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REVIEW

The effect of combined cognitive intervention and physical exercise on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials

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Abstract

Background The state of mild cognitive impairment (MCI) provides an optimal window for preventing progression to dementia. Combined cognitive intervention and physical exercise may yield additive and synergistic effects on cognition in older adults with MCI.

Objectives The purpose of this study was to assess the efficacy of a combined intervention to improve cognition in older adults with MCI by comparing a control group that underwent only cognitive intervention, a control group that underwent only physical exercise, and a control group that did not undergo cognitive intervention or physical exercise.

Design Meta-analysis of randomized controlled trials (RCTs).

Data sources The online databases of PubMed, Web of Science, Embase, the Cochrane Library, PsycINFO, and CINAHL were systematically searched.

Review methods The outcomes were global cognition, memory, and executive function/attention. A sensitivity analysis was conducted when the I^2 statistic was > 50%.

Results A total of 16 studies were included. The results showed that the combined intervention had positive effects on global cognition compared to the effects of the other control group [SMD = 0.27, 95% CI (0.09, 0.44), $p = 0.003$]. Regarding memory, the combined intervention had positive effects compared to the effects observed in the single physical exercise group [SMD = 0.25, 95% CI (0.07, 0.44), $p = 0.006$] and the other control group [SMD = 0.29, 95% CI (0.12, 0.47), $p = 0.001$]. For executive function/attention, the combined intervention had also positive effects compared to the effects of the single cognitive intervention group [SMD = 0.28, 95% CI (0.09, 0.47), $p = 0.004$], the single physical exercise group [SMD = 0.32, 95% CI (0.16, 0.49), $p = 0.0002$], and the other control group [SMD = 0.23, 95% CI (0.05, 0.41), $p = 0.01$].

Conclusions The combined intervention resulted in cognitive benefits in older adults with MCI and exhibited limited superiority over the single cognitive intervention and the single physical exercise on cognitive subdomains.

Keywords Cognitive dysfunction · Older adults · Cognitive intervention · Exercise · Cognition

Introduction

As the population ages, the number of people worldwide with dementia is expected to reach 82 million by 2030, with one new case every 3 s [1]. Dementia seriously affects the quality of life and well-being of older adults and causes a heavy burden on families and society [2]. Therefore, effective interventions are urgently needed to prevent dementia.

Mild cognitive impairment (MCI) is the intermediate phase between normal age-related cognitive decline and dementia [3]. The mean annual conversion rate of MCI to dementia is approximately 10%, which is far higher than the

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annual incidence (1–2%) in the general population [4, 5]. However, MCI provides an optimal window for preventing the progression to dementia [6].

Cognitive intervention and physical exercise are more suitable for improving cognitive function in older adults with MCI [7]. Many systematic reviews and meta-analyses have shown that cognitive interventions are effective for improving cognition [8–10]. Moreover, two previous systematic reviews reported positive effects of physical exercise on global cognition in older adults with MCI [11, 12].

Combining a single cognitive intervention with a single physical exercise intervention (referred to as a combined intervention) would greatly increase the likelihood of cognitive benefit. Meta-analyses have indicated that the combined intervention positively affect global cognition compared to no cognitive intervention or physical exercise in healthy older adults and older adults with cognitive impairments [13, 14]. However, some studies did not observe the positive effect of the combined intervention on global cognition in older adults with MCI [15, 16], while a new study has shown its effectiveness [17]. It is necessary to update the data.

Additionally, a combined intervention may yield additive and synergistic effects. However, the efficacy of the combined intervention compared to a single cognitive intervention and a single physical exercise intervention remained unclear in older adults with MCI. A recent study found that compared to a group that underwent only cognitive intervention and a group that underwent only physical exercise, the combined intervention significantly improved memory but did not significantly improve global cognition or executive function [18]. However, another new study showed positive effects of the combined intervention on global cognition and executive function compared to a group with only physical exercise [19]. However, a recent systematic review including randomized controlled trials (RCTs) focused on the effects of the combined intervention on cognition in older adults with MCI. It did not separately analyze the effects of the combined intervention, comparing to a group with only cognitive intervention and a group with only physical exercise [20]. Therefore, it is essential to reintegrate the evidence and perform quantitative analysis to clarify the cognitive efficacy of the combined intervention in older adults with MCI.

To explore the cognitive benefits of the combined intervention, the meta-analysis quantified the overall effect of the combined intervention on cognitive function (global cognition, memory, and executive function/attention). This was done by comparing the combined intervention group to the control group that received only cognitive intervention (referred to as the single cognitive intervention group), to the control group that received only physical exercise (referred to as the single physical exercise group), and to the control group that did not receive cognitive intervention or physical exercise (referred to as the other control group).

Methods

The work was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21].

Search strategy

We performed a systematic literature search in two steps. First, we conducted a systematic search of six English databases: PubMed, Web of Science, Embase, the Cochrane Library, PsycINFO, and CINAHL. All databases were searched up to February 2021 based on two main concepts to identify search terms. For the first concept, we used the words related to "mild cognitive impairment" as the search terms. For the second concept, we used the words related to "combined intervention" as the search terms, including a combination of "cognitive intervention" terms, "physical exercise" terms, and combined terms, and supplementing special terms for the combined intervention. Then, the two concepts were combined to retrieve articles. Second, references of selected articles and related reviews were further screened to retrieve additional articles. The full search strategy for PubMed is presented in Supplementary Table 1.

Study selection criteria

Studies were selected according to the following inclusion criteria: (1) patients screened or diagnosed with MCI over the age of 50 years; (2) intervention group with cognitive intervention and physical exercise; (3) control group without cognitive intervention or physical exercise, with only cognitive intervention or with only physical exercise, and the intervention may include other components (e.g., omega-3 fatty acid supplementation); (4) enough information to calculate effect sizes for at least one cognitive outcome (global cognition, memory or executive function/attention); and (5) randomized controlled trial. Studies were excluded if they (1) were unpublished articles; (2) were not written in English; or (3) included patients with MCI caused by brain injury or cancer or with a history of other neurological diseases (e.g., dementia, stroke, Parkinson's disease) or psychiatric disorders (e.g., depressive or anxiety disorders). Two reviewers screened articles based on title and abstract separately, following further full-text evaluation. If there were disagreements between the two reviewers, the discussion was conducted with a third reviewer to reach a consensus.

