

Review Article

Effects of Combined Physical Activity and Cognitive Training on Cognitive Function in Older Adults with Subjective Cognitive Decline: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Qianqian Sun,^{1,2} Shurui Xu,^{1,2} Shuai Guo,^{1,2} Yue You,^{1,2} Rui Xia,² and Jiao Liu ^{1,2,3,4}

¹College of Rehabilitation Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China

²National-Local Joint Engineering Research Center of Rehabilitation Medicine Technology, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China

³Traditional Chinese Medicine Rehabilitation Research Center of State Administration of Traditional Chinese Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China

⁴Key Laboratory of Chinese Medicine Orthopedics and Sports Rehabilitation of Ministry of Education, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China

Correspondence should be addressed to Jiao Liu; liujiao0415@outlook.com

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Background. Subjective cognitive decline (SCD) is recognized as the earliest prodromal stage of Alzheimer's disease (AD). Emerging studies explored the effects of combined physical activity and cognitive training interventions on cognitive ability, psychological well-being, and emotion of older adults with SCD, but the results are now still controversial. **Objective.** This study systematically evaluated the enhancement effects of the combined physical-cognitive interventions on memory self-efficacy, objective cognitive function, psychological well-being, and emotion of older adults with SCD. **Methods.** Data sources PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang degree and conference papers database, Chinese Science and Technology Periodical (VIP) databases from their inception to 28 February 2020, the Cochrane Central Register of Controlled Trials (Cochrane Library, 2020, Issue 3), and the reference lists of all retrieved articles were searched. Data analysis and bias risk evaluation were conducted in 2020. Two reviewers (SG and YY) independently evaluated the risk of bias of the included studies using the RoB 2 tool. **Results.** Eleven RCTs involving 1713 participants with SCD (age 68.0 ± 6.1) were included for review and meta-analysis. The interventions in the included studies were physical activity combined with cognitive training. Multiple-modality exercise with mind-motor training, supervised strategy-based memory training sequentially after stationary cycling, Dejian Mind-Body intervention, and physical activity and cognitive stimulation were also practiced. **Conclusions.** Compared to the active or nonactive control groups, the combined interventions are effective in improving objective cognitive function in SCD which may show the potential value of combined physical-cognitive interventions in improving objective cognitive ability and preventing the conversion of SCD to MCI or AD and no adverse effects. However, owing to the limitations of the included studies, these findings should be interpreted cautiously.

1. Introduction

As the population ages, concerns about cognitive decline increase. 2020 Alzheimer's disease (AD) facts and figures described that total payments are to be \$244 billion in 2019 for health care, long-term care, and hospice services for people aged ≥ 65 years with dementia in the United States.

The average per-person Medicare payments for services to beneficiaries of age ≥ 65 years with (AD) or other dementias are more than three times as great as payments for beneficiaries without these conditions (more than 23 times as great) [1]. AD remains the most common cause of dementia [1, 2]. Early detection and intervention of Alzheimer's disease offer numerous medical, emotional, and financial

benefits that accrue to affected individuals and their families as well as to the society at large [3].

Studies have been made to identify individuals who are at increased risk of AD and to test interventions that might delay the progression of preclinical stage prodromal to full-blown dementia [4–6]. Subjective cognitive decline (SCD) has been identified as a condition where some individuals experience subjective cognitive complaints, but the cognitive performance by neuropsychological tests and daily function shows no evidence of objective cognitive impairment. SCD is increasingly recognized as the earliest prodromal stage of AD [7–10]. 74% of people aged 70 years and older who perform normally on standard cognitive tests self-report a subjective decline in cognitive functioning [11]. SCD individuals showing the positivity of pathophysiological AD biomarkers show a risk of progression similar to MCI patients [6]. Some studies showed that amyloid and tau protein PET imaging investigations in cohorts of aging individuals (>60 years of age) who were cognitively unimpaired showed a quantitative association between the extent of either amyloid or tau pathology with the severity of cognitive concerns experienced by individuals [12–14]. Other studies have investigated markers of neurodegeneration in individuals with SCD. In particular, cross-sectional studies [15–17] have shown that these individuals have small reductions in the volume of brain regions that typically show loss of volume in the early stages of AD (e.g., the medial temporal lobe) when compared with control groups of individuals without SCD. Besides, some studies [16, 18] have identified AD-associated patterns of glucose hypometabolism in individuals with SCD, whereas other studies [19] have not. In addition, individuals with SCD who harbor the major genetic risk factor APOE ϵ 4 for AD are at an increased risk of being at individuals with SCD who do not carry the disease-associated APOE ϵ 4 [20]. It is likely that a relationship between APOE ϵ 4, SCD, and AD exists, though its exact nature remains undetermined [21].

Livingston et al. considered SCD as a critical window of opportunity to intervene and alter the trajectory of both cognitive and functional decline in seniors [22]. It would be more appropriate to prevent or postpone the AD process by intervention in the SCD stage. However, until now, the positive effect on the cognitive ability and behavioral symptoms of SCD individuals of medication was controversial [23–26]. The available evidence suggests that non-pharmacologic interventions may benefit current cognitive function in persons with SCD [27, 28]. Extensive evidence indicates that physical activity may improve cognitive health outcomes such as mental health, physical health, and quality of life for older adults with SCD. Tailored physical activity guidelines are needed to support strategies for dementia risk reduction [29]. Emerging reviews of the evidence have led international health organizations, including the World Health Organization (WHO), the American National Institutes of Health, and the British National Institute of Health and Care Excellence, to advocate for physical activity as both a primary prevention (in cognitively healthy individuals) and a secondary prevention (in individuals who have no dementia but already experience cognitive decline)

strategy for reducing dementia risk [30–33]. The Canadian Physical Activity Guidelines for adults with SCD also have been developed [34].

Physical activity was associated with brain health benefits, including possible improved cognitive function, reduced anxiety, and depression risk, and improved sleep and quality of life [35]. Recent meta-analyses of randomized controlled trials show that physical activity also may be a promising intervention in the cognition of included subjects with dementia and mild cognitive impairment (MCI) [36, 37]. Cross-sectional studies, longitudinal observational studies, and prospective intervention trials also supported this evidence [38, 39].

By adding, exposure to a cognitively challenging environment could enhance the neural and cognitive benefits elicited by physical activity in humans and animals [40, 41]. A review indicated that the new generation of prevention trials is addressing some of the problems encountered in previous trials by testing interventions during the optimum window of exposure (i.e., earlier in the course of the disease, even in the preclinical phase), using multidomain rather than single-domain intervention strategies [42]. Some studies observing the synergistic effect of exercise and cognitive training interventions were associated with improved cognitive performance in older adults [43, 44]. A meta-analysis found that combined cognitive and physical exercise training can improve global cognition in older adults with MCI or AD and were beneficial for activities of daily living and mood [45].

