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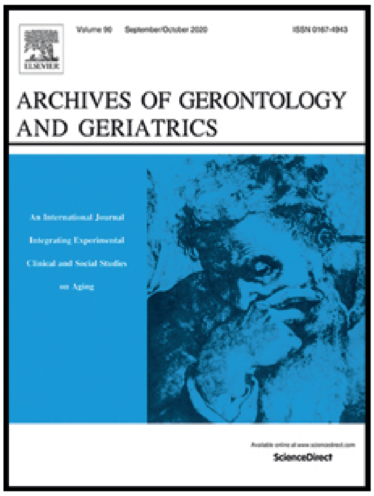

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Review

Effects of multi-component non-pharmacological interventions on cognition in participants with mild cognitive impairment: a systematic review and meta-analysis

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AD: Alzheimer´s disease; ADL: activities of daily living; CR: cognitive rehabilitation; CS: cognitive stimulation; CT: cognitive training; MCI: Mild cognitive impairment; MMSE: Mini-mental State Examination; MNPI: Multicomponent non-pharmacological intervention; QoL: Quality of life; PT: physical training; PE: physical exercise.

Highlights

1. Multicomponent interventions improve global cognition in MCI subjects.

2. Two-component interventions can contribute to neuroplasticity.

3. Cognitive and physical interventions may offer benefits in global cognition.

4. Cognitive and physical interventions are preferred to cognitive-only interventions.

Abstract

Background and Purpose: Mild cognitive impairment (MCI) describes a stage of intermediate cognitive dysfunction where the risk of conversion to dementia is elevated. Given the absence of effective pharmacological treatments for MCI, increasing numbers of studies are attempting to understand how multicomponent non-pharmacological interventions (MNPI) could benefit MCI. The purpose of this systematic review and meta-analysis were to assess the effects of two-component MNPI (simultaneous cognitive intervention based on cognitive stimulation, cognitive training and/or cognitive rehabilitation or combined cognitive and physical interventions) on global cognition and cognitive functions in older adults with MCI and to compare the degree of efficacy between the two interventions.

Methods: After searching electronic databases (PubMed, Web of Science, Scopus and Cochrane Central) for randomized controlled trials and clinical trials published from 2010 to 18 January 2021, 562 studies were found. 8 studies were included in this review, with a fair to good quality according to the PEDro scale.

Results: From a random-effects model meta-analysis, the pooled standardized MMSE mean difference between the intervention and control groups showed a significant small-to-medium effect in global cognition in MMSE score (0.249; 95% CI = [0.067, 0.431]), which seemed to be greater for combined physical and cognitive interventions. However, the meta-analyses did not show any effects regarding specific cognitive functions.

Conclusion: Our analyses support that MNPI could improve the global cognition in older adults with MCI. However, more studies are needed to analyze the potential benefits of MNPI on older adults with MCI.

Keywords: Cognitive Training, Cognitive Rehabilitation, Cognitive Stimulation, Cognitive intervention, Physical Training, Mini-Mental State Examination.

1. INTRODUCTION

Predictions for the upcoming decades suggest an increase in the number of older adults in Europe due to the rise in life expectancy (Rózyk-Myrta et al., 2021). Mild Cognitive impairment (MCI) is one of the most common age-related pathologies, with an estimated global prevalence of 9.6-21.6% (Lara et al., 2016). People with MCI show a cognitive decline characterized by impaired memory, attention, orientation, and executive functions (Mrakic-Sposta et al., 2018), which is greater than expected for their age and education level. MCI patients also show a reduction in their motor capacities (Combourieu Donnezan et al., 2018), but it does not interfere with their activities of daily living (ADL) (Lara et al., 2016). MCI often represents a middle point in the transition from healthy aging to early dementia (Petersen, 2004) or Alzheimer's disease (AD) (Mrakic-Sposta et al., 2018); the annual conversion rate of MCI patients to AD is about 12%, far from the 1-2% observed in healthy individuals (Petersen et al., 1995).