Risk of bias assessment

The Cochrane Collaboration Risk of Bias Tool was used for quality assessment [22]. It consisted of six domains biases: selection, performance, detection, attrition, reporting, and another bias. Each domain was rated as "low", "high", or "unclear" for each study by two reviewers. Differences were resolved by discussion with another reviewer.

Data extraction

We extracted five types of characteristics from the included studies, including study characteristics (author, published year, and country), sample characteristics (sample size, mean age, percentage of females, education level, and diagnosis criteria), combined intervention group characteristics (combined component, technology, mode of combination, frequency, duration and sessions, and setting), control group characteristics (the single cognitive intervention group, the single physical exercise group, the other control group), and outcome characteristics (neuropsychological tool used for measuring global cognition, memory and executive function/attention at preintervention and postintervention).

The summary statistics were the means and standard deviations (SDs) and the number of participants in each group preintervention and postintervention. When means and SDs were not available, we contacted the corresponding authors for missing data.

Two authors extracted the data individually and discussed them with another author to resolve disagreements.

Data synthesis and statistical analysis

Review Manager Version 5.0 was used for all analyses. The standardized mean difference (SMD) was calculated to measure the effect of the combined intervention from preintervention to postintervention between the combined intervention group and the control group. Pooled SMDs were calculated by averaging the effect size of all cognitive tests measuring the same outcome. The pooled SMDs were regarded as the effect size of each outcome (global cognition, memory, and executive function/attention) [23]. Pooled SMDs were weighted for the sample size of individual studies with 95% confidence interval (CI). These pooled effect sizes were ranked as small (0.2), moderate (0.5) and large (0.8) [24].

The *h* test was conducted by Statistic I^2. The level of heterogeneity was classified as small (25%), moderate (50%), or large (75%) for I^2 [23]. If $I^2 > 50\%$, the fixed-effects model was replaced by the random-effects model [23].

Given the limited number of included studies, funnel plot asymmetry examination was not performed to test publication bias [25]. When $I^2 > 50\%$, sensitivity analysis was conducted [25].

Results

Identification of studies

Figure 1 shows the process of study selection in detail. We identified 2569 articles initially. After removing duplicates, 1258 articles remained. Then, 1187 articles were excluded by screening titles and abstracts. Out of the remaining 71 articles screened by full text, 16 studies were included.

Figure 2 shows the results of risk-of-bias assessment. Nine studies [15, 17, 18, 26–31] used computer-generated random sequences and concealed assignment. Two studies [32, 33] performed random sequences using computers and did not specify allocation concealment. Other studies [16, 19, 34–36] did not introduce random sequence generation or allocation concealment in detail. Some studies had blind designs (single-blind $n=7$ [16–18, 28, 29, 31, 33]; double-blind $n=3$ [15, 26, 27]), while others did not mention it. In addition, seven studies [17, 19, 30, 31, 34–36] lost participants in follow-up and did not process the missing data with proper methods. One study [33] did not report the results of the mentioned measurement, which may have affected the results of the analysis. As a potential factor affecting the results, the intervention setting (e.g., supervised or unsupervised), was considered as another bias. Trained assistants or experienced therapists supervised the participants of 13 studies [15–19, 26, 28–31, 34–36] during the intervention. Other studies [27, 32, 33] did not mention the supervision.

Study characteristics

Table 1 summarizes the characteristics of the included studies. Sixteen studies were conducted in America ($n=3$) [15, 32, 34], Australia ($n=1$) [26], Belgium ($n=1$) [16], China ($n=3$) [18, 31, 33], France ($n=1$) [35], Germany ($n=1$) [36], Korea (n = 1) [30], Japan ($n=2$) [17, 28], Thailand ($n=1$) [29], Pakistan ($n=1$) [19] and the Slovak Republic ($n=1$) [27]. The total number of samples was 1337, ranging from 11 to 424. All participants were screened or diagnosed with MCI or mild neurocognitive disorders (mNCD) [29], which was a new term that had been used to replace MCI in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American Psychiatric Association (APA) in 2013 [37]. Diagnostic criteria included the Mayo Criteria [26], the International Working Group (IWG) or the Key Symposium Criteria [15, 17, 28, 33, 35, 36], the National Institute of Aging-Alzheimer's Association (NIA-AA) Criteria [18], the International Classification of Disease, Ninth Revision, Clinical Modification, MCI

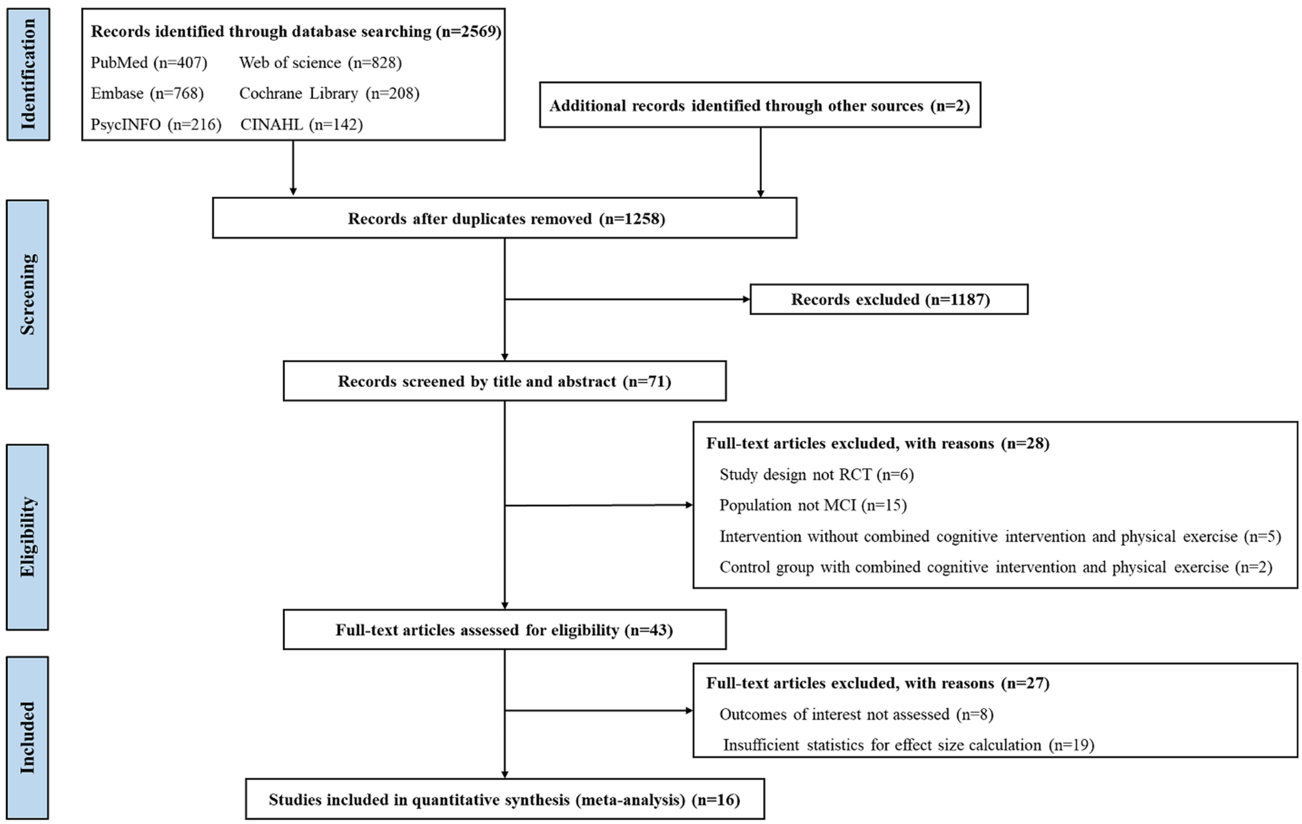

Fig. 1 Searching flow

(ICD-9-CM 331.83) [27], the DSM-5 [29], and the criteria established by themselves [32, 33]. However, some included studies did not describe the diagnosis criteria and only mentioned that subjects were diagnosed with MCI by neurologists in hospitals [16, 19, 30, 31, 34]. The mean age of the participants was 73.33 years, and the percentage of females was 57.82%. The average level of education for each group was at least 3 years.

Out of sixteen studies, four studies [18, 26, 33, 35] used a four-group design. However, the social group in the study of Lam et al. [33] was excluded due to the mixed social component. One study [31] used three-group design. However, the health advice control group in the study of Zijun et al. [31] was excluded. The health advice control group did not contain the risk factor modification component that was included in the combined intervention. Other studies used a two-group design, including one study [30] comparing a combined intervention group to a single cognitive intervention group, four studies [19, 27, 34, 36] comparing a combined intervention group to a single physical exercise group, and six studies [15–17, 28, 29, 32] comparing a combined intervention group to another control group.

The combined interventions were different in regard to the combined components, mode, frequency, duration, and setting. For the cognitive component of the combined intervention, 11 studies specifically described the cognitive domain of intervention, such as memory ($n=7$) [16, 19, 26, 27, 29, 30, 36] and executive function/attention ($n=9$) [15, 16, 26, 27, 29, 30, 32, 34, 35]. For the physical component of the combined intervention, seven studies [17, 19, 28, 32, 34–36] involved aerobic exercise, one study [26] involved resistance training, six studies [15–18, 27, 28] involved balance training, five studies [17, 18, 27, 28, 30] involved strengthening, and three studies [29, 31, 33] involved mind–body exercise. In addition, four studies [16, 18, 31, 36] included other components (e.g., usual care, omega-3 FA, and nurse-led risk factor modification). The combined modes of cognitive intervention and physical exercise varied, including sequential combination ($n=4$) [26, 31, 33, 36], simultaneous combination (six studies [15, 16, 19, 31, 32, 34] for exergame and two studies [18, 35] for dual-task) and mixed combination ($n=4$) [17, 27–29]. Exergame used different technologies (e.g., Kinect, recumbent stationary bike, wireless remote device, BioRescue platform, inertial sensors, touchscreen monitor, grip air bulb, joysticks, attachments) to control progress of virtual world or attainment of goals. The frequencies varied from one session/week [17, 27, 32] to seven sessions/

