

Retraction

Retracted: Meta-Analysis on Cognitive Benefit of Exercise after Stroke

Complexity

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

- (1) Discrepancies in scope
- (2) Discrepancies in the description of the research reported
- (3) Discrepancies between the availability of data and the research described
- (4) Inappropriate citations
- (5) Incoherent, meaningless and/or irrelevant content included in the article
- (6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

- [1] B. Yang and S. Wang, "Meta-Analysis on Cognitive Benefit of Exercise after Stroke," *Complexity*, vol. 2021, Article ID 5569346, 12 pages, 2021.

Review Article

Meta-Analysis on Cognitive Benefit of Exercise after Stroke

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ObjectiveThe objective of this paper is to evaluate the cognitive benefit of exercise after stroke, so as to provide more accurate and reliable guidance for targeted exercise intervention. **Methods** Randomized controlled trials of the relationship between exercise and cognition after stroke were identified in Cochrane Library and PubMed. Methodological quality was assessed using the Cochrane tool of bias. SMD and 95% confidence intervals were calculated, and Chi-squared test (Q) was adopted to estimate the heterogeneity. **Results** (a) Twenty-three studies met inclusion criteria, including 1528 participants. Heterogeneity was from low to high such as attention ($I^2 = 0.00\%$), executive function ($I^2 = 0.00\%$), cognition ($I^2 = 64\%$), and working memory ($I^2 = 77\%$). (b) The overall effect on cognition was small (SMD = 0.16 [0.04, 0.28]) but significant and there is a difference between cognitive domains in attention (SMD = -0.35 [-0.57, -0.14]), executive function (SMD = -0.24 [-0.40, -0.08]), and working memory (SMD = 0.36 [0.20, 0.53]). (c) Exercise training was less effective before the 18th month after stroke. Higher benefits on cognition were found after combined therapy compared with other exercise programs, and the older the stroke survivors, the less the cognitive benefit of exercise. **Conclusion** Small-to-moderate effect of exercise on cognitive benefit after stroke was found, and the effect was moderated by treatment protocols and sample characteristics.

1. Introduction

Cognitive and motor dysfunction is a common symptom after stroke; more than 80% of the patients have different degrees of cognitive and limb motor impairment during 3 to 12 months after stroke [1], which is associated with memory decline, attention deficits, and executive dysfunction [2]. Although survivors can get timely treatment, sedentary behavior caused by long recovery cycle of limb function can further lead to anxiety, depression, and other bad emotional states, which in turn hinder the recovery process, such as poor adherence to rehabilitation plan, high recurrence rate of stroke, and high mortality involved with suicide [3].

Blood supply disorders associated with ischemic or hemorrhagic stroke can provoke hypoxic death of nerve cells, altering neuronal structures and causing partial or complete loss of neuronal function [4]. Accordingly, timely treatment during the critical period after stroke will greatly affect the neural plasticity and functional recovery of the brain. At present, drugs that modulate

neurotransmission are mainly adopted for functional recovery after stroke. Serotonin reuptake inhibitors, for example, can facilitate synaptic plasticity and functional connections between synapses by increasing the concentration of serotonin transporters between synapses of neurons, thus laying a physiological foundation for the recovery of sensorimotor and long-term memory function [5]. On the other hand, Amphetamine-like agents, by promoting the release of epinephrine, norepinephrine, and dopamine from the presynaptic terminal, accelerate the process of functional recovery after central nervous system injury [6]. However, studies have pointed out that [7] long-term use of Amphetamine can also cause adverse side effects, such as increased blood pressure and heart rate, and it is controversial for adverse symptoms such as tension, insomnia, addiction, or anorexia after rehabilitation. Other pharmacotherapies like antipsychotics and antiepileptic drugs not only aggravate muscle stiffness but also cause metabolic abnormalities and unpredictable toxic effects [8].

Given that there is a lack of ideal pharmacotherapy to reverse the decline of cognitive function after stroke, it is imperative to find a cheap and reliable alternative. As the cognitive benefit of exercise intervention has also been confirmed in animal models [9] and elderly people with cognitive dysfunction [10], physical exercise and cognitive training are considered the primary treatments for improving age-related cognitive decline [11]. Early studies have shown that exercise intervention after stroke can effectively avoid further cognitive function decline [12]; a recent study also showed that moderate-to-high-intensity exercise will effectively promote cognitive function recovery after stroke, improving the level of cardiopulmonary adaptation [13] and facilitating the speed and endurance of physical activity, and then will reduce risk of recurrence of stroke and cardiovascular events [14]. In fact, the cognitive benefit of exercise was mainly induced by increased cerebral blood flow and neurotrophic factor secretion (BDNF, IGF-1), so as to facilitate structural and functional recovery of damaged parts of the brain [15] then restore cognitive function while raising the level of brain arousal, and ultimately strengthen the ability of the brain in limbs coordination and control and ease anxiety and depression caused by cognitive and motor loss [16]. Interestingly, the latest meta-analysis showed that [17] although exercise is helpful in cognitive function recovery after stroke, the improvement was not reflected in all aspects; only attention and cognitive processing speed were significantly improved. Working memory and executive dysfunction were not included. Besides, cognitive improvement did not occur in all types of exercise intervention, and only the combination of aerobic exercise and physiotherapy was shown to be effective. This completely contradicts the conclusion of a recent research [18]. In addition, since previous studies were based on small samples size and restricted to specific exercise types and sample characteristics, an updated quantitative exercise recommendation for cognitive promotion in stroke survivor is needed.

Here, we provide a meta-analysis on cognitive benefit of exercise in stroke survivors, examining the specific cognitive benefit on executive function, attention, and working memory. Additionally, sample characteristics such as session duration, frequency, intervention length, type of exercise, and the time from stroke onset to initiation of the intervention, which may moderate the exercise-cognition relationship, have also been rated, so as to identify the optimal exercise training dose parameters and then maximize cognitive benefit of exercise after stroke.