Pharmacological treatments for MCI have no effect, and new therapeutic approaches are needed (Tricco et al., 2013) to slow down or prevent cognitive decline (Rodakowski et al., 2015). Thus, non-pharmacological intervention, as cognitive intervention would be an alternative. Patients with MCI could benefit from multicomponent non-pharmacological interventions (MNPI) (Bae et al., 2019) since their cognitive plasticity and learning potential may be intact (Li et al., 2011).

MNPI comprise more than one type of intervention and may include cognitive interventions, physical training (PT), and social activities (Bae et al., 2019). Regarding cognitive interventions, three different approaches has been identified (Clare & Woods, 2003). Cognitive stimulation (CS), referring to the involvement in group activities designed to increase cognitive and social functioning; Cognitive rehabilitation (CR) based on individualized interventions focusing on the patient cognitive behavioral deficits; Cognitive training (CT) which comprises exercises aiming to provide a set of standardized tasks. PT may consist of aerobic exercise, resistance training or postural balance, among others (Suzuki et al., 2013). Social activities are tasks with low physical or cognitive demands (Lam et al., 2015) within a community network (Li et al., 2011).

Previous studies about cognitive interventions (Gómez-Soria et al., 2021; Sherman et al., 2017), non-pharmacological intervention (cognitive or motor) (Teixeira et al., 2012) and physical exercise (PE) (Biazus-Sehn et al., 2020) evidence positive effects on global cognitive function in older subjects with MCI. Moreover, some authors analyzed effects of the combination of cognitive and physical interventions in participants with MCI (Bruderer-Hofstetter et al., 2018; Ozbe et al., 2019; Yang et al., 2020) or cognitive impairment, finding effects on cognitive abilities (Ozbe et al., 2019) and on global cognitive function (Yang et al., 2020). In addition, CT plus PE seem to induce higher effects than PE or CT alone (Bruderer-Hofstetter et al., 2018). However, the difference in the effects on global cognition comparing two types of cognitive interventions (CS, CT, or CR) and one type of cognitive intervention together with PE or PT have not been studied.

The primary aim of this systematic review and meta-analysis was to evaluate the effects of MNPI in older adults with MCI using two components: simultaneous cognitive intervention (based on cognitive stimulation, cognitive training and/or cognitive rehabilitation) and cognitive and physical interventions on global cognition assessed by the Mini-Mental State Examination (MMSE) and cognitive functions, as well as to compare the degree of efficacy between the two interventions. The secondary objective was to explore the ADL by Bayer ADL, the mood by the Montgomery Asberg Depression Rating Scale, and 15-item version of the Geriatric Depression Scale, and quality of life (QoL) by the Quality of Life-Alzheimer's Disease and Functional Rating Scale of Symptoms of Dementia.

2. METHODS

This work adheres to the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] guidelines (Rethlefsen et al., 2021) (Table 1SM (Supplementary Material)) and was registered in PROSPERO (CRD42021232373).

2.1. Information Sources and Study Selection: Literature search

We searched for randomized controlled trials and clinical trials published from 2010 to 18 January 2021, exploring the effects of MNPI based on two simultaneous types of cognitive intervention or cognitive intervention in combination with PT. Only studies conducted after 2010 were included because the classification of cognitive intervention, which we have followed on this review by Clare & Woods was introduced in 2003. In our a first search for articles starting from 2003, we noticed that was hardly to find studies about multicomponent interventions in mild cognitive impairment before 2010; actually, there is only one study about two-component intervention in MCI patients published before 2010. Therefore, we conclude that our search from 2010 does not result in missing information, due to the lack of multicomponent studies prior to this date. The online repositories PubMed, Web of Science, Scopus, and Cochrane Collaborative Central Register of Controlled Trials were used in this study. The specific search parameters used in all repositories are fully described in Table 2SM. The search terms were adjusted to each respective database.