However, for the elderly with SCD, combined physical-cognitive interventions on cognitive function are equivocal. The topic of interventions in this population has been relatively unexplored. For instance, compared with an active or nonactive control group, whether combined physical-cognitive interventions prevent cognitive decline is unclear. In the present study, we aimed to systematically evaluate the effect of combined physical-cognitive interventions on memory self-efficacy, objective cognitive function, general psychological well-being, and emotion.

2. Methods

2.1. Selection and Identification of Studies. Seven electronic databases, including PubMed, EMBASE, Web of Science (SCI, Science Citation Index), China National Knowledge Infrastructure (CNKI), Wanfang degree and conference papers database, Chinese Science and Technology Periodical (VIP) databases from their inception to 28 February 2020, and the Cochrane Central Register of Controlled Trials (Cochrane Library, 2020, Issue 3), were searched without language restrictions. Relevant keywords related to physical activity as Medical Subject Heading terms and text words (e.g., “Multiple training modalities” or “Physical activity” and “Activity”) were used in combination with words related to subjective cognitive decline (e.g., “Subjective Cognitive Decline,” “Subjective Cognitive Impairment,” “Cognitive complaints,” “Subjective Memory Decline,” and “Subjective Memory Impairment”). The unpublished/grey literature was searched using ClinicalTrials.gov, the National Research

Register, the Chinese Master's Theses Full-Text Database, China Doctor Dissertation Full-Text Database, and China Proceedings of Conference Full-Text Database. Additional trials were found through the reference lists of all retrieved articles (please see the full search strategy in Table 1). Literature search, study identification, and data extraction were conducted from February to April 2020. All searched records were imported into the reference management software (Note Express V.3.2) to eliminate duplicate records. The full texts of the studies that potentially met the inclusion criteria were obtained to further evaluate their eligibility. Any disagreements were resolved by discussion with the third reviewer (QS). The review was registered at the International Prospective Register of Systematic Review, PROSPERO (Registration number: CDR42020181482, <https://www.crd.york.ac.uk/prospERO/>).

2.2. Inclusion Criteria. The trials selected in this review met the following inclusion criteria: (1) study design: published randomized controlled trials (RCTs) were included; (2) participants should be older adults (age: 55 years and older) with self-reported cognitive complaints, without objective evidence of deficits on cognitive tests and unaccounted for medical or psychiatric causes (e.g., dementia, MCI); (3) intervention: physical activities (e.g., aerobic activity, muscle-strengthening activity, bone-strengthening activity, balance activity, and multicomponent activity) combined with cognitive training (e.g., cognitive training, memory training, psychological interventions) were practiced in the experimental group for at least 2 weeks; (4) control should be memory intervention, mental training, or health education (e.g., psychoeducation, cognitive restructure, stress management, relaxation, and mindfulness); (5) outcomes: we used subjective memory measures as the primary outcome and objective cognitive function, psychological well-being, and emotion as the second outcomes. Those without available data were excluded.

2.3. Data Extraction. The data were extracted by one reviewer (SX) using the prepared form and checked for accuracy by another reviewer (QS). The extracted information from eligible studies included participants' characteristics, sample size, study design, methodological information of study quality, experimental and control intervention, duration, frequency, intensity and style of aerobic exercise, outcomes, and adverse events.

2.4. Assessment of Risk of Bias in Individual Studies. Two reviewers (SG and YY) independently evaluated the risk of bias of the included studies using the RoB 2 tool, a revised Cochrane risk of bias tool for RCTs, which is a widely used quality assessment tool for evaluating RCTs [46]. The RoB 2 tool includes domains such as randomization process, deviations from intended interventions, missing outcome data, outcome measurement, selection of the reported result, and overall bias [46]. The overall judgment of each item for each study was categorized as "low risk," "high risk," and "some

concerns" according to the levels of bias. Discrepancies between reviewers were resolved by the third reviewer (JL).

2.5. Statistical Analysis. Review Manager Software V.5.3 was used for the statistical analysis which was provided by Cochrane Collaboration, and the statistical significance was defined as a two-sided P value < 0.05 . Data were summarized using relative risk with 95% CI for binary outcomes and mean difference (MD) or standardized MD (SMD) with corresponding 95% CI for continuous outcomes. The pooled effect was calculated using the fixed-effect model if data were available and no significant heterogeneity was detected. Otherwise, the random-effect model was applied. Statistical heterogeneity was assessed using the I^2 statistic. However, the overall pooled analysis was not considered appropriate when the heterogeneity among studies was high ($I^2 > 75%$); clinical or methodological heterogeneity was considered the potential causes. Heterogeneity among studies was explored using a χ^2 test and Higgins I^2 values [46]. In view of possible heterogeneity between studies, studies with different intervention types were divided into subgroups for analysis according to different factors.

Due to the diversity of the outcome measures related to objective cognitive function in the included studies, and the relatively small number of studies meeting the inclusion criteria, we chose to combine outcomes of global cognitive ability and specific domains of cognition (i.e., memory, attention, executive ability, and verbal fluency) into objective cognitive function. Moderator analyses will be used conducted to explain the variance between groups if the heterogeneity among studies was high ($I^2 > 75%$).

3. Results

3.1. Study Selection. 2100 records were identified from preliminary searches according to the predetermined search strategy. Two reviewers (SX, GS) disregarded obviously irrelevant records based on the abstract or title. A total of 53 potential studies were further evaluated for their eligibility, and 15 studies ultimately fulfilled the inclusion criteria [47–62]. However, 4 studies did not provide the original data [49, 50, 60, 61]. We attempted to contact the original authors by e-mail but did not receive any responses. Therefore, we excluded these studies. Finally, 11 studies involving 1713 participants with SCD were included in the review. The detailed literature search and screening flow is presented in Figure 1.

3.2. Study Characteristics. The characteristics of each included study were summarized in Table 1. Eleven RCTs involving 1713 participants with SCD (age 68.0 ± 6.1) were included for review. The included studies came from Canada (two) [47, 60], United States (four) [51, 56, 58, 59], China (one) [52], Australia (two) [53, 57], and France (two) [54, 55]. Participants were recruited from community [47, 51, 55, 56], social centers [52], social clubs, or personal [54, 58, 59], memory clinics [57, 60], or hospitals [53]. All included studies reported clear diagnostic inclusion and

TABLE 1: Characteristics of included studies.

Author/Year	Mean age	N(M/F)	Intervention	Frequency, duration and intensity	Outcomes/measure
Boa et al. 2020 [47–50]	T: 67.6± 7.5 C: 67.4± 7.2	127 (37/90)	T: Physical activity combined cognitive training C: Active control	60 min/day, 3 days/week, 24 weeks 65–85% of maximum HR	Working memory/ Monkey Ladder Spatial short-term memory/Spatial Span Verbal working memory/Digit Span Visuospatial paired associate learning/ Paired Associates Composite memory/ Verbal and Visual Memory Test Attention/Stroop Test Executive function/CNS Processing speed/CNS Memory/HKLLT Immediate recall/WMS-III-VR delayed recall/WMS-III-VR Global cognitive function/CDR, ADAS-Cog immediate recall/word list
McEwen et al. 2018 [51]	T: 65.4± 3.0 C: 67.0± 5.1	55 (17/38)	T: Memory training after station cycling (SEQ) C: Active control	120 min/day, 2 days/week, 4 weeks 65% HRR	Global cognitive function/CDR, ADAS-Cog immediate recall/word list
Chan et al. 2017 [52]	T: 68.3± 4.4 C: 69.5± 6.9	48 (12/36)	T: Dejian Mind-Body C: Active control	150 min/day, 1 days/week, 10 weeks	Global cognitive function/CDR, ADAS-Cog immediate recall/word list
Lautenschlager et al. 2008 [53]	T: 68.6± 8.7 C: 68.7± 8.5	170 (84/86)	T: Physical activity C: Active control	50 min/day, 3 days/week, 24 weeks Moderate intensity	Global cognitive function/CDR, ADAS-Cog immediate recall/word list
Fabre et al. 1999 [54]	AMT: 64.9± 3.9 AT: 65.4± 6.2 C: 67.5± 3.4	24	AMT: Physical activity combined cognitive training AT: Physical activity C: Control	90 min/day, 1 days/week, 2 months	Global cognitive function/Composite score Memory/WMS Depression/BDI Mentality/ MCS Physical fitness/ PCS Memory/SQLP Depression/SQLP Mentality/SQLP Physical fitness/SQLP
Andrieu et al. 2017 [55]	T: 75.0± 4.1 C: 75.1± 4.3	770 (266/504)	T: Physical activity combined cognitive training C: Control	120 min/day, 2 days/week for the first month, and 120 min/day, 1 day/week for the second month, then 1 60 min/month, 36 months	Global cognitive function/Composite score Memory/WMS Depression/BDI Mentality/ MCS Physical fitness/ PCS Memory/SQLP Depression/SQLP Mentality/SQLP Physical fitness/SQLP Global cognitive function/Composite score Memory/FCSRT Executive function/TMT-B Information processing speed/DSST Verbal fluency/COWAT Attention/Ten MMSE orientation items Depression/GDS Mentality/ Consequences of everyday life Subjective memory function/Memory functioning Physical fitness/SPPB Depression/PSS Mentality/MUNSH Subjective memory function/FOF Physical fitness/CHIPS
Zuniga et al. 2016 [56]	T 66.4± 5.7	179 (62/117)	T: Physical activity C: Active Control	60 min/day, 3 days/week, 12 months 50–75% HRR	Global cognitive function/Composite score Memory/FCSRT Executive function/TMT-B Information processing speed/DSST Verbal fluency/COWAT Attention/Ten MMSE orientation items Depression/GDS Mentality/ Consequences of everyday life Subjective memory function/Memory functioning Physical fitness/SPPB Depression/PSS Mentality/MUNSH Subjective memory function/FOF Physical fitness/CHIPS

TABLE 1: Continued.

Author/Year	Mean age	N(M/F)	Intervention	Frequency, duration and intensity	Outcomes/measure
Cox et al. 2013 [57]	T: 68.2± 9.8 C: 65.6± 4.7	170 (84/86)	T: Combined C: Control	50 min/day, 3 days/week, 6 months Moderate intensity	Mentality/SCI Memory/VLM
Small et al. 2006 [58]	T: 54± 12 C: 53± 10	17 (6/11)	T: Physical activity combined cognitive training C: Control	30-45 min/day, 7 days/week, 2 weeks	Verbal fluency/Word-generation (letter-fluency) test Subjective memory function/MFQ Global cognitive function/Composite score
Barnes 2013 [59]	T: 74.8± 6.1 C: 73.9± 6.3	95 (34/61)	MA-I/EX-I: Physical activity combined cognitive activity MA-C/EX-I: Physical activity C: Active control	60 min/day, 3 days/week, 6 months 65–85% of maximum HR	Memory/RAVLT Executive function/TMT-B Information processing speed/DSST Verbal fluency/Letter and Category Attention/UFVO
Nagamastu et al. 2013 [60]	T: 75.6± 3.6 C: 75.1± 3.6	58	T: Physical activity C: Active control	60 min/day, 2 days/week, 6 months 40–80% HRR	Verbal Memory and Learning/RAVLT

CNS, computerized CNS Vital Signs Memory Protocol test; HKLLT, Hong Kong list learning test; WMS-III-VR, visuospatial reproduction subtest of the Wechsler Memory Scale III; CDR, Clinical Dementia Rating; ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive Subscale; DSC, digit symbol coding; VFT, verbal fluency total; BDI, Beck Depression Inventory; MCS, Medical Outcomes 36-Item Short Form (SF-36) mental component summary; PCS, SF-36 physical component summary; WMS, Wechsler Memory Scale; SQLP, the Subjective Quality of Life Profile; FCSRT, Free and Cued Selective Reminding Test; TMT-B, Trail Making Test B; DSST, Digit Symbol Substitution Test; COWAT, Controlled Oral Word Association Test; MMSE, Mini-Mental State Examination; GDS, the Geriatric Depression Scale; SPPB, the Short Physical Performance Battery; PSS, Perceived Stress Scale; MUNSH, Memorial University of New Foundland Scale of Happiness; FOF, Frequency of Forgetting scale; CHIPS, Cohen-Hoberman Inventory of Physical Symptoms; SCI, the Stage of Change Instrument; VLM, verbal learning and memory test; MFQ, The Memory Functioning Questionnaire; RAVLT, Rey Auditory Verbal Learning Test; UFVO, Useful Field of View.

exclusion criteria for their participants. The interventions of the included studies were physical activity combined with cognitive training. Multiple-modality exercise with mind-motor training (M4) [47], supervised strategy-based memory training sequentially after stationary cycling (SEQ) [51], Dejian Mind-Body intervention (DMBI) [52], and physical activity and cognitive stimulation [55] were also practiced. The majority of interventions occurred in physical activity combined with cognitive training, except for four studies reporting the physical activity.

The frequency of intervention varied from 1 to 5 sessions weekly and 30–150 mins per session. The duration of the intervention was from 2 weeks to 36 months. Of these, 11 studies compared combined physical-cognitive interventions with stretching and/or tone exercise, cognitive training, social activities, or health education. Since the lower intensity of those activities did not significantly alter the exercise habits of the participants, we believed that those activities did not differ. A heart rate reserve [51, 56, 60] from 40% progressed to 80%; 60–85% of maximum heart rate [47, 54, 59] or “moderate intensity” [53, 57] was applied to control the intensity of physical activity in the included studies; there was no description in others [52, 55, 58]. The intervention in the control group

was the very low intensity of activity/exercise such as social activities, stretching, balance and tone exercise, or health education.

The meta-analysis was conducted to analyze the cognitive outcomes and self-report outcomes, including cognitive function, psychological well-being, and emotion. There was a wide variety of measurement tools applied to evaluate the same cognitive domain within a study or among studies, including MMSE, ADAS-Cog, CDR, Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-LM), digit symbol coding (DSC), Trail Making Test (Parts A and B), Stroop test, letter verbal fluency test (LVFT), and category verbal fluency test (CVFT). Otherwise, there were kinds of scales to evaluate the mentality and physical fitness (i.e., The Short Form-12, SF-36), depression (i.e., BDI, 15-item Geriatric Depression Scale), and subjective memory impairment (i.e., Frequency of Forgetting Scale, Memory Performance).

3.3. Risk of Bias of Included Studies. The quality of the RCTs included was assessed by two reviewers independently by using the RoB 2 tool, a revised Cochrane RoB tool for randomized trials [56]. The risk of bias in each study is illustrated in Figure 2.

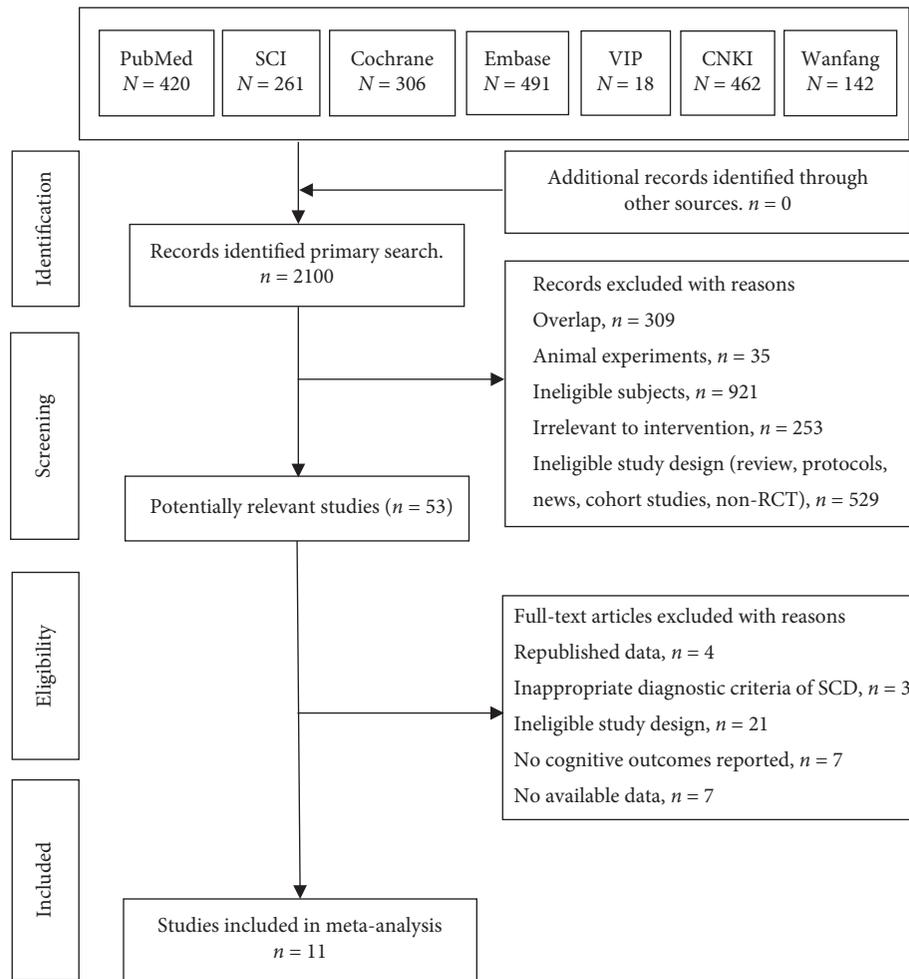


FIGURE 1: The literature searches and select flow diagram of the included studies. SCI, science citation index; VIP, Chinese Science and Technology Periodical database; CNKI, China National Knowledge Infrastructure; SCD, subjective cognitive decline; RCT, randomized controlled trial.

Five studies [47, 53, 55, 57, 60] were identified as having low risk in the randomization process, and six studies [51, 52, 54, 56, 58, 59] were identified as having uncertain risk. The risk of deviations from intended interventions was low in six studies [47, 53, 55, 57, 59, 60] and uncertain in five studies [51, 52, 54, 56, 58]. All studies [47, 51–60] had a low risk for missing outcome data. Seven studies [47, 53–55, 57, 59, 60] were identified as having low risk and four studies [51, 52, 56, 58] were identified as having high risk related to measurement of the outcome. Furthermore, seven studies [51, 53, 56–60] were uncertain risk and one study [52] was high risk in terms of the reported result selection. Finally, the risk of overall bias was noted as low in two studies [53, 55], uncertain in five studies [47, 54, 57, 59, 60], and high [51, 52, 56, 58] in four studies.

3.4. Effects of Interventions

3.4.1. Memory Self-Efficacy (MSE). Two studies [55, 58] involving 787 participants compared the combined cognitive-physical interventions with control groups in terms of

subjective memory function measured by memory functioning [55] and the Memory Functioning Questionnaire (MFQ) [58]. Compared with the control group, no significant improvement was found in the combined physical-cognitive interventions group in the subjective memory function ($n = 787$, $SMD = 0.04$, 95% CI -0.10 to 0.18 , $P = 0.54$; Figure 3).

3.4.2. Objective Cognitive Function. Seven studies [55, 59] reported the effects of combined cognitive-physical interventions on objective cognitive function in participants with SCD including global cognitive function, memory, executive ability, attention, and verbal fluency.

Three studies reported the effects of combined physical-cognitive interventions on composite memory, which were measured by the Free and Cued Selective Reminding Test, WMS, Verbal, and Visual Memory Test [51, 54, 55]. Two studies [47, 52] reported the effects of combined physical-cognitive interventions on immediate memory ability which was measured by Spatial Span and WMS. Three studies [51, 55, 59] involving a number of 889 participants

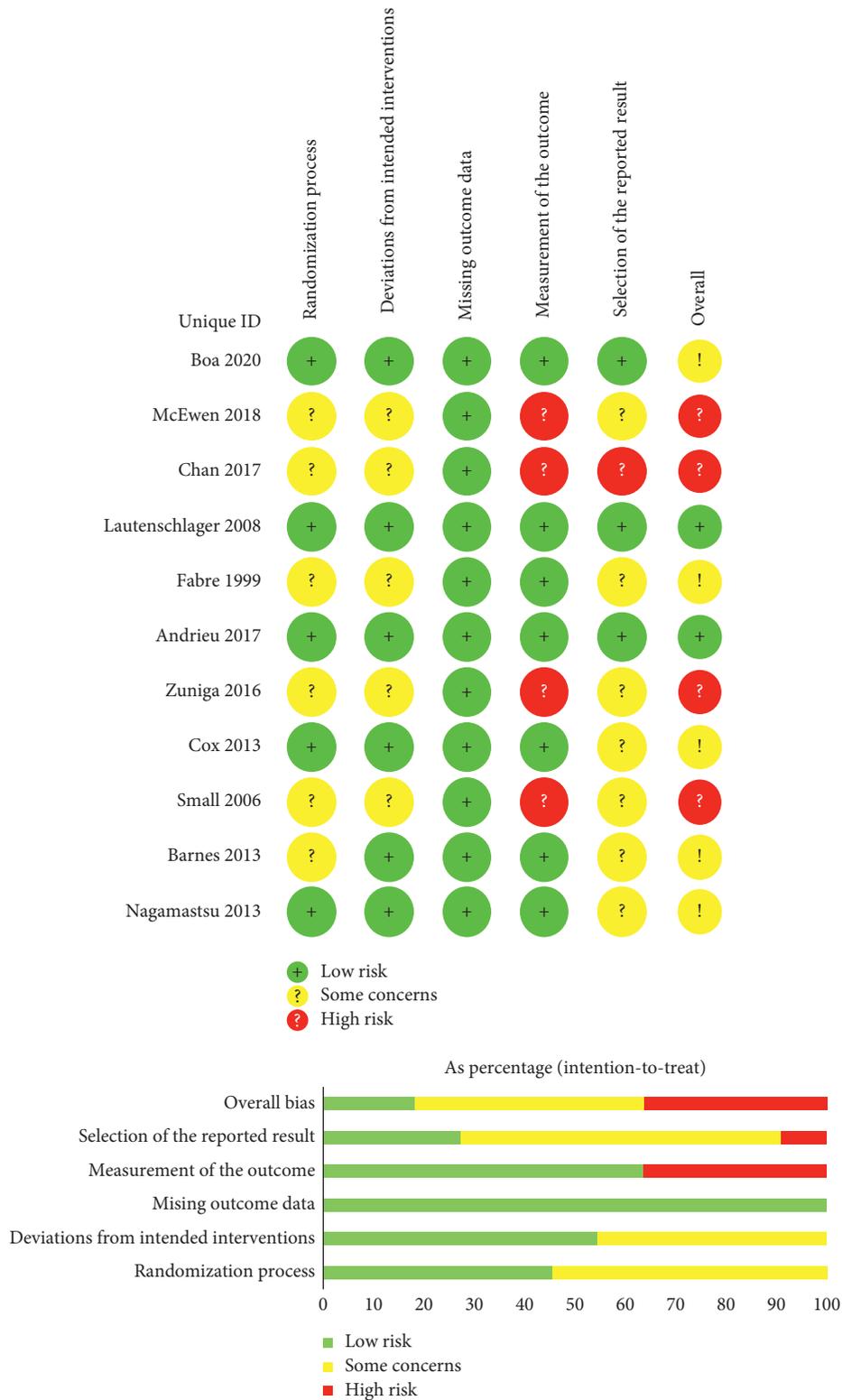


FIGURE 2: Summary of the risk of bias of the included studies: review authors’ judgments about each risk of bias item for each included study.

compared the combined physical-cognitive interventions and control groups in terms of attention, which was measured by Stroop test [51], ten MMSE orientation items [55], and Useful Field of View (UFOV) [59]. The effects of combined physical-cognitive interventions on executive

ability were evaluated in three studies [51, 55, 59] with a total of 882 participants using the Trail Making Test part B [55, 59] or CNS [51]. Three studies with 851 participants assessed verbal fluency using the COWAT [55], word-generation (letter-fluency) test [58], or verbal fluency test

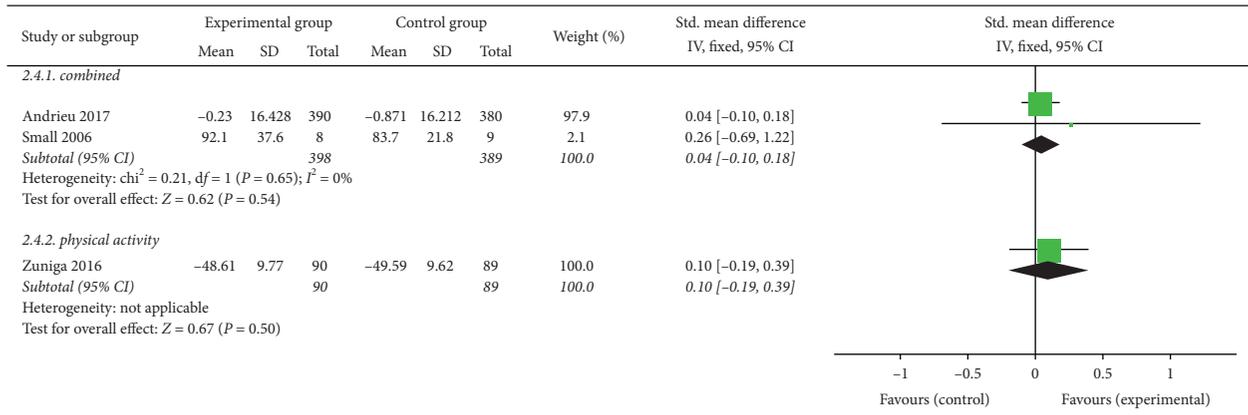


FIGURE 3: Forest plot for combined physical-cognitive interventions or physical activity on MSE. Combined: combined physical-cognitive interventions.

[59]. Owing to the different tools, we used SMD scores. The results showed that participants in the combined physical-cognitive interventions group had a significant improvement in SMD scores of objective cognitive function compared with the controls ($n = 5679$, $SMD = 0.12$, 95% CI 0.07 to 0.17, $P < 0.001$; $I^2 = 0\%$, the fixed-effect model; Figure 4). Moderator analyses were not conducted because of the heterogeneity statistics for the fixed-effect model confirming that there was no heterogeneity ($I^2 = 0\%$).

The effects of physical activity on objective cognitive function were evaluated in four studies [53, 54, 59, 60]. Meta-analysis showed that physical activity had a significant improvement in SMD scores of objective cognitive function compared with controls ($n = 1328$, $SMD = 0.13$, 95% CI 0.03 to 0.24, $P = 0.02$; $I^2 = 0\%$, the fixed-effect model; Figure 5).

3.4.3. Psychological Well-Being. Two studies [54, 55] reported the effects of combined physical-cognitive interventions on mentality, which was measured by SQLP [54], and the consequences of everyday life [55]. The results showed that participants in the combined physical-cognitive interventions group had no significant improvement in SMD scores compared with controls ($n = 786$, $SMD = 0.12$, 95% CI -0.02 to 0.26 , $P = 0.09$; Figure 6). Four studies [53, 54, 56, 57] involving 535 participants assessed the effects of physical activity on mentality measured by SF-36 mentality component summary [53], SQLP [54], Memorial University of Newfoundland Scale of Happiness [56], and the Stage of Change Instrument [57]. Meta-analysis showed physical activity had significant improvement of mentality ($n = 535$, $SMD = 0.22$, 95% CI 0.05 to 0.39, $P = 0.01$, $I^2 = 22\%$, the fixed-effect model; Figure 6).

3.4.4. Emotion (Depression). Three studies with 851 participants assessed depression using the Subjective Quality of Life Profile (SQLP) [54], Geriatric Dementia Scale (GDS) [55], and Perceived Stress Scale (PSS) [56]. Meta-analysis showed that combined physical-cognitive interventions had no significant improvement in depression ($n = 965$,

$SMD = -0.09$, 95% CI -0.21 to 0.04 , $P = 0.18$; Figure 7). Compared to the usual care control group, there was no significant improvement in the Beck Depression Inventory (BDI) scores in the physical activity group in two studies involving 186 participants ($n = 186$, $SMD = -0.11$, 95% CI -0.39 to 0.18 , $P = 0.47$; Figure 7).

3.4.5. Safety and Adverse Events. No serious adverse events were reported during combined physical-cognitive interventions in the included studies. One study [53] reported one participant with foot pain and gout intervention, and another study [60] reported two people with shortness of breath and four falls; however, they were without any physical injury.

4. Discussion

4.1. Some Findings. In this present review, we explore the effect of combined physical-cognitive interventions on MSE, objective cognitive ability, psychological well-being, and emotion in comparison with the usual lifestyle in the elderly with SCD. Eleven eligible studies were included, and pooled analyses were not performed, due to different assessment scales and number of participants, kinds of activities, and methodological quality of the included studies. The results indicated a positive association in the elderly with SCD intervention trials to date, including objective cognitive function and well-being, combined physical-cognitive interventions, or only physical activity intervention, and they were added to the qualitative review because only RCTs were included.

Regarding objective cognitive function, the pooled results showed that combined physical-cognitive interventions yielded significant improvements in SCD elderly in our meta-analysis. We found that combined cognitive-physical interventions conferred a significant benefit on attention, which is partly consistent with other studies. A review has shown the beneficial effects of combined cognitive and exercise training for improving cognitive functions and functional status in older adults with and without cognitive impairment. In line with this, a meta-analysis revealed

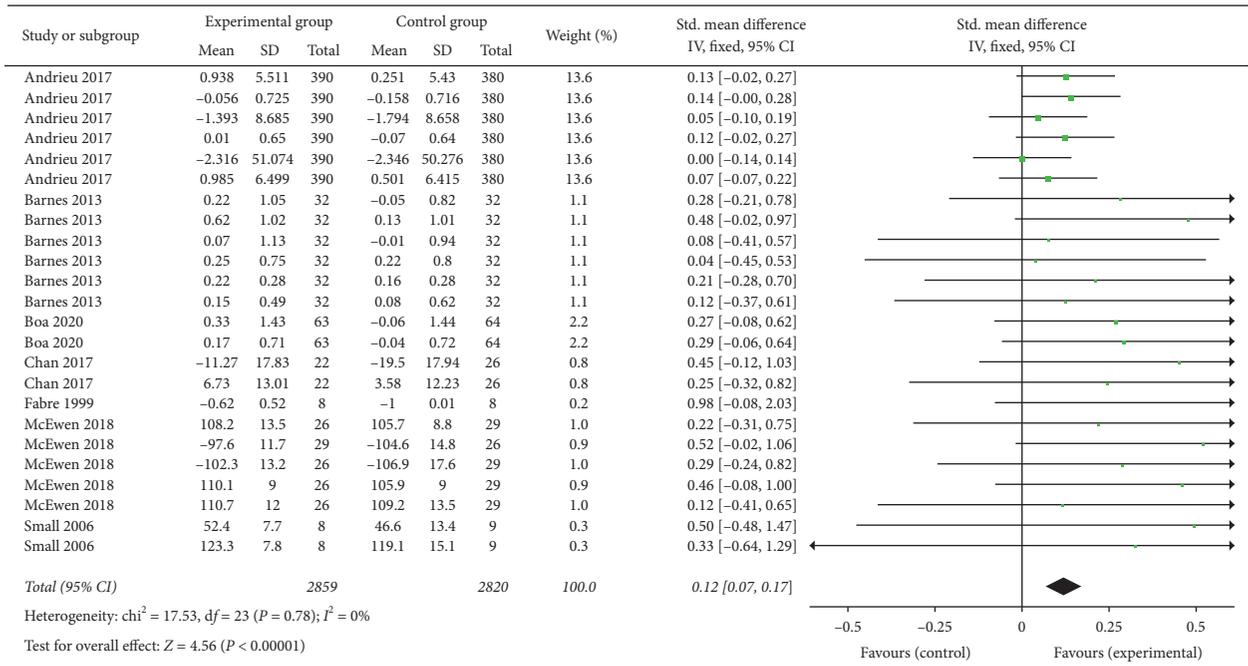


FIGURE 4: Forest plot for combined physical-cognitive interventions on objective cognitive function.

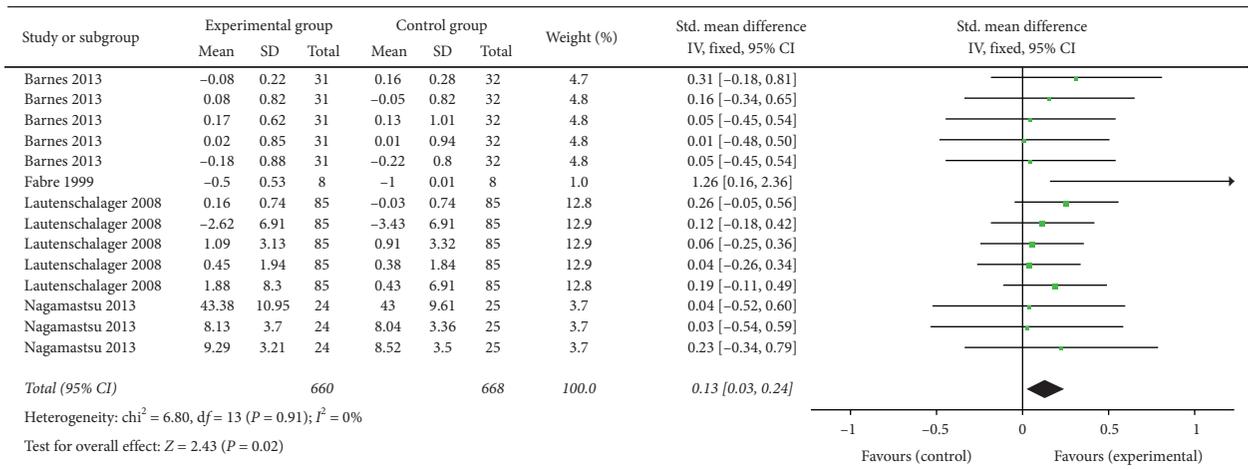


FIGURE 5: Forest plot for physical activity on objective cognitive function.

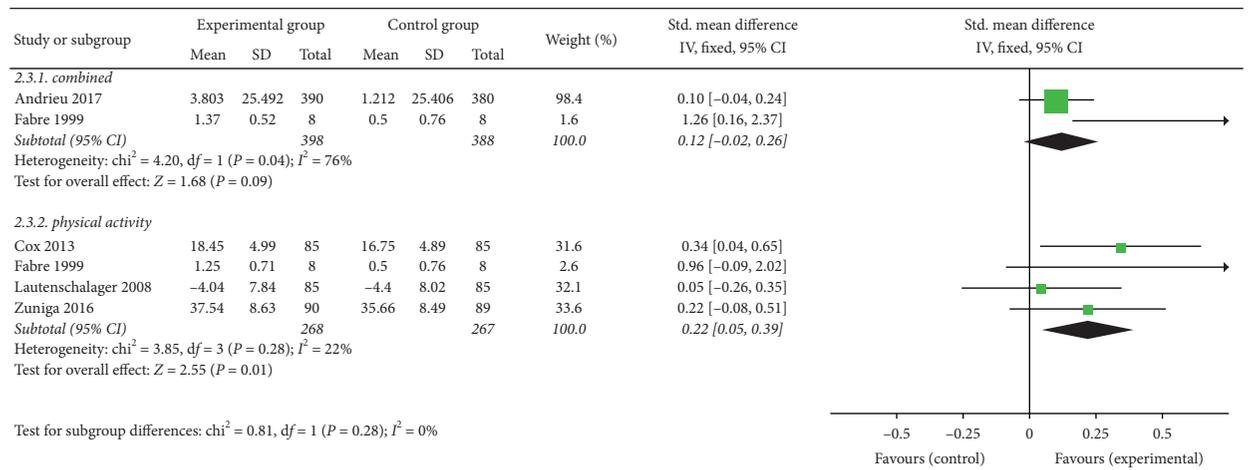


FIGURE 6: Forest plot for combined physical-cognitive interventions or physical activity on psychological well-being. Combined: combined physical-cognitive interventions.

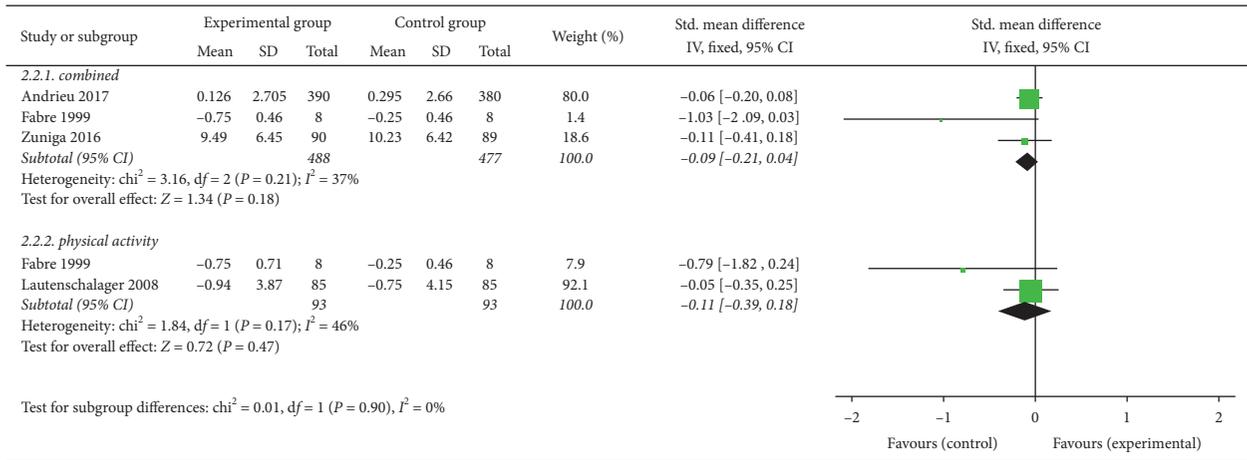


FIGURE 7: Forest plot for combined physical-cognitive interventions or physical activity on depression. Combined: combined physical-cognitive interventions.

significantly larger effects of combined cognitive and physical interventions, compared with both single exercise training and a control group on attention in healthy older adults [63]. McEwen's study showed that the SEQ group has a significantly increased reaction time while single stationary cycling training showed no significant changes in 55 older adults with subjective memory impairment [51].

In addition, we found a positive effect of combined physical-cognitive interventions on verbal fluency; this finding was consistent with the results of Small and colleagues which reported that a 14-day healthy longevity lifestyle program objectively demonstrated greater verbal fluency scores in older individuals with mild self-reported memory complaints but normal baseline memory performance scores [58].

In the present study, our results showed that the combined interventions are effective in improving objective cognitive function in subjective cognitive decline (SCD) older adults. As we know, SCD is identified as a condition where some individuals experience subjective cognitive complaints, but the objective examination did not show signs of cognitive decline. For the patients with SCD, the decline in cognitive function is relatively slight; therefore, the significant improvement with large SMD after the intervention may be not easy. For example, a systematic review and meta-analysis suggested that cognitive training interventions led to a small, statistically significant improvement in objective cognitive performance for SCD ($g = 0.13$, 95% CI 0.01 to 0.25; $P = 0.03$).

However, SCD is considered as the state between normal aging and (MCI) and may be the preclinical stage of (AD), with high risks of conversion to MCI or AD [52]. SCD may be a key window treatment period to delay the deterioration of cognitive function; early intervention and rehabilitation can help the reversal of cognitive decline [52]. Therefore, the effective difference may show the potential value of combined physical-cognitive interventions in improving objective cognitive ability and preventing the conversion of SCD to MCI or AD. However, due to the small SMD, the clinical importance may be not clear; further studies will be

needed to explore the potential benefits of this therapy in preventing the conversion of SCD to MCI or AD.

Previous studies suggested that a cognitively challenging environment may enhance the neural and cognitive benefits that are elicited by physical activity [63, 64]. Animal studies showed that combined physical activity and environmental enrichment induce a significant enhancement in dendritic arborization of CA3 hippocampal neurons than either physical activity or an enriched environment, each on its own [41]. We consider that simultaneous physical exercise and cognitive training might increase the impact on neuroplasticity based on human and animal research, which has found that combined physical exercise and cognitive training yielded greater increases in new neurons in mice than either intervention alone [41, 43, 44]. Further study will be needed to verify the results.

Whether combined physical-cognitive interventions could improve memory ability is a controversial issue. Several studies have shown that combined physical-cognitive interventions have improved memory function, including composite memory, recent memory, and delayed memory [52–54, 59, 60]. Conversely, the remaining studies included showed combined physical-cognitive interventions to have negative results in memory ability [47, 51, 54, 65]. The changes in executive functioning differed significantly compared with the control group in only one study [52]. A meta-analysis of controlled trials with older adults presented a potential advantage at improving executive functions by physical and cognitive interventions. We speculate that there were several reasons. Firstly, the mode of combination, intervention frequency, intervention length, session length, and setting also were considered as potential moderators; secondly, the small sample size and lack of monitoring of the compliance of participants prevent any firm conclusions from being drawn; furthermore, the measures of cognition used varied across the studies that included cognitive tests, limiting its comparability. Further studies will be needed to explore the effects of combined physical-cognitive interventions on global cognitive function and

the specific domains of cognition, including memory ability and executive ability.

Self-report memory complaints may predict the potential increased risk of dementia in objective cognitive performance. The English Longitudinal Study of Aging found that aged 50 years and above had a negative correlation between subjective memory complaints and objective performance in all cognitive domains [8]. In Zuniga's study, a significant main effect of subjective memory on measures of well-being indicated that individuals with the fewest memory complaints were significantly happier and lower perceived stress/physical symptoms reported across all measurement occasions [56]. However, our meta-analysis containing three studies did not show significant improvement in MSE in the combined physical-cognitive interventions [55, 56, 58]. To consider that the small sample size and the MSE were not a primary outcome for any of the combined physical-cognitive interventions studies, in these studies, further work is required to explore the role of combined physical-cognitive interventions in improving MSE.

In other cases, SCD may be associated with emotion, personality, and physical health concerns. Our findings indicated that there was a statistically significant improvement in well-being with only physical activity intervention. The present findings are comparable with a previously published meta-analysis, which conferred a small but significant benefit on psychological well-being after cognitive training interventions in older adults with SCD [66]. In Zuniga's study, a significant main effect of subjective memory on measures of well-being indicated that individuals with the fewest memory complaints were significantly happier and lower perceived stress/physical symptoms reported across all measurement occasions [56]. Significantly high importance was attributed to changes in self-efficacy in home-based physical activity programmers with older adults with memory complaints [57]. However, it is important to note that there is sometimes an unproven assumption that physical activity enhances a patient's overall well-being by preserving cognitive function [53]. The ground on these pieces of evidence, the well-being of supports that suggests cognitive impairment may have a negative impact on quality of life indicators in SCD elderly.

In the present study, we found that the combined interventions are effective in improving objective cognitive function in SCD older adults which may show the potential value of combined physical-cognitive interventions in improving objective cognitive ability and preventing the conversion of SCD to MCI or AD. However, due to the small SMD, the clinical importance may be not clear. Further studies will be needed to explore the potential benefits of this therapy in preventing the conversion of SCD to MCI or AD.

4.2. Strengths and Limitations. The strengths of this review belong to its systematic approach in which methodologically stronger study designs were used. First, we focused on types of combined physical activity and cognitive training, rather

than nonpharmacologic interventions or all interventions. Furthermore, only RCTs were included in this meta-analysis. In addition, to reduce potential confounding bias, we only investigated older adults with SCD.

There are several limitations in the present study. First, the included studies with different levels of quality demonstrated methodologically heterogeneity that may have impacted our interpretation of the results. Second, the heterogeneity of intervention characteristics in the included studies should be considered, including the type and time, frequency, and duration. The type and time of combined physical-cognitive interventions used in the included studies were physical activity (e.g., walking, Dejian mind-body intervention, aerobic cycling, stretching, and jogging) and cognitive training (e.g., memory training, cognitive stimulation), which varied from 45 to 150 min per session. The intervention duration of the included studies ranged from 2 weeks to 3 years. Studies have investigated the decay after intervention cessation was less. Therefore, the optimal intervention design for the intervention effects remains unclear; more research is warranted. Third, a variety of noncompatible measurement tools were used in the included studies. Future studies should use more objective testing methods or instruments (e.g., functional MRI, event-related potential, and PET). Fourth, few studies (only two studies) reported the comparison between the combined interventions and cognitive or physical activity alone on SCD according to our current knowledge (according to the selection/identification/inclusion criteria of studies in the present study). In addition, there are no common outcomes in the two studies above; therefore, the meta-analysis of the combined interventions as compared to cognitive or physical intervention alone does not include common outcomes in the main findings. We will continue to pay attention to this issue in the future. Furthermore, most included studies were small samples. Last but not least, it is impossible to blind participants in a physical activity intervention trial; therefore, performance bias may be inevitable.

4.3. Clinical Implications and Recommendations for Future Studies. The combined interventions are effective in improving objective cognitive function in SCD older adults which may show the potential value of combined physical-cognitive interventions in improving objective cognitive ability and preventing the conversion of SCD to MCI or AD and no adverse effects. We provide clinicians with positive evidence of an effective option to recommend those older adults with SCD who would benefit from increasing combined physical-cognitive training.

Future studies in this field should use appropriate exercise modes, exercise prescriptions including training intensity, and frequency, such as the exercise training principles suggested by Bherer [63] or the global recommendations on physical activity for health provided by the WHO. In addition, if possible, the duration of training should be at least 6 months or longer [35]. Furthermore, more sensitive and objective measurement tools should be used. Finally, authors should follow the CONSORT guidelines when reporting their studies to allow better evaluation of the quality.

5. Conclusion

The combined interventions are effective in improving objective cognitive function in SCD older adults which may show the potential value of combined physical-cognitive interventions in improving objective cognitive ability and preventing the conversion of SCD to MCI or AD. However, considering the quality of included studies, discrepancies in the types, frequencies, and durations of interventions, as well as the limitations of the included studies, the findings must be interpreted cautiously. To draw specific and accurate conclusions regarding the potential enhancement effects of combined physical activity and cognitive training interventions on the objective cognitive ability, well-being, and MSE of SCD elderly, more rigorously designed and standardized training protocols of large-scale RCTs are required in future research.

Data Availability

All data analyzed during this study are included in this article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Additional Points

Search Strategy. #1 (((("subjective cognitive impairment") OR "cognitive complaints") OR "subjective cognitive decline") OR "memory complaints") OR "subjective memory impairment") OR "Subjective memory decline". #2 ((("intervention") OR "training") OR "exercise") OR "activity". #3 #1AND#2.

Disclosure

The funders have no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to report.

Authors' Contributions

LJ conceived and designed the study and wrote and revised the manuscript; SQQ, XSR, GS, and YY were the research assistants who helped with data search, extraction, methodological assessment, and other aspects of the study; XR revised the manuscript; SQQ and XSR contributed equally to this study. All authors contributed to the writing of the manuscript and have read and approved the final manuscript version for publication.

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