2. Methods

2.1. Search Criteria. Based on existing meta-analysis (from July 2001 to 2017), our initial literature search retrieved 405 records from the Cochrane Library and PubMed (from July 2017 to January 2021) under the condition of independent double-blind experiment, where 183 remained after deleting inconsistent researches. There were 23 articles that fulfilled all eligibility criteria and they were included after excluding 55 duplicate articles, 63 reviews, 10 meta-analyses, and 22 articles with incomplete data after contact with the

corresponding author. The keywords of the search are as follows: (physical activity OR TaiChi OR physiotherapy OR Ba duan jin OR fitness OR aerobic exercise OR dance OR resistance training) AND (cognitive function OR cognition OR attention OR memory OR executive function OR neuropsychological test) AND (stroke OR cerebrovascular accident OR brain ischemia OR poststroke OR post stroke).

2.2. Study Selection. Selection criteria are as follows: (1) stroke survivors (e.g., ischemic or hemorrhagic stroke) older than 18 years of age; (2) randomized controlled trials, including exercise type, frequency, intensity, session duration, intervention length, mean age, and course of disease; (3) existence of baseline and postintervention reports prior to the experiment (for unmonitored training studies (i.e., family interventions), changes in body function before and after exercise training must be observed, such as physical fitness improvement); and (4) excluding conference papers, research reviews, non-RCT research, inconsistent research content, duplication of literature, and book chapters. Finally, 23 articles, including 24 independent studies, were included [2, 14, 18–38] (Figure 1).

2.3. Data Collection and Extraction. One author performed the initial articles search according to the title and abstract of the article. Two authors extracted information independently, including (a) demographic information (number of total participants in experimental and control groups, sex, and the mean age and age range of participants in each group); (b) exercise intervention features (exercise type in each group, exercise frequency in each group, intensity of physical exercise for two groups, session duration, intervention length, course of disease, drugs taken during trials and tests, adherence, dropouts, and adverse effect); (c) outcome evaluation tools, including Mini-Mental State Examination, Wechsler Memory Scale, Functional Independence Measure, Montreal Cognitive Assessment, Trial Making Part B, Digit Span, Stroop Test, Addenbrooke's Cognitive Examination Revised, Stroke Impact Scale, Go/No-go, and Dual Task; and (d) the results of each cognitive test in pre- and postexercise intervention which were categorized in the light of cognitive function they tested, including the mean scores or the mean change of the overall cognitive function, working memory, attention, and executive function. For some studies which only show the result of standard deviation or standard error of these values, we calculate it by specific formula. Besides, the numbers of participants in experiment and control groups were also abstracted. Finally, e-mail will be sent to the author when there is no sufficient information in all included studies to calculate effect sizes. Disagreements were resolved by discussion and consensus with corresponding author of the team.

2.4. Quality Assessment. Two authors assessed the methodological quality of included trials by the Cochrane risk of bias tool. The quality assessment was performed by the

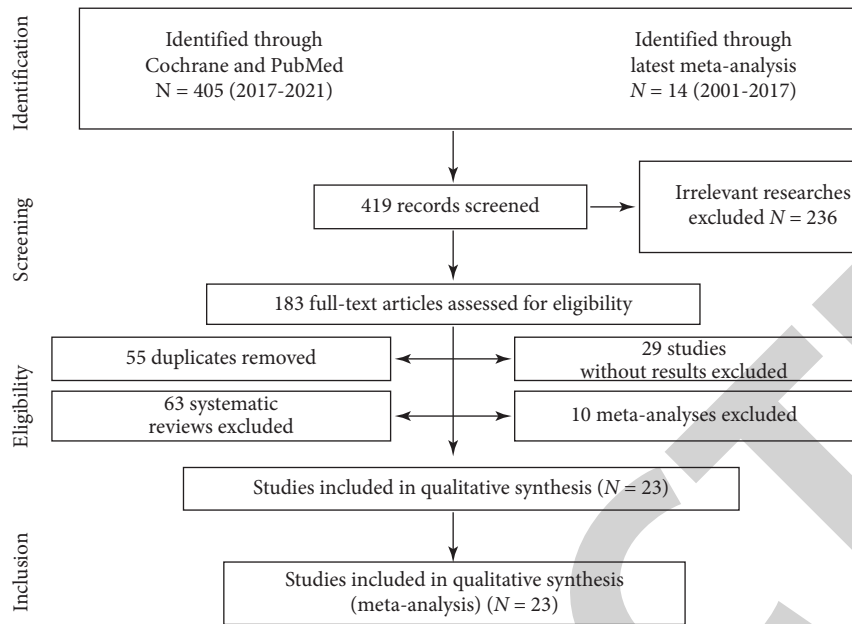


FIGURE 1: PRISMA flow diagram of included studies.

software Review Manager 5.3, which sets six criteria according to the responses “low risk,” “high risk,” and “unclear risk” to the following domains: random allocation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective reporting.

2.5. Data Analysis. Statistical analysis was performed using Review Manager 5.3 and Stata 15.1. Exercise effects of each study were represented by standardized mean differences (SMD) and confidence intervals (CI) in condition of fixed-effects or mixed-effects model, and only the baseline data and the data at the end of the intervention were used for effect sizes calculation. Effect sizes were interpreted as small (≤ 0.2), moderate (0.5), or large (≥ 0.8). We calculated standard deviation (SD) from the standard error (SE; $SD = SE \sqrt{n}$) if it is not available in the article. Q statistics and I^2 were calculated for heterogeneity evaluation between studies.

Using a fixed-effects model, we performed an overall meta-analysis on cognitive benefit of exercise; as for trials with multiple cognitive outcomes, effect sizes were calculated separately for each domain. Studies were distinguished in terms of sample characteristics, intervention details, and outcome measures; and subgroup analysis was conducted for several characteristics. First, two subgroup analyses on subdomains of sample characteristics such as age group (49–55 Y, 56–60 Y, 60–65 Y, and > 65 Y) and course of disease (< 3 months after stroke, 3–6 months after stroke, 10–18 months after stroke, and ≥ 18 months after stroke) were conducted. Second, five subgroup analyses on subdomains of study design including exercise type (aerobic exercise, physiotherapy, and combination of aerobic exercise/physiotherapy/cognition therapy),

frequency (2 to 3 times per week and 5 times per week), intensity (moderate or acute), session duration (≤ 30 min, 45–60 min, 75–90 min, and ≥ 90 Min), and intervention length (< 4 weeks, 6–10 weeks, 12–14 weeks, and ≥ 14 weeks) were conducted. In addition, three separate meta-analyses on subdomains of cognition were performed: working memory, attention, and executive functions. Last, funnel plot asymmetry was used to detect whether there was publication bias.