Four different search categories were established:

1- Intervention: "multicomponent intervention" OR "multicomponent cognitive intervention" OR "cognitive intervention".

2- Intervention: "cognitive intervention" OR "cognitive stimulation" OR "cognitive rehabilitation" OR "cognitive training" AND "physical exercise" OR physical activities" OR "physical training".

3- Cognition global: "Mini-Mental State Examination" OR "MMSE".

4- Participants: "Cognitive Dysfunction" [Mesh] OR "cognitive impairment" OR "mild cognitive impairment".

These categories were combined using the following Boolean operators: (1 OR 2) AND (3 AND 4).

The search was complemented by scanning the reference lists of included studies and using the same terms in a clinical trial repository (clinicaltrials.gov).

2.2. Study Inclusion and Exclusion Criteria

The inclusion criteria were established according to the following PICOS strategy:

1) Participants: Older adults over 65 years diagnosed with MCI by Petersen criteria (R. C. Petersen, 2004) or International Classification of Diseases Clinical Modification (Albert et al., 2011).

2) Intervention: MNPI based in two components

The first component is one of two types of cognitive interventions according to the classification of (Clare & Woods, 2003) based on a traditional (pencil and paper) or computerized intervention.

The second component is either a cognitive intervention, as previously classified, PT or PE.

3) Comparator: Passive (no intervention) or active controls.

4) Outcome: Global cognition by MMSE.

5) Study design: Randomized controlled trials and clinical trials.

The exclusion criteria were:

1) Participants diagnosed with other cognitive impairments.

2) Studies including mixed participants (MCI mixed with healthy and/or dementia subjects) which did not perform independent statistical analysis for the MCI group.

3) MNPI that included two components different from those established in the inclusion criteria, or more than two components.

5) Publications in languages other than English or Spanish.

2.3. Data Extraction and Assessment of Studies

Two independent reviewers (IG-S, EC) initially evaluated the studies according to title and abstract, identified by the search strategy. Then, the reviewers evaluated the articles and selected studies according to the previously mentioned eligibility criteria. Disagreements between the reviewers were resolved by consensus, when consensus could not be reached, arbitration by a third reviewer was applied (JM-P).

Two of the authors of the study (IG-S, and EC) independently extracted data from the included articles, completing data tables which were standardized prior to the execution of the search. Extracted data Tables were reviewed by a third author (JM-P) to ensure accuracy.

Different aspects related to the study design, participant characteristics and type of interventions were extracted from the selected studies and can be consulted in Table 1. Additionally, the information regarding the assessment of the primary and secondary outcome variables and the observed effect in each individual study is available in Table 2.

The main outcome was global cognition assessed by MMSE. The MMSE is a universal cognitive screening test, commonly used in both clinical and research settings (Tombaugh & McIntyre, 1992). Based on optimal cut-off values, scoring lower than 28 points would suggest MCI (Patten, 2018). Specific cognitive domains were also evaluated by different tools.

2.4. Quality and Bias

Publication bias was examined performing Egger's Regression Test for Funnel Plot Asymmetry (Egger et al., 1997), which did not suggest the existence of bias. Further confirmation was obtained by visual inspection of funnel plot symmetry, plotting the effect size in relation to the standard error (Figure 1SM).

2.4.1. Risk of Bias Assessment in Individual Studies

Additionally, the PEDro scale (Maher et al., 2003) was used for the assessment of the quality of the studies included in the qualitative and quantitative analyses (see Table 3SM). The PEDro scale is a valid measure of the methodological quality of clinical trials and is used on non-pharmacological therapies. PEDro scale total score can be treated as an interval level measurement and subjected to parametric statistical analysis (de Morton, 2009). Items are scored as either present (1) or absent (0) with a 10 as a total score maximum. Scores ≤ 3 indicate poor study quality, 4-5 fair quality, 6-8 good quality and 9-10 excellent quality (Cashin & McAuley, 2020). The selected studies obtained total scores for methodological quality ranged from 4 to 7 points, concluding that the majority of the studies included present fair to good quality.