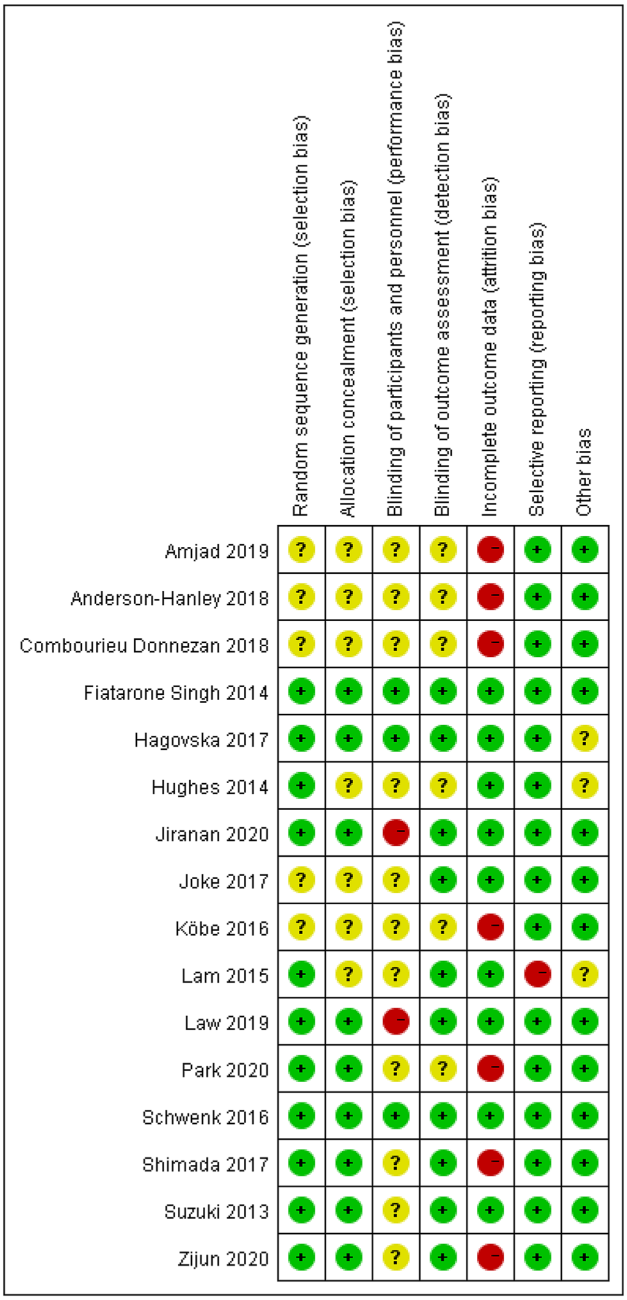

Fig. 2 Risk of bias assessment

week [27], with two sessions/week mostly [15, 16, 28, 29, 35, 36]. The durations varied from 4 weeks [15] to 40 weeks [17], with 24 weeks mostly [26, 28, 32, 34]. Eight studies [15, 18, 19, 26–29, 31] were conducted in a medical setting. Three studies [17, 32, 33] were conducted in a social setting. Four studies [15, 19, 30, 34] were conducted in the form of individuals. Seven studies [18, 26, 28, 29, 32, 33, 35] were conducted in the form of a group. Two studies [31, 36] were conducted in the form of individuals and groups. Thirteen studies [15–19, 26, 28–31, 34–36] were conducted under professional supervision. Other studies do not specify the setting.

For the control group, five studies [26, 27, 33–35] used the same single cognitive intervention and single physical exercise as those used for the combined intervention. Four studies [18, 19, 30, 36] used a single cognitive intervention and a single physical exercise that was different from the combined intervention. Another control group (e.g., healthy education, watching videos, no training, usual lifestyle, usual care, and nurse-led risk factor modification) was used in ten studies [15–18, 26, 28, 29, 31, 32, 35].

Table 2 summarized the outcome measures. For assessing global cognition, the included studies used the Mini-Mental State Examination (MMSE) ($n=5$) [17, 19, 27, 28, 33], Montreal Cognitive Assessment (MoCA) (n = 5) [15, 16, 19, 30, 31], Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) ($n=4$) [26, 28, 31, 33], Neurobehavioral Cognitive Status Examination (NCSE) ($n=1$) [18], and Computerized Assessment of Mild Cognitive Impairment (CAMCI) ($n=1$) [32]. To measure memory, the List Learning subsection of the ADAS-Cog ($n=2$) [26, 34], List Learning Delayed Recall test for episodic memory ($n=1$) [33], Rey Auditory Verbal Learning Test ($n=3$) [17, 27, 36], Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word-List Learning Test ($n=1$) [29], Verbal Learning Test ($n=1$) [18], Wechsler Memory Scale-Revised Logical Memory II ($n=1$) [17], Auditory Logical Memory I and II subtests of the Wechsler Memory Scale-Third Edition ($n=2$) [26, 28], and visual via Benton Visual Retention Test-Revised Fifth Edition ($n=1$) [26] were used. Executive function/attention was measured by the Trial Making Test ($n=9$) [15, 17–19, 27, 29, 30, 33, 36], Stroop test ($n=4$) [27, 34–36], Digit span ($n=6$) [29, 30, 33–36], Symbol Digit Modalities Test ($n=1$) [26], Verbal Fluency Test ($n=4$) [17, 26, 29, 33], Matrix Reasoning test ($n=1$) [35], Matrices and Similarities subtests of the Wechsler Adult Intelligence Scale third Edition ($n=1$) [26], Color Trials ($n=1$) [34], Disjunctive Reaction Time ($n=1$) [27], Block Design ($n=1$) [29], and Tracking A and B ($n=1$) [32].

Effects analyses of combined intervention

We summarized the results of all forest plots (the number of studies, SMD, 95% CI, p, I^2 and p for I^2) in Table 3. All forest plots can be seen in the supplementary material.

Effects of combined intervention on global cognition

As Table 3 shows, compared to the single cognitive intervention and the single physical exercise, the effects of the combined intervention on global cognition were not significant, with high heterogeneity [SMD = 0.81, 95% CI (−0.09, 1.71),

Table 1 Study characteristics

Study	Country	Sample				Diagnosis criteria	Combined intervention group							Control group		
		Size	Age	Female (%)	Education level		Combined component			Technology	Mode	Frequency, Duration and Sessions	Setting	Single cognitive intervention group	Single physical exercise group	Other control group
							Cognitive intervention	Physical exercise	Other component							
Amjad et al. [19]	Pakistan	CP: 20 PE: 18	CP: 62.800 ± 5.084 PE: 65.556 ± 4.996	CP: 31.82 PE: 27.27	——	MCI	VR game: Logic, physical, memory, reflexes, and math	Different physical movements	None	Screen + Xbox 360 Kinect	Parallel (Exergame)	25–30 min/session; 5 sessions/week 6 weeks 30 sessions	Hospital; Individual; Supervised		Normal joint range of motion and stretching exercises of upper and lower limbs	
Anderson-Hanley et al. [34]	America	CP: 7 PE: 7	CP: 75.4 ± 9.83 PE: 80.9 ± 12.3	CP: 43 PE: 57	CP: 16.6 ± 2.76 PE: 14.9 ± 2.3	MCI	VR game: planning, tracking, multi-tasking, and strategizing	Pedal	None	Virtual reality enhanced, recumbent stationary bike	Parallel (Exergame)	20–45 min/session; 2–5 sessions /week 24 weeks	—— Individual; Supervised		Pedal	
Combourieu Donnezan et al. (2018)	France	CP: 21 CI: 16 PE: 18 CG: 14	CP: 75.2 ± 1.3 CI: 76.3 ± 1.5 PE: 77.1 ± 1.44 CG: 79.2 ± 4	——	CP: 5.9 ± 0.31 CI: 5.5 ± 0.36 PE: 6.1 ± 0.34 CG: 5.8 ± 0.4	MCI (IWG Criteria)	Computerized game ("HAPPYneuron" and Presco): attention and executive functions (working memory, mental flexibility, inhibition, reasoning and updating)	Aerobic training (bikes)	None	Screen + bike	Parallel (dual task)	60 min/session; 2 sessions/week 12 weeks 24 sessions	A small room; Group; Supervised	Computerized game ("HAPPYneuron" and Presco)	Aerobic training (bikes)	Usual lifestyle
Fiatarone Singh et al. [26]	Australia	CP: 27 CI: 24 PE: 22 CG: 27	70.1 ± 6.7	68	——	aMCI (Mayo Criteria)	Computerized game (COGPACK program): memory, executive function, attention, and speed of information processing	High intensity progressive resistance training	None	Touch screen + pneumatic resistance machines	Serial	100 min/session; 2–3 sessions /week; 6 months	Clinic; Group; Supervised	COGPACK program, and Sham Exercise	High intensity progressive resistance training, and Sham Cognitive	Sham Cognitive and Sham Exercise

Table 1 (continued)

Study	Country	Sample					Combined intervention group							Control group		
		Size	Age	Female (%)	Education level	Diagnosis criteria	Combined component			Technology	Mode	Frequency, Duration and Sessions	Setting	Single cognitive intervention group	Single physical exercise group	Other control group
							Cognitive intervention	Physical exercise	Other component							
Hagovska et al. (2017)	Slovak Republic	CP: 40 PE: 40	CP: 68.22 ± 6.78 PE: 65.95 ± 5.68	CP: 45 PE: 52.5	CP: 25% University 75% Secondary PE: 37.5% University 62.5% Secondary	MCI (ICD-9-CM331.83)	VR game (CogniPlus program): attention, short-term and long-term memory, executive functions and visual-motoric coordination	Strengthen leg muscles and maintain balance	None	——	Parallel (dual-task); Serial	30 min/session; 2 sessions/week 10 weeks 20 sessions 30 min/session; 7 sessions/week 10 weeks 70 sessions	Outpatient Psychiatric Clinic; —— ——		Strengthen leg muscles and maintain balance	
Hughes et al. [32]	America	CP: 10 CG: 10	CP: 78.5 ± 7.1 CG: 76.2 ± 4.3	CP: 80 CG: 60	CP: 13.8 ± 2.4 CG: 13.1 ± 1.9	MCI (Monongahela-Youghiogheny Healthy Aging Team (MYHAT) cognitive classification)	Nintendo Wii™ game: attentional resources, processing speed, visuospatial and visuomotor abilities	Arms and/or bodies action	None	gaming console + wireless remote device with motion-sensing capabilities	Parallel (Exergame)	90 min/session; 1 session/week; 24 weeks 24 sessions	Church; Group; ——			Healthy education
Jiranan et al. (2020)	Thailand	CP: 35 CG: 35	CP: 60–69 years 50% 70–79 years 50% CG: 60–69 years 50% 70–79 years 50%	CP: 50 CG: 50	CP: 4 ± 0 CG: 3.97 ± 0.79	mNCD (DSM-5 Criteria)	Multifaceted cognitive training: attention, memory, and executive function physical movement activity: cognitive function and thinking	Mind–body: physical movement activity	None	None	Parallel (dual-task); Serial	60–90 min/session 2 sessions/week; 12 weeks 24 sessions 20–30 min/session 2 sessions/week; 12 weeks 24 sessions	Hospital; Group; Supervised			No training

Table 1 (continued)

Study	Country	Sample					Combined intervention group							Control group		
		Size	Age	Female (%)	Education level	Diagnosis criteria	Combined component			Technology	Mode	Frequency, Duration and Sessions	Setting	Single cognitive intervention group	Single physical exercise group	Other control group
							Cognitive intervention	Physical exercise	Other component							
Joke et al. (2017)	Belgium	CP: 8 CG: 9	CP: 86.9 ± 5.6 CG: 87.5 ± 6.6	CP: 80 CG: 50	——	MCI	VR game: memory, attention	Balance (weight bearing)	Usual care	Screen + BioRescue platform	Parallel (Exergame)	18-30 min/session; 2 sessions/week; 6 weeks; 12 sessions	—— —— Supervised			Usual care
Köbe et al. [36]	Germany	CP: 13 CG: 9	CP: 70 ± 7.2 CG: 70 ± 5.2	CP: 30.77 CG: 44.44	CP: 16.1 ± 4.1 CG: 16.5 ± 2.9	MCI (IWG Criteria)	Cognitive activities (AKTIVA program): using cognitively stimulating leisure activities and memory strategies, and conveying a positive attitude towards aging, disease, and self-perception supplemented by home-based activities	Aerobic exercise (cycle)	Omega-3 FA	None	Serial	90 min/session 13 sessions 45 min/session; 2 session/week; 24 weeks; 48 sessions	—— Group and individual; Supervised		Non-aerobic exercise: stretching and toning condition (balance, coordination) omega-3 FA	
Lam et al. [33]	China	CP: 132 CI: 145 PE: 147	CP: 76.3 ± 6.6 CI: 74.4 ± 6.4 PE: 75.5 ± 6.7	CP: 78.79 CI: 79.31 PE: 76.87	CP: 3.4 ± 3.3 CI: 3.9 ± 3.8 PE: 4.0 ± 3.6	aMCI (IWG Criteria) naMCI (Lam 2001)	Cognitive activities: reading and discussing newspapers, playing board games supplemented by home-based activities	Mind body exercise (e.g. Tai Chi)	None	None	Serial	60 min/session; 3 sessions/week	Social centers; Group; ——	Cognitive activities (e.g. reading and discussing newspapers, playing board games)	Stretching & toning exercise, mind body exercise and aerobic exercise	

Table 1 (continued)

Study	Country	Sample					Combined intervention group							Control group		
		Size	Age	Female (%)	Education level	Diagnosis criteria	Combined component			Technology	Mode	Frequency, Duration and Sessions	Setting	Single cognitive intervention group	Single physical exercise group	Other control group
							Cognitive intervention	Physical exercise	Other component							
Law et al (2019)	China	CP: 14 CI: 15 PE: 16 CG: 14	CP: 71.57 ± 7.43 CI: 76.93 ± 6.79 PE: 77.94 ± 6.11 CG: 75.14 ± 8.53	CP: 71.4 CI: 53.3 PE: 50 CG: 64.3	Not clear	MCI (NIA–AA criteria)	Cognitive demanding (specific patterns of movement and sequence)	Object placing and collection, incorporated sit-stand movements (stretching, strengthening, endurance, and balance)	Usual care	None	Parallel (dual-task)	8 weeks 12 sessions	Clinic and community center; Group; Supervised	Usual care + computer cognitive training program	Usual care + moderate intensity aerobic exercise	Usual care + normal activity or exercise pattern
Park et al. [30]	Korea	CP: 18 CI: 17	CP: 75.8 ± 8.5 CI: 77.2 ± 7.2	CP: 80 CI: 58.8	CP: 83.3% Elementary school and below 16.7% Middle school and above CI: 82.4% Elementary school and below 17.6% Middle school and above	MCI	Virtual reality-based cognitive-motor rehabilitation: attention, memory, problem-solving, and executive training	Ranges of motion and strength of the upper limbs	None	MOTOCOG ® system + touch-screen monitor, grip air bulb, and joysticks or attachments	Parallel (Exergame)	30 min/session; 5 sessions/week; 6 weeks; 30 sessions	—— Individual; Supervised	tabletop activities		
Schwenk et al. [15]	America	CP: 11 CG: 9	CP: 77.8 ± 6.9 CG: 79.0 ± 10.4	CP: 58.33 CG: 50	CP: 14.2 ± 2.3 CG: 15.9 ± 2.7	aMCI (IWG Criteria)	Computerized game: attention, executive function and visuomotor	Balance exercise (ankle joint rotation and leg lift)	None	Screen + inertial sensors	Parallel (Exergame)	45 min/session; 2 session/week; 4 weeks 8 sessions	Memory Clinic; Individual; Supervised			No training

Table 1 (continued)

Study	Country	Sample					Combined intervention group							Control group		
		Size	Age	Female (%)	Education level	Diagnosis criteria	Combined component			Technology	Mode	Frequency, Duration and Sessions	Setting	Single cognitive intervention group	Single physical exercise group	Other control group
							Cognitive intervention	Physical exercise	Other component							
Schimada et al. (2017)	Japan	CP: 129 CG: 137	CP: 71.6 ± 5.0 CG: 71.6 ± 4.9	CP: 50 CG: 50	CP: 10.9 ± 2.6 CG: 10.8 ± 2.2	MCI (IWG Criteria)	—— Supplemented by education about cognition	Aerobic exercise, muscle strength training and postural balance retraining	None	None	Parallel (dual-task); Serial	90 min/session; 1 session/week; 40 weeks 40 sessions	Fitness facility; —— Supervised			Health education (except cognition and exercise)
Suzuki et al. [28]	Japan	CP: 47 CG: 45	CP: 74.8 ± 7.4 CG: 75.8 ± 6.1	CP: 50 CG: 48	CP: 10.9 ± 2.8 CG: 10.4 ± 2.4	MCI (IWG Criteria)	Not clear	Aerobic exercise, muscle strength training and postural balance retraining	None	None	Parallel (dual-task); Serial	90 min/session; 2 sessions/week; 6 months; 40 sessions	Geriatric rehabilitation; Group; Supervised			Health education (except cognition and exercise)
Zijun et al. (2020)	China	CP: 5 CG: 6	CP: 70.67 ± 4.23 CG: 76.43 ± 4.47	CP: 66.7 CG: 71.4	——	MCI	Cognitive activities: reading and discussing newspapers, playing board games supplemented by home-based activities	Mind body exercise (Tai Chi)	Nurse-led risk factor modification	None	Serial	60 min/session; 3 sessions/week; 12 weeks 30 min/session; 3 sessions/week; 12 weeks	Clinic; Group/Individual; Supervised			nurse-led risk factor modification

Note CP intervention group with Cognitive intervention and Physical exercise, *CI* control group with only Cognitive Intervention, *PE* control group with only Physical Exercise, *CG* Control Group without cognitive intervention and physical exercise, —— not mentioned, *Not clear* related information was mentioned but not clear, *MCI* mild cognitive impairment, *aMCI* amnestic mild cognitive impairment, *naMCI* non-amnestic mild cognitive impairment, the International Working Group or the Key

Symposium Criteria: the IWG Criteria, *NIA-AA* Criteria the National Institute of Aging-Alzheimer's Association Criteria, DSM-5 the Diagnostic and Statistical Manual of Mental Disorders, MCI: ICD-9-CM 331.83 the International Classification of Disease, Ninth Revision, Clinical Modification

Table 2 Outcome measures of included studies

Study	Global cognition	Memory	Executive function/attention
Amjad et al. [19]	MMSE; MoCA		TMT
Anderson-Hanley et al. [34]		ADAS-Cog list learning	Stroop; digit span; color trials
Combourieu Donnezan et al. (2018)			Stroop color word test; digit span; matrix reasoning test
Fiatarone Singh et al. [26]	ADAS-Cog	ADAS-Cog list learning; WMS-III auditory logical memory I and II; benton visual retention test-revised 5th Edition	Symbol digit modalities test; verbal fluency (controlled oral words association test and animal naming); WAIS-III matrices and similarities
Hagovska et al. (2017)	MMSE	RAVLT	TMT; stroop; disjunctive reaction time
Hughes et al. [32]	CAMCI		Tracking A and B;
Jiranan et al. (2020)		CERAD word-list learning test	TMT; digit span; verbal fluency test (letter and category); block design
Joke et al. (2017)	MoCA		
Köbe et al. [36]		RAVLT	TMT; stroop color-word test; digit span
Lam et al. [33]	MMSE; ADAS-Cog	List learning delayed recall test for Episodic memory	TMT; digit span; verbal fluency test (category);
Law et al. [18]	NCSE	Verbal learning test	TMT
Park et al. [30]	MoCA		TMT; digit span
Schwenk et al. [15]	MoCA		TMT
Shimada et al. (2017)	MMSE	RAVLT; WMS-revised logical memory II	TMT; verbal fluency test (letter and category);
Suzuki et al. [28]	MMSE; ADAS-Cog	WMS-III auditory logical memory I and II	
Zijun et al. [31]	ADAS-Cog; MoCA		

Note MMSE mini-mental state examination, *ADAS-Cog* Alzheimer's disease assessment scale-cognitive subscale, *MoCA* montreal cognitive assessment, *CAMCI* computerized assessment of mild cognitive impairment, *NCSE* neurobehavioral cognitive status examination, *RAVLT* rey auditory verbal learning test, *CERAD* consortium to establish a registry for alzheimer's disease, WMS-III wechsler memory scale third edition, *TMT* trial making test, *WAIS-III* Wechsler adult intelligence scale third edition