3. Results

3.1. Characteristics of Included Studies. After systematic retrieval, 23 studies met all inclusion criteria, including 1528 participants with mean age of 62.2 years (SD: 6.2 years). The mean trial length was 11.3 weeks (SD: 5.6 weeks), and exercise frequency was divided into 2 to 3 times per week and 5 times per week. The mean duration of each session was about 69.3 minutes (SD: 45.6 minutes). To assess the influence of time from stroke to intervention, the course of disease before intervention was also investigated, which was about 20.8 months (SD: 22.1 months). Regarding types of exercise, three types of exercise intervention were adopted: aerobic exercise, physiotherapy, and combination of aerobic exercise/physiotherapy/cognition therapy. The control group was treated with general care, walking, passive stretching, and social communication (Table 1).

3.2. Quality Assessment. All studies included were RCT studies, and two studies reached the criteria of high methodological quality assessments in six aspects. Three studies were designed by independent double-blind experiment; one was nonblind design and another one was unknown as

TABLE 1: Characteristics of the included studies.

Study	Number	Age (mean)	Time from stroke to int.	Trial length	Session duration	Frequency	Exercise mode	Control type	Cognitive outcomes
Nilsson [19]	Ex: 36; Con: 37	Ex: 54.0; Con: 56.0	< 1 M	9.5 W	30 min	5t/W	Aerobic	Track walking with physiotherapist	③
Ozdemir [20]	Ex: 30; Con: 30	Ex: 59.1; Con: 61.8	1.28 M	9.0 W	120 min	5t/W	Physiotherapy	Conventional PA at home	①
Fang [21]	Ex: 78; Con: 78	Ex: 65.6; Con: 61.8	≤0.23 M	4.0 W	45 min	5t/W	Physiotherapy	Conventional PA at home	①
Studenski [22]	Ex: 44; Con: 49	Ex: 68.5; Con: 70.4	2.53 M	1 2 W	30 min	3t/W	Physiotherapy	Conventional PA at home	③
Chen [23]	Ex: 25; Con: 20	Ex: 66.2; Con: 67.3	< 6 M	1 2 W	45–60 min	2t/W	Physiotherapy	Conventional PA at home	①
Mead [24]	Ex: 32; Con: 34	Ex: 72.0; Con: 71.7	5.67 M	1 2 W	75 min	3t/W	Combined	Progressive muscle relaxation	③
Quaney [25]	Ex: 19; Con: 19	Ex: 64.1; Con: 59.0	58.8 M	8.0 W	45 min	3t/W	Aerobic	Home-based stretching exercises	②⑤⑦
Tamawy [26]	Ex: 15; Con: 15	Ex: 48.4; Con: 49.7	3–18 M	8.0 W	75 min	3t/W	Combined	Home-based stretching exercises	⑧
Immink [27]	Ex: 11; Con: 11	Ex: 56.1; Con: 63.2	52.5 M	1 0 W	40–90 min	1t/W	Yoga	Conventional PA at home	⑨
Moore [28]	Ex: 20; Con: 20	Ex: 68.0; Con: 70.0	18.5 M	1 9 W	45–60 min	3t/W	Combined	Stretching training	⑧
Liu [29]	Ex: 11; Con: 14	Ex: 62.9; Con: 66.9	32.4 M	2 4 W	60 min	2t/W	Combined	Conventional PA at home	⑦⑤⑥
Schachten [30]	Ex: 7.0; Con: 7.0	Ex: 55.1; Con: 53.1	44.0 M	1 0 W	60 min	2t/W	Golf training	Standard care	⑩
Gonzalo [31]	Ex: 16; Con: 16	Ex: 61.2; Con: 65.7	46.92 M	1 2 W	< 4 min	2t/W	Resistance training	Conventional PA at home	⑥⑦⑤
Tang [32]	Ex: 22; Con: 25	Ex: 65.9; Con: 66.9	>12 M	2 4 W	60 min	3t/W	High-intensity exercise	Stretching, balance, strength training	⑥⑦⑤
Kim [33]	Ex: 14; Con: 15	Ex: 50.7; Con: 51.9	12.24 M	6.0 W	90 min	5t/W	Combined	Stretching, balance, strength training	④
Meester [34]	Ex: 26; Con: 24	Ex: 60.9; Con: 62.3	43.64 M	1 0 W	30 min	2t/W	Aerobic	Conventional PA at home	⑪
Wang a [35]	Ex: 42; Con: 47	Ex: 65.1; Con: 64.4	< 6 M	1 2 W	50 min	3t/W	Aerobic	Conventional PA at home	⑤⑦⑥
Wang B [36]	Ex: 44; Con: 47	Ex: 66.7; Con: 64.4	< 6 M	1 2 W	110 min	3t/W	Combined	Conventional PA at home	⑤⑦⑥
Nagy [37]	Ex: 19; Con: 16	Ex: 59.0; Con: 62.0	11.4 M	2 0 D	60 min	5t/W	Combined	Conventional PA at home	③⑥
Hansen [38]	Ex: 108; Con: 101	Ex: 71.4; Con: 72.0	3 M	1 8 M	75–90 min	2-3 t/W	Aerobic	Conventional PA at home	①
Khatab [39]	Ex: 25; Con: 25	Ex: 65.9; Con: 66.9	36 M	6.0 M	60 min	3t/W	Aerobic	Balance training	⑤⑦⑥
Yeh [40]	Ex: 15; Con: 15	Ex: 50.6; Con: 60.2	71.15 M	12–18 W	60 min	2-3 t/W	Combined	Aerobic	④②
Koch [41]	Ex: 86; Con: 45	Ex: 59.0; Con: 58.0	5 M	1 2 W	80-100 min	3t/W	Combined	Conventional PA at home	④
Swank [42]	Ex: 37; Con: 36	Ex: 61.2; Con: 61.3	1 M	4.0 W	240 min	5/W	Physiotherapy	Conventional PA at home	③