2.5. Quantitative analysis

The standardized mean difference was chosen as the effect size metric to combine the results. When it was not directly provided by the authors, it was calculated from the mean, standard deviation, and sample size. For studies with more than one measurement method for the same cognitive variable, the most common method of the studies was chosen to produce a single standardized mean difference. As such, each study was represented by one score and contributed only one effect size in each meta-analysis.

Then, all results were pooled using the DerSimonian-Laird method in a random-effects meta-analysis with the OpenMetaAnalyst software (Wallace et al., 2012). The test for heterogeneity was based on Cochran's Q test and its associated p-value. The I^2 statistic was also calculated, although it was reported mainly for descriptive purposes, as this may not be an adequate measure of inconsistency and its generalizability is limited (Borenstein et al., 2017).

3. RESULTS

3.1. Literature Search

The initial search provided a total of 536 records. The process used to detect duplicates was carried out through Microsoft Excel and the process was repeated twice, with a final manual revision. After removing duplicates and including studies identified through reference scanning, 478 potentially relevant studies were found, which were further filtered based on their title and abstract, remaining solely 15 of them. After reading the full text, eight articles were finally included in the qualitative and quantitative analyses (Barban et al., 2016; Buschert et al., 2011, 2012; Hagovská & Olekszyová, 2016; Jeong et al., 2016; Kounti et al., 2011; Rojas et al., 2013; Styliadis et al., 2015). The PRISMA diagram for the study selection is detailed in Figure 1.

3.2. Study characteristics

Five of the studies were focused on simultaneous cognitive interventions: CS and CT (Buschert et al., 2011, 2012; Rojas et al., 2013), CT and CR (Jeong et al., 2016) and computerized CT and reminiscence therapy (Barban et al., 2016) and the other three studies were focused on CT in combination with different PT: kinetic exercise (Kounti et al., 2011), game-based PE (Styliadis et al., 2015) and balance training (Hagovská & Olekszyová, 2016).

3.2.1. Participant characteristics and sample size

The key characteristics of the included studies are described in Table 1. A total of 592 participants (67.67% women) with MCI were analyzed among all studies, and the individual number of participants ranged from 24 (Buschert et al., 2011, 2012) to 224 (Jeong et al., 2016). In the intervention group (IG) the mean age of the participants was 71.4 years, with varied education level from 6.1 (Styliadis et al., 2015) to 12.3 years (Buschert et al., 2011, 2012). Participants were mainly recruited from medical/ research settings such as medical center, clinics, or hospitals and day care centers. From all included studies, 71.43% were conducted in Europe (Barban et al., 2016; Buschert et al., 2011, 2012; Hagovská & Olekszyová, 2016; Kounti et al., 2011; Styliadis et al., 2015), 14.28% of studies were conducted in America (Rojas et al., 2013), and 14.28% in Asia (Jeong et al., 2016).

3.2.2. Experimental design of the reviewed studies

The studies were randomized controlled trials and clinical trials; however, their design was diverse. Three studies performed more than one follow-up (3, 6, 15 and 28 months after the intervention) (Barban et al., 2016; Buschert et al., 2012; Jeong et al., 2016). Additionally, Barban et al., 2016 chose to follow a crossover design, which included participants with mild AD and MCI but they were analyzed separately (Barban et al., 2016).

Two studies included in the present review (Buschert et al., 2011, 2012) belong to different time points within the same project, and therefore, they will be treated as a single study when discussing the qualitative and quantitative results.

3.2.3. Multicomponent intervention characteristics

Intervention characteristics are shown in Table 1. Studies were grouped according to the type of intervention: simultaneous cognitive interventions or cognitive interventions with PT. Five studies applied simultaneous cognitive intervