha responses between groups at rest or during exercise suggesting that no resting FAA existed between groups and that the changes in alpha activity, indicative of improved affect, previously found post-exercise (39, 69) do not occur during exercise. FAA has been found across MI populations with depression (4, 6, 24–26) however, there is also evidence disputing the effectiveness of alpha asymmetry in diagnosis of depression due to non-generalizable results (52). The mechanisms behind differences in FAA are not yet fully elucidated but may include age, gender and symptom severity (52) forms of depression (76) and medication responses (53) and these factors may explain our lack of FAA findings.

The gamma response in those with MI was significantly higher than in the AH group, suggesting the usefulness of gamma responses to act as a biomarker for MI. The differences between groups in gamma activity may be due to altered neural dysfunction in those with depression. Gamma has been shown to decrease following use of neurotransmitter medication, thus, this altered neural function may also be indicative of changes in neurotransmitter responses found in depression (63, 64) which contribute to the emotional and cognitive disturbances found in depression (77).

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Charles Sturt University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CVR contributed to the study design, data collection, data analysis, and manuscript writing. MS, GW, JRH, and TDM contributed to the data collection and manuscript review. TEH contributed to the study design, data collection, and manuscript review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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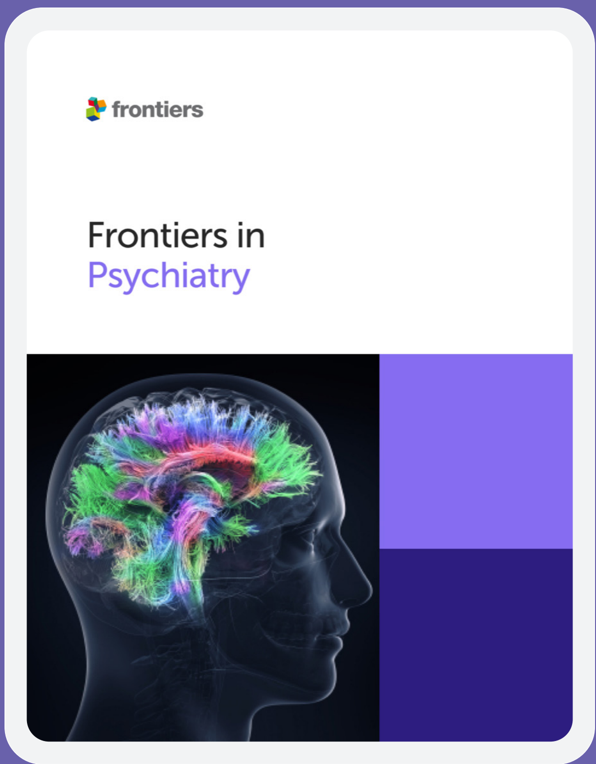

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