① MMSE: Mini-Mental State Examination ; ② WCST : Wechsler Memory Scale ; ③ FIM: Functional Independence Measure; ④ MOCA: Montreal Cognitive Assessment ; ⑤ TMT B : Trial Making Part B ; ⑥ DS : Digit Span; ⑦ Stroop Test ; ⑧ ACE-R : Addenbrooke's Cognitive Examination Revised ; ⑨ SIS : Stroke Impact Scale ; ⑩ Go/No-go ; ⑪ Dual Task ; W: week; M: month; D: day.

regards blinding of participants and outcome assessment; and since the participants needed to sign informed consent in other experiments, the remaining experiments were single-blind trials, the risk of incomplete outcome indicators in eighteen articles was unknown, and the overall quality assessment of the included literature was high (Figure 2).

3.3. Summary of Results (Meta-Analysis)

3.3.1. *Heterogeneity Test.* Heterogeneity tests showed that there is no significant heterogeneity in attention and executive function, but significant heterogeneity was found in working memory and total cognitive function. This indicates

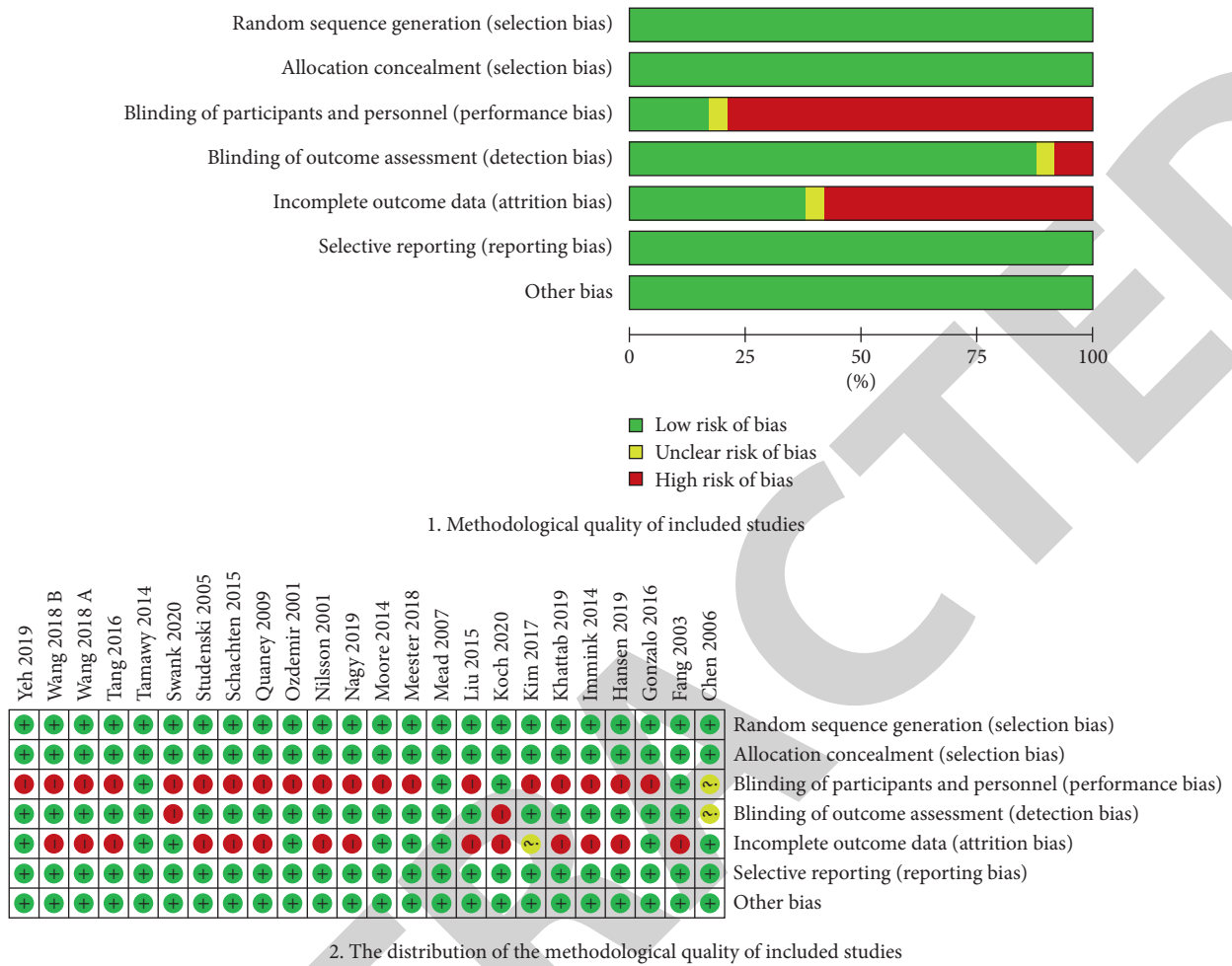


FIGURE 2: Quality assessment of included studies in the meta-analysis.

that there are potential unknown factors moderating the effect of exercise on the recovery of cognitive function after stroke, so the potential moderating factors will be explored through subgroup analysis (Table 2).

3.3.2. *Effects of PA Training on Cognition.* Of all included studies, fourteen trials examined overall cognitive function, fourteen examined working memory, six examined attention, and nine examined executive function. The meta-analysis on cognitive benefit of exercise showed that there was a significant and positive effect of physical activity on cognitive function after stroke (SMD = 0.16; CI: 0.04–0.28; $P < 0.05$) with moderate heterogeneity ($Q [df] = 36.01 [13]$; $P < 0.001$; $I^2 = 64%$) within the group (Figure 3), indicating that some variables may moderate the effect of exercise; then mixed-effect models were used for moderating analyses for they assume that variability between studies may be attributable to fixed and random components, as well as subject-level sampling error.