Table 3 Effect sizes of combined intervention on outcomes

Outcomes	Combined intervention group *vs*	No. of studies	SMD	95% CI	p	I^2(%)	p
Global cognition	Single cognitive intervention group	4	0.81	[−0.09,1.71]	0.08	90	$<0.001^{***}$
	Single physical exercise group	5	0.41	[−0.06,0.89]	0.09	79	$<0.001^{***}$
	Other control group	8	0.27	[0.09,0.44]	0.003^{**}	0	0.68
Memory	Single cognitive intervention group	3	0.00	[−0.20,0.21]	0.97	44	0.17
	Single physical exercise group	6	0.25	[0.07,0.44]	0.006^{**}	11	0.35
	Other control group	5	0.29	[0.12,0.47]	0.001^{**}	0	0.55
Executive function/attention	Single cognitive intervention group	5	0.28	[0.09,0.47]	0.004^{**}	0	0.43
	Single physical exercise group	8	0.32	[0.16,0.49]	0.0002^{***}	0	0.72
	Other control group	7	0.23	[0.05,0.41]	0.01^{*}	0	0.70

Note vs Versus, *No* number, *SMD* standardized mean difference, *CI* confidence interval. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

$p=0.08$; $I^2=90\%$, p for $I^2<0.001$]; [SMD = 0.41, 95% CI (−0.06, 0.89), $p=0.09$; $I^2=79\%$, p for $I^2<0.001$]. Compared to the other control group, the effect of the combined intervention on global cognition was significant, with low heterogeneity [SMD = 0.27, 95% CI (0.09, 0.44), $p=0.003$; $I^2=0\%$, p for $I^2=0.68$].

Effects of combined intervention on memory

As Table 3 shows, compared to the single cognitive intervention, the effect of the combined intervention on memory was not significant, with moderate heterogeneity [SMD = 0.00, 95% CI (−0.20, 0.21), $p=0.97$; $I^2=44\%$, p for $I^2=0.17$].

Compared to the single physical exercise group and the other control group, the effects of the combined intervention on memory were significant, with low heterogeneity [SMD = 0.25, 95% CI (0.07, 0.44), $p = 0.006$; $I^2 = 11\%$, p for $I^2 = 0.35$]; [SMD = 0.29, 95% CI (0.12, 0.47), $p = 0.001$; $I^2 = 0\%$, p for $I^2 = 0.55$].

Effects of combined intervention on executive function/attention

As Table 3 shows, compared to the single cognitive intervention group, the single physical exercise group, and the other control group, the effects of the combined intervention on executive function/attention were significant, with low heterogeneity [SMD = 0.28, 95% CI (0.09, 0.47), $p = 0.004$; $I^2 = 0\%$, p for $I^2 = 0.43$]; [SMD = 0.32, 95% CI (0.16, 0.49), $p = 0.0002$; $I^2 = 0\%$, p for $I^2 = 0.72$]; [SMD = 0.23, 95% CI (0.05, 0.41), $p = 0.01$; $I^2 = 0\%$, p for $I^2 = 0.70$].

Sensitivity analysis

Compared to the single cognitive intervention group and the single physical exercise group, the effects of the combined intervention on global cognition exhibited high heterogeneity ($I^2 = 90\%$, p for $I^2 < 0.001$; $I^2 = 79\%$, p for $I^2 < 0.001$). Thus, sensitivity analysis was conducted to evaluate the effects of each included study on the heterogeneity. As Table 4 shows, the I^2 values and p for I^2 were obviously changed when the study of Park et al. (2020) was omitted. As Table 5 shows, the I^2 values and p for I^2 were almost unchanged when each included study was omitted, which indicated the stability of our meta-analysis results.

Discussions

This meta-analysis included 16 RCTs and explored the effect of the combined intervention on cognitive function (global cognition, memory, and executive function/attention) in older adults with MCI by comparing it to the single cognitive intervention group, the single physical exercise group, and the other control group. We found that the combined intervention has small-to-medium effect on global cognition compared to the other control group, and a small-to-medium effect on memory compared to the single physical exercise group and the other control group, and moreover, a small-to-medium effect on executive function/attention compared to the single cognitive intervention group, the single physical exercise group, and the other control group.

Table 4 Results of sensitivity analyses for the combined intervention comparing to the single cognitive intervention group on global cognition

Study omitted	SMD	95% CI	p	I^2(%)	p
Fiatarone Singh [26]	1.13	[−0.31, 2.56]	0.12	93	< 0.001***
Lam [33]	1.14	[−0.41, 2.69]	0.15	92	< 0.001***
Law [18]	0.97	[−0.24, 2.19]	0.12	94	< 0.001***
Park [30]	0.15	[−0.06, 0.35]	0.17	0	0.73

Note SMD standardized mean difference, *CI* confidence interval

Table 5 Results of sensitivity analyses for the combined intervention comparing to the single physical exercise group on global cognition

Study omitted	SMD	95% CI	p	I^2(%)	p
Fiatarone Singh [26]	0.59	[0.06, 1.13]	0.03*	79	0.002**
Lam [33]	0.54	[−0.14, 1.21]	0.12	80	0.002**
Hagovska 2017	0.41	[−0.22, 1.04]	0.21	82	< 0.001***
Law [18]	0.38	[−0.17, 0.92]	0.18	83	< 0.001***
Amjad [19]	0.19	[−0.16, 0.54]	0.28	57	0.07

Note SMD standardized mean difference, *CI* confidence interval

Interpretation of results and comparison with previous research

To our knowledge, this is the first meta-analysis examining the effect of the combined intervention on cognition in older adults with MCI by comparing it to three different types of control groups. Zhu et al. [13] investigated the effect of the combined intervention on cognition in healthy older adults in a meta-analysis. Twenty studies were included, of which 14 studies were RCTs. The meta-analysis showed positive effects of the combined intervention on global cognition, memory, executive function, and attention when comparing the combined intervention to the other control group, which was consistent with our findings. Zhu et al. found a small-to-medium effect of the combined intervention on global cognition when comparing the combined intervention to a single physical exercise, which was in contrast with our current data. We thought that Zhu et al. [13] should be more cautious in interpreting their results, as the results are based on only one article. In addition, the methods used to measure cognition varied across studies, which limited their comparability.

Karssemeijer et al. [14] conducted a meta-analysis examining the efficacy of the combined intervention on global cognition, memory, and executive function/attention in older adults with MCI or dementia compared to the other control group. Ten RCTs were included, of which only three studies were conducted in older adults with MCI. The meta-analysis showed a positive small-to-medium effect of the combined intervention on global cognition, but no significant effect of the combined intervention on memory and executive function/attention, which was different from our results that the small-to-medium effect of the combined intervention on memory and executive function/attention compared to the other control group. The results of Karssemeijer et al. [14] were influenced by dementia. Perhaps the combined intervention has difficulty improving the cognition of dementia, which has more seriously impaired cognition than MCI.

A recent systematic review conducted by Yang et al. [20] reviewed the effectiveness of the combined intervention in older adults with MCI based on ten RCTs. Most studies reported a significant improvement in global cognition, memory, executive function, and attention. The preliminary results showed positive effects of the combined intervention on cognition in older adults at risk of developing dementia. This meta-analysis added new evidence to the qualitative review of Yang et al., and we were able to quantify the magnitude of the overall effect, confirming the efficacy of the combined intervention in older adults with MCI.

Studies have shown that cognitive intervention and physical exercise are clinically effective for cognitive improvement [8–12]. Neural plasticity is a probable explanation for positive training effects [38]. Brain plasticity refers to the brain's capacity to change and adapt, physically and functionally, including the potential of neurons to change their synaptic connections [39]. Animal experiments have revealed that physical exercise can facilitate neuronal proliferation and that cognitive intervention can increase the survival of these proliferating neurons and guide these neurons to integrate into the working brain network by activity-dependent synaptic adaptation to maintain the last positive plastic changes [40–42]. Therefore, we assumed that the combined intervention was more effective than the single-component intervention on cognition. However, our results were contrary to our hypothesis. Lam et al. [33] observed the same negative results. Perhaps the combined intervention meant double challenges, which may cause excessive stress and lead to weakened cognitive benefits of single cognitive intervention and single physical exercise in the combined intervention. The interaction between combined components may inhibit rather than promote neural plasticity, making unobserved cognitive enhancement effects of the combined intervention [26].

Interestingly, a significant improvement in memory with the combined intervention was observed when compared to single physical exercise but was not observed when compared to single cognitive intervention. We hypothesized that a single cognitive intervention would improve memory more than a single physical exercise during MCI [38]. The effectiveness of a single physical exercise on memory was too small to offset the negative effect of the combination of the two components, so the combined intervention had a less positive effect on memory than a single cognitive intervention. In contrast, the effectiveness of a single cognitive intervention on memory was large enough to offset the negative effect of the combination of the two components so that the combined intervention had a more positive effect on memory than a single physical exercise. MCI is a critical period during which cognitive restructuring and neuroplasticity such as compensation still occur [38]. Perhaps single cognitive intervention is meaningful for MCI to maintain the survival of existing neurons and increase plasticity, rather than the effect of single physical exercise on increasing new neurons.

Although the effectiveness of the combined intervention on executive function/attention supported our hypothesis, it still did not determine the separate effects of the combined intervention on executive function and attention. Moreover, executive function and attention are very complex cognitive subdomains [43]. Executive function includes planning, decision-making, working memory, responding to feedback/error correction, overriding habits/inhibition, and mental flexibility [44]. Attention includes sustained attention, divided attention, selective attention, and processing speed [44]. Patients with AD often perform poor selective and divided attention, failed inhibition of interfering stimuli, and poor manipulation skills. Therefore, it is important to identify the role of the combined intervention in improving executive function, attention, and their subdomains to decrease the likelihood of AD progression during MCI.

Strengths and limitations

The most significant advantage of the present study was that the included studies were all RCTs. The characteristics of each included study were summarized from five perspectives (study, sample, combined intervention group, control group, outcome). Furthermore, focusing on the cognitive domains (global cognition, memory, and executive function) was more important for MCI. In addition, the cognitive benefits of the combined intervention on cognitive function were further clarified by comparing the combined intervention group to the single-component intervention group.

However, there were still deficiencies in our research, which limited the interpretation of the results. First, MCI diagnostic criteria are important for the definition of the study populations. The Mayo criteria, the IWG criteria, the NIA-AA criteria, ICD-9-CM 331.83, and DSM-5 were conceptually similar [37], but some included studies did not mention MCI diagnostic criteria, which makes it impossible to interpret the findings better. Second, due to the small number of included studies, publication bias analysis was not performed, and subgroup analysis was not conducted on the factors affecting the combined intervention, such as combined mode and the level of exposure to the intervention. Sensitivity analysis showed that Park et al. [30] caused the large heterogeneity when comparing the effect of the combined intervention to the single cognitive intervention group on global cognition. Perhaps the combined mode of cognitive intervention and physical exercise in the study of Park et al. [30] was virtual reality-based exergame, which was different from the other three studies. However, the limited included studies make cautious in interpretating the heterogeneity. Third, we did not explain the efficacy of the combined intervention based on subdomains of memory, executive function, and attention. Fourth, some articles were excluded due to incomplete data and language restrictions.

Implications for future research

In the future, more RCTs with rigorous designs, such as multiarm designs, will be needed to provide high-quality evidence for exploring the effects of combined interventions, since our results only partially supported the hypothesized superiority of the combined interventions. In addition, using standardized tools with high sensitivity and specificity to assess cognition will increase the credibility of the results. Moreover, evaluating the maintaining effect of combined intervention on cognitive function will be meaningful. Finally, some researchers [45, 46] proposed that simultaneous cognitive intervention and physical exercise might be crucial for interaction effects between cognitive and physical components. Thus, comparing different combined interventions may help understand the factors that influence combined interventions to develop optimally combined intervention programs.

Conclusion

The results of this meta-analysis showed that combined interventions effectively improved global cognition, memory, and executive function/attention in older adults with MCI. However, combined interventions demonstrated superiority over single physical exercise on memory and executive function/attention and superiority over single cognitive intervention on executive function/attention. In this meta-analysis, the number of included studies was limited and showed a large methodological heterogeneity in intervention characteristics. Thus, the current results should be interpreted with caution. In the future, there is the need for well-designed RCTs with multiple arms, including combined intervention control groups and standardized tools assessing various cognitive domains, to explore further the immediate and long-term effect of combined intervention on cognitive function.

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Declaration

Conflict of interest None.

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