

INPLASY PROTOCOL

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Effects of Combined Multicomponent Exercise and Cognitive Training on Cognitive Function and Physical Function in Older Adults with Mild Cognitive Impairment: A Systematic Review and Meta-Analysis

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Review question / Objective: (1) to compare the effects of combined intervention with inactive control, single exercise intervention and single cognitive intervention in older adults with MCI;(2) to evaluate effectiveness combined intervention on the subdomains of specific domains cognitive; (3) to directly assess efficacy of the three main types of combination strategies on certain cognitive and physical function.

Condition being studied: MCI is the intermediate phase between normal age-related cognitive decline and dementia[5],characterized by cognitive decline that is larger than expected considering a person's age and education, though without notably interference in daily-life activities [6]. It is frequently associated with an predict which patients with amnesic MCI will progress to AD[7]. Indeed, MCI is classified in two types: amnesic (memory deterioration) and non-amnesic (cognitive function impairment)[8].The mean annual conversion rate of MCI to dementia is approximately 10%, which is far higher than the annual incidence (1–2%) in the general population [9, 10]. However, MCI provides an optimal window for preventing the progression to dementia [11].

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 November 2022 and was last updated on 24 November 2022 (registration number INPLASY2022110121).

INTRODUCTION

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METHODS

Search strategy: We searched MEDLINE, Embase, Cochrane Library and PsycINFO from inception to 7 July 2022 to identify RCTs examining the effects of combined intervention on cognitive or physical functional outcomes. No restrictions Journal on language or publication type were applied. The articles in the selected journals were further screened and additional searches were conducted using the same search terms in Google Scholar to identify other potentially relevant articles. EndNote20 was used to store and sort the retrieved randomized controlled trials and delete duplicate documents. Two individuals independently screened titles and abstracts according to the predefined inclusion criteria. The full text of all trials that met the inclusion criteria was searched based on the title and abstract, which was the basis for identifying the articles included in this study. Inconsistent results were determined by additional discussion or decided by a third examiner. The electronic search was complemented by hand-searching the references of included papers and previous reviews.

Participant or population: Older adults with mild cognitive impairment.

Intervention: Combined exercise and cognitive training.

Comparator: Single exercise, single cognitive training and inactive control group.

Study designs to be included: RCT.

Eligibility criteria: 2.3.1 Types of studies Published, peer-reviewed reports of RCTs investigating the effects of a combined cognitive and physical exercise intervention on one or more cognitive, physical outcome in older adults with MCI were included. No restrictions on the type or size of randomized trials were applied in order to ensure that all relevant literature was included. The primary outcome was cognitive function and physical function; therefore, eligible studies needed to provide at least one cognitive outcome or physical function. Studies were included if they compared a combined intervention with cognitive or physical training alone, and or a passive control group. Randomized crossover trials were included, but only the first treatment phase was considered for analysis to avoid the influence of potential carryover effects. 2.3.2 Types of participants Studies were included if they focused on older adults aged of 55 years or older. This included only population older adults with MCI, which diagnosed by psychologists or psychiatrists, based on criteria proposed by European Consortium on Alzheimer's Disease Working Group on MCI or with standard clinical examinations in line with the criteria of ICD-9-CM(reference); no medical record of neurodegenerative disease; not in post-amputation condition on extremities and no bone fractures in the last six months; no neurological injuries (such as traumatic brain injury, stroke, etc.); no report of any neurosurgical procedures; and no major unstable medical diseases. 2.3.3 Types of interventions Interventions protocol is combined multicomponent exercise and process-based cognitive training. Process-based

cognitive training was defined as repeated practice on tasks targeting one or several cognitive domains, as opposed to explicit learning of strategies[51]. Combined interventions could be delivered[2] as (1) simultaneous training: cognitive training and physical exercise delivered concurrently in a dual-task format; (2) sequential training: cognitive training and physical exercise delivered in separate sessions, either on the same day or on different days; or (3) exergaming: physically active video games including cognitively challenging tasks. Exergaming interventions were included if the games placed cognitive demands, such as requiring attention and processing speed. pure exercise or sport games, such as yoga or balance exercises were excluded.

2.3.4 Types of controls Studies were included if they compared a combined intervention with exercise or cognitive training, a sham intervention (e.g. health education, relaxation, stretching or non-specific cognitive activities such as data entry on a computer) or a passive control group (wait-list, no-contact). In multi-arm studies, all eligible control conditions were included. Moreover, present study also included studies that compared simultaneous combined intervention to sequential combined intervention or sequential combined intervention to simultaneous combined intervention.

2.3.5 Types of outcomes Outcomes included were change from baseline to post-intervention on measures of untrained cognitive outcomes (global or domain-specific), performance-based physical exercise outcomes (strength, mobility, balance or gait, physical activity and ADL).

Information sources: We searched MEDLINE, Embase, Cochrane Library and PsycINFO.

Main outcome(s): Cognitive function and physical function.

Quality assessment / Risk of bias analysis: The risk of bias criteria of randomized controlled trials (RCT) in the Review Manager 5.4.1 were adopted to perform qualitative evaluation of seven aspects of

RCT: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias, and each index was judged by “low bias risk,” “uncertain bias risk,” or “high bias risk.”

Strategy of data synthesis: Using Review Manager 5.4.1 for the literature data process, this paper had the combined effect size and heterogeneity test and drew a forest diagram, literature outcome indicators were all continuous variables. Since all data were continuous information and were pooled by the same outcome using inconsistent scales, we selected the Standardized Mean Difference (SMD) as an effective indicator and provided the 95% confidence interval (CI). The pooled SMDs were regarded as the effect size of each outcome (global cognition, memory, executive function, attention and mobility function etc). This meta-analysis strictly follows the PRISMA guidelines and used the P value and I² for the heterogeneity test. If there was no statistical heterogeneity between the results of each study (I² ≤ 50%, P > 0.10), the fixed-effects model would be selected. Conversely, if the heterogeneity was considered to be significant, we selected the random-effects (RE) model and performed a subgroup analysis and sensitivity analysis to identify the factors that contributed to the heterogeneity. Given that the enough number of studies included to compare the effects of the combined intervention and inactive control groups, we conducted subgroup analyses of two domains cognitive. Specifically, the current study performed subgroup analysis of executive function and memory based on the criteria of classifying sub-domains and no less than 4 or 3 of the included studies respectively. Conversely, we conducted a qualitative analysis of the combined intervention group and single cognitive training and single physical training because fewer studies were included to perform a meta-analysis. Moreover, due to

the limit number of included studies on the effectiveness of simultaneous combined intervention compared to sequential combined intervention, we only performed meta-analyses of outcomes such as global cognitive function and executive function for data included in two different studies, and conducted qualitative analyses for other outcomes such as memory and gait.

Subgroup analysis: Specific domains cognitive such as executive function and memory.

Sensitivity analysis: if $I^2 > 50\%$.

Country(ies) involved: China.

Keywords: Cognitive dysfunction; combined intervention; cognitive gains; cognitive performance.

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