3.3.3. *Subgroup Analyses.* Mixed-effect analysis showed that cognitive benefit of exercise varied significantly ($QB = 10.42$; $P < 0.05$) among different age groups. Moderating-effect

TABLE 2: Heterogeneity analysis.

Cognitive domains	Q	P	I^2 (%)	Z	P
Attention	4.09	0.54	0.00	3.18	≤ 0.001
Executive function	6.53	0.59	0.00	2.87	≤ 0.001
Working memory	57.39	≤ 0.001	77.00	4.46	≤ 0.001
Cognitive function	36.01	≤ 0.001	64.00	2.59	≤ 0.001

analysis shows that cognitive benefit of exercise training was most significant at age of 49 to 55 years in stroke survivors (SMD = 0.59; CI: 0.05–0.45; $P < 0.05$), followed by 60 to 65 years (SMD = 0.25; CI: 0.25–0.93; $P < 0.05$), whereas patients aged 56 to 60 years and above showed poor cognitive gain (Figure 4).

Mixed-effect analysis of stroke course showed that there was no significant difference in cognitive gain after exercise in patients with different course of disease ($QB = 7.09$; $P < 0.05$), which means that earlier exercise intervention after stroke was not associated with greater cognitive gain. The cognitive benefit of exercise intervention was maximum at 18 months since stroke onset (SMD = 0.59; CI: 0.21–0.98; $P < 0.05$), while the cognitive gain for survivors that initiated exercise intervention within 18 months after stroke was not significantly changed compared with controls (Figure 4).

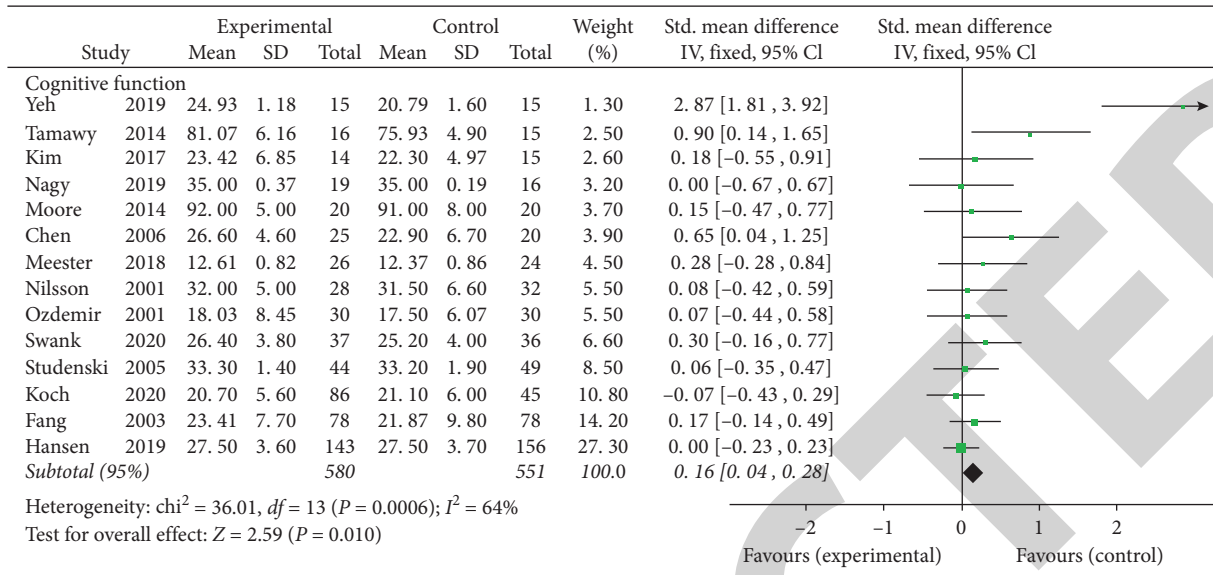


FIGURE 3: Meta-analysis on the cognitive benefit of exercise.

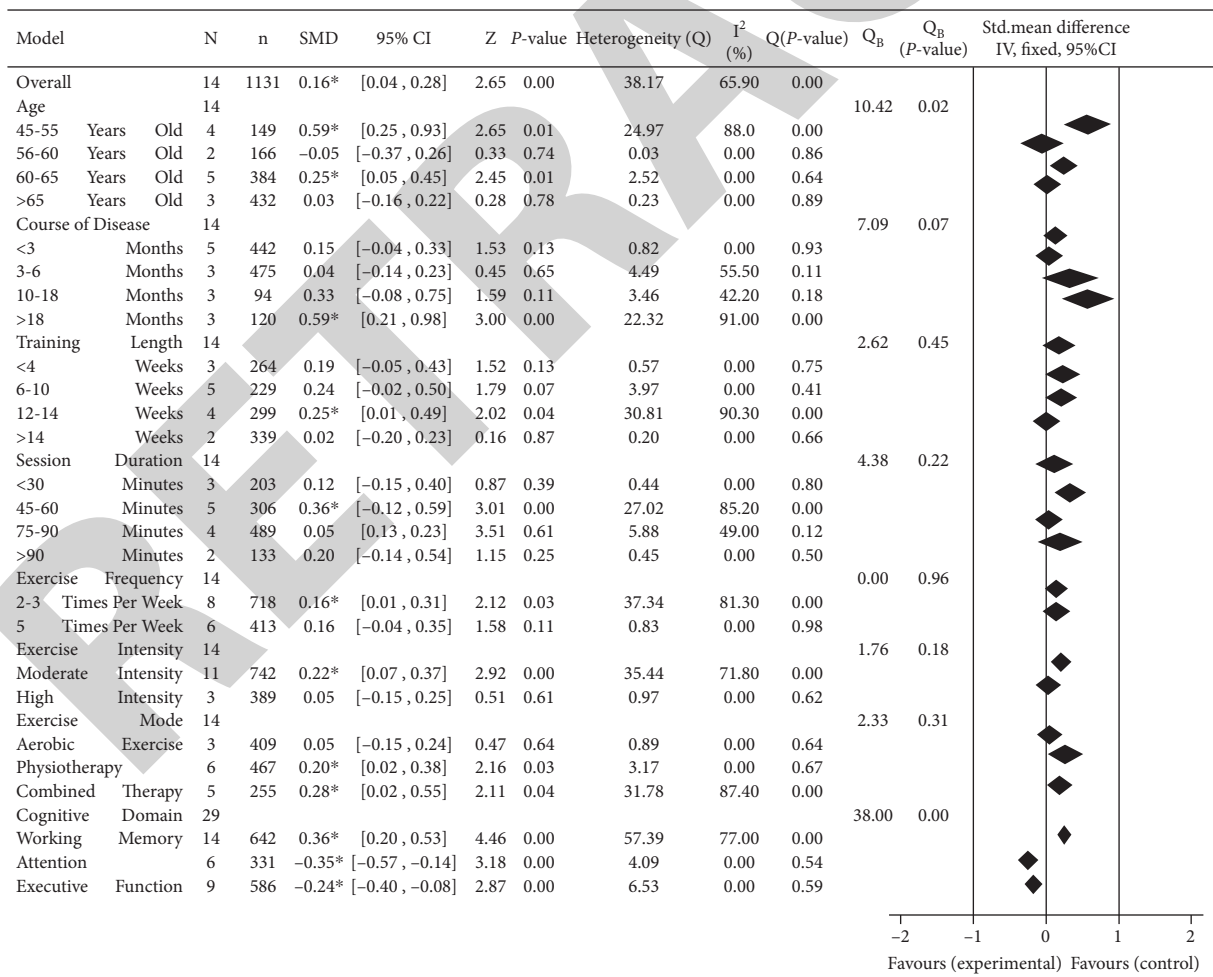


FIGURE 4: Effect sizes for each subgroup within the included studies.

To assess the influence of trial length, studies were stratified based on trial length, and the mixed-effect analysis showed that longer intervention length did not yield better cognitive gain ($QB = 2.62$; $P > 0.05$). Moderating-effect analysis revealed that 12 to 14 weeks' exercise intervention was associated with the greater magnitude of cognitive gains ($SMD = 0.25$; $CI: 0.01-0.49$; $P < 0.05$), but longer or shorter intervention showed less effectiveness on improving cognitive function ($P < 0.05$).

As for the influence of exercise frequency, mixed-effect analysis of intervention frequency showed that higher-frequency intervention did not associate with the better cognitive gains ($QB = 0.00$; $P > 0.05$). While moderating-effect analysis demonstrated that 2 or 3 times per week may maximize cognitive gains ($SMD = 0.16$; $CI: 0.01-0.31$; $P < 0.05$), excessive exercise did not have a significant effect on cognitive gains ($SMD = 0.16$; $CI: -0.04-0.35$; $P < 0.05$) (Figure 4).

Of the studies that examined the effects of session duration, no significant difference was found between different durations ($QB = 4.38$; $P > 0.05$). While moderating-effect analysis showed that the cognitive gains were not increased with longer duration, 40–60 minutes' training for each session had favourable effects on cognitive function ($SMD = 0.36$; $CI: 0.12-0.59$; $P < 0.05$). However, once the session duration beyond this range could not produce significant cognitive benefit (Figure 4).

We also examined whether the magnitude of cognitive gains differed depending on exercise intensity. Mixed-effect analysis demonstrated that high-intensity exercise was not associated with better cognitive gains ($QB = 1.76$; $P > 0.05$). On the contrary, moderate-intensity exercise training was most likely to maximize cognitive gains ($SMD = 0.22$; $CI: 0.07-0.37$), while the pooled effect size for trials using high-intensity exercise was not ideal in cognitive improvement ($SMD = 0.05$; $CI: -0.15-0.25$; $P > 0.05$) (Figure 4).

The type of exercise training was also assessed to examine the influence of different exercise training on cognitive function involving (1) aerobic exercise, (2) physiotherapy, or (3) combination of aerobic exercise/physiotherapy/cognitive training. However, no significant difference was found between three physical activities in cognitive improvement ($QB = 2.33$; $P > 0.05$). Moderating-effect analysis shows that the cognitive improvement from aerobic exercise alone was not significant ($SMD = 0.05$; $CI: -0.15-0.24$; $P > 0.05$). On the contrary, physiotherapy with strength/endurance/flexibility/balance may generate relatively ideal cognitive gains ($SMD = 0.20$; $CI: 0.02-0.38$; $P < 0.05$), while combined therapy generates the largest cognitive benefits ($SMD = 0.28$; $CI: 0.02-0.55$; $P < 0.05$) (Figure 4).

We also investigated the specific benefit and difference among three cognitive domains induced by exercise training, and significant differences were found in cognitive gains between three domains ($QB = 38.0$; $P < 0.05$). Of the three domains, exercise training generated the greatest and most significant effect on working memory ($SMD = 0.36$; $CI: 0.20-0.53$; $P < 0.05$), followed by attention ($SMD = 0.36$; $CI:$

$0.20-0.53$; $P < 0.05$) and executive function ($SMD = 0.36$; $CI: 0.20-0.53$; $P < 0.05$) (Figure 5).

3.4. Publication Bias. We created funnel plots by plotting the cognitive benefit of exercise training against the reciprocal of the standard error of the exercise efficacy. The funnel plot of overall cognitive function, attention, and executive function was symmetrical around the mean effect size line. For working memory, the funnel plot suggests the occurrence of publication bias. The asymmetry of graphic plot might be owing to the fact that smaller sample studies showing less effectiveness were reported in the literature, and the omission of the unpublished trials may also contribute to the biased estimation (Figure 6).

4. Discussion

Impairment of cognitive and motor function after stroke seriously affects the quality of life, while physical activity is highly praised for its high practicability in cognitive and motor function recovery after stroke. These meta-analytical findings indicated a small but significant positive effect of exercise on cognition in survivors after stroke relative to controls, and moderating-effect analysis showed that cognitive benefits are affected by different moderators by which exercise-related benefits for cognition can be optimized. Mixed-effects analysis showed that the cognitive benefits of exercise appear to be selective rather than general, as effect sizes differed significantly between the age groups. Moreover, our subgroup analysis further indicated that the lower the age of stroke survivors (49–55 years), the better the cognitive recovery after exercise training. However, cognitive benefits of exercise decrease with age (60–65 years), especially when the stroke survivors are above 65 years of age; it is difficult to obtain any effective cognitive improvement from exercise training. The reason may be that the volume of hippocampus and the thickness of white matter and gray matter in prefrontal cortex which related to cognitive function decrease with age. At the same time, due to the narrowing of blood vessels, the blood flow through the brain decreases, which hinders the formation of new capillaries, thus leading to the loss of existing nerve cells and synapses and further degeneration of myelin sheath, blocking the functional connection between nerve synapses, and ultimately affecting cognitive function [39]. However, exercise training exerts greater effects on many of the aforementioned processes. For instance, a certain degree of exercise training can promote the normalization of growth factor secretion (BDNF, IGF-1, NGF, and VEGF) [40], reversing the atrophy of hippocampal volume and prefrontal cortex effectively and then delaying the decline of cognitive function [41]. However, due to the motor dysfunction after stroke and the inability of elderly survivors to adapt to high-intensity physical activities, it is difficult for exercise training to play its due role.

Regarding the influence of time from stroke onset to initiation of the intervention, our analysis demonstrated that neither exercise training soon after stroke within three

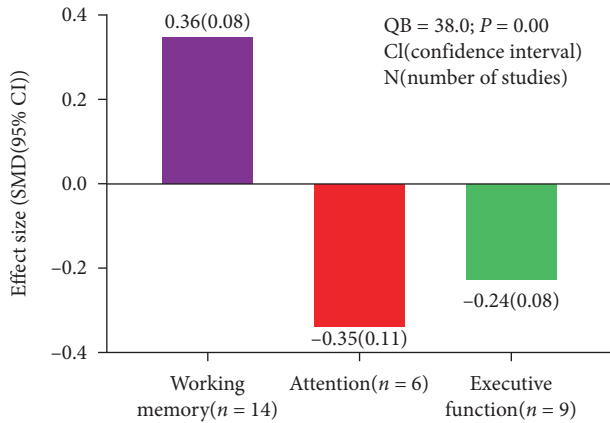


FIGURE 5: Mean effect of PA on cognitive domain. Significant difference ($P < 0.05$) was observed between three domains.

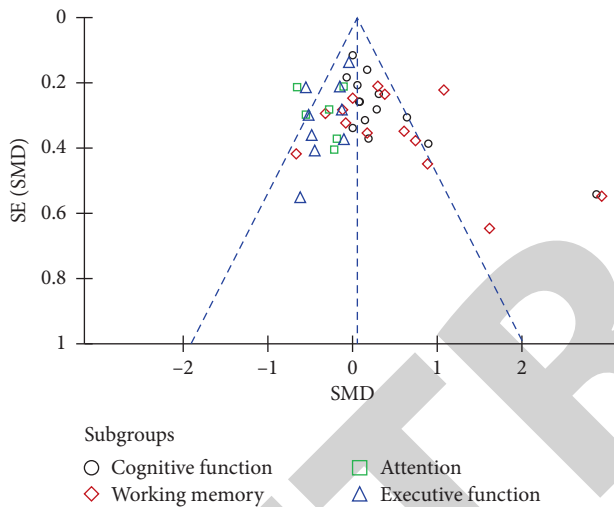


FIGURE 6: Funnel plot of cognitive benefit of exercise.

months nor that from month three to month eighteen after stroke exerts fewer positive effects on cognition. On the contrary, exercise training after 18 month of stroke onset can effectively promote the recovery of impaired cognitive function, and this conclusion is consistent with the existing studies [17]. The unsatisfactory effect among trials introducing exercise training within 3 months after stroke may, in part, be a consequence of conflicts with the short-lived plasticity window after stroke, for most spontaneous recovery phase of endogenous repair occurring in the first three months after stroke, which also is the best sensitive period of brain plasticity after stroke [42]. At this moment, the primary task is to recuperate the body to restore the body function and immunity. Meanwhile, psychological guidance is also needed for stroke survivors to shape an optimistic and positive attitude in the long-term rehabilitation process. Introducing exercise training in this time may hinder the potential plasticity change of the damaged brain area and aggravate the trauma [43]. Other studies show that exercise training within 24 hours after stroke increases the concentration of hyperglycolytic related markers and the risk of

apoptotic cell death [44]. Nonetheless, the existing animal model studies support the priority of early exercise intervention (1–7 days) in reducing lesion volume in damaged brain regions, preventing further damage of surrounding tissues from inflammation and oxidation [40, 45], and then promoting nerve regeneration. However, there is still insufficient evidence to support that the best sensitive period in animal models applies equally to human rehabilitation [46].

The effect size of exercise varied in different exercise training lengths. Moderating-effect analysis revealed that exercise training length neither less than 4 weeks nor from 6 to 10 weeks can generate insufficient effect accumulation. However, cognitive function improved significantly only in trial with exercise period of 12 to 14 weeks, while once the training cycle extended beyond 14 weeks, the cognitive benefit disappeared again, which is consistent with the prior studies [47]. At present, the cycle of exercise intervention after stroke is mainly controlled within 12 weeks. So far, no clear optimal cycle has been proposed in existing study. But known studies have shown that [48] aerobic training after stroke lasts at least eight weeks to have a positive effect on cardiopulmonary and cognitive function, and a recent study further demonstrated [49] that 12-week aerobic exercise not only has good patient tolerance but also produces appropriate long-term potentiation on physical and mental health.

Our analysis also found that session duration for each exercise intervention should be controlled within an appropriate range to produce the ideal cognitive gain, and extra time cannot generate additional cognitive improvement. Among them, cognitive benefits of exercise training may not be significantly improved if the exercise training time was less than 30 minutes for each session duration. Similarly, if the session duration was beyond one hour for each time, the cognitive function cannot be significantly improved as well. In contrast, only when the intervention time is controlled within 45 to 60 minutes can the cognitive benefit reach a significant level. The reason why the cognitive benefits of this exercise duration reach the maximum level in 45 to 60 minutes may be because the exercise intervention of this duration can obviously improve the glucose tolerance [27] and insulin sensitivity [50] of patients, while restoring motor and balance ability [51], reversing the decline of cardiopulmonary function caused by impaired motor function, and gradually improving self-perception [52] of the body and cognitive function [53].

As for exercise frequency, our subgroup analysis indicated that there was no significant difference in cognitive benefit between different exercise training frequencies for each week, and higher-frequency training did not significantly improve cognitive function. Instead, maintaining exercise training 2 to 3 times per week is more conducive to the improvement of cognitive function. This is in line with the latest international stroke exercise care guidelines [53]. The cognitive benefit of aerobic exercise is a cumulative process, and it is mainly determined by the interaction of frequency, intensity, and duration. At present, the exercise training frequency in the known studies mainly ranges from 2 to 5 times per week but more often 3 times per week according to the baseline fitness levels at the initial stage of

the intervention [54], the status of cardiopulmonary function and nervous system injury, the existence of comorbidity, and so forth. This may be because exercise intervention should ensure the maximum cognitive benefit and higher compliance of the subjects after each session. However, studies have shown that [55] only when the training frequency is kept at 2 to 3 times per week can the survivors show the highest compliance of 23%, and once the exercise frequency is increased to 4 times per week, the compliance is slightly reduced to 19%. However, when the frequency reaches 5 times per week, the compliance of subjects is only 9%. Therefore, after considering the cognitive gain of exercise and the participants' compliance comprehensively, it is considered that 2 to 3 times per week of exercise can maximize the cognitive gain.

Moreover, we found that cognitive benefit was not related to the higher exercise intensity. Moderating-effect analysis further shows that high-intensity exercise does not generate higher cognitive gain. Instead, exercise training at moderate intensity is more conducive to the improvement of cognitive function. This may be because the rehabilitation programs after stroke are based on health status and physical response to exercise training, by optimizing the dose-response relationship among exercise frequency, duration, and intensity with cognitive function, to avoid muscle soreness and fatigue during training and alleviate further cognitive damage [56]. Other studies also show that [57, 58] low-intensity physical activity is insufficient to generate enough cognitive benefit similar to moderate-intensity aerobic exercise. Therefore, it is necessary to ensure sufficient exercise dose/intensity to produce cognitive improvement effect while avoiding adverse physical reactions caused by excessive stress. Therefore, higher intensity within a reasonable range can generate greater improvement in cardiopulmonary and cognitive functions. However, before the best cognitive gain is achieved, safety and feasibility must be considered. Therefore, at the beginning of rehabilitation exercise program, participants should start with moderate intensity with lower risk of abnormal reaction [59].

We also investigated differences in efficacy as a function of type of exercise regimen, and the result indicated that exercise training involving only aerobic exercise did not yield significant cognitive benefits. While physiotherapy consisting of stretching/balance/strength training achieved significant effects in cognitive improvement, combined therapy (aerobic exercise/physiotherapy/cognitive training) generated the largest cognitive benefit. Although the negative results of aerobic exercise only here may be due to insufficient statistical test, there are still empirical studies pointing out the limitations of aerobic exercise alone [60]. Moreover, there is ample evidence that multiway combination therapy can not only avoid monotonicity and improve participants' compliance [61] but also improve efficiency of cognitive recovery and shorten exercise training length [62].

Our final analysis of exercise efficacy on cognitive domains showed that there were significant differences in the improvement of three cognitive domains by exercise training, indicating that not all domains of cognitive

function get equal improvement, among which exercise has the greatest effect on improving working memory, followed by attention and finally executive function. These results are more specific than those of the previous meta-analysis [17]. First of all, due to the insufficient power ($n = 5$) in detecting the effectiveness of exercise training on working memory, the results are suspected of overestimation. A total of 14 relative studies on working memory were included in our analysis to avoid errors caused by small samples. Secondly, the included studies on executive function are also increased compared with the previous meta-analysis, and the corresponding cognitive benefit has also reached a significant level among the experimental groups, relative to controls. However, analysis on attention performance has not changed compared with the previous meta-analysis, which to some extent makes up for the shortcomings of previous studies.

5. Summary

In summary, results from our quantitative synthesis and meta-analysis support a small but significant improvement of cognitive function after stroke after aerobic exercise training. Our findings indicated that cognitive benefits can be maximized in specific exercise regimen; all types of exercise training seem to be effective, but combined exercise therapy promises more pronounced cognitive benefits compared with aerobic exercise alone and physiotherapy. The positive efficacy of exercise on cognitive function cannot be maximized by roughly increasing the total dose. Instead, under the premise of moderate-intensity exercise, we recommend the 2 to 3 times a week, 45 to 60 min for each session duration and lasting for 12 to 14 weeks to maximize their cognitive benefits. Additionally, exercise training is less effective in the earlier stage after stroke; 18 months after stroke is optimal for the initiation of exercise interventions; exercise training generated the most favourable effects for survivors aged 49 to 55 years. Beyond recommendations for optimizing cognitive performance from different exercise regimen, our findings have further implications for future study, including identifying the effects of cognitive level at the initiation of the training and its interaction with exercise regimen, avoiding the interference of baseline cognition level to the overall effect of the exercise training. Moreover, the optimal training parameters also need to be considered carefully to realize the precision of exercise intervention effect.

However, some limitations still remain in this study. For example, because of the stricter inclusion criteria, a limited number of studies were included; therefore significant heterogeneity remained after subgroup analysis. Furthermore, as all data analyzed in this study were abstracted from published literature results instead of raw data, the authenticity of data cannot be guaranteed, and the publishing bias is therefore unavoidable. In addition, the included studies are all from English-based journals, which may ignore the potential differences between countries. Based on the above risks, larger trials are needed to evaluate the cognitive benefit of exercise, in order to better understand

the moderator effect of session duration, exercise intensity, and training length. Finally, future research should be carried out to evaluate the effect of long-term adherence to exercise after stroke.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest reported in this paper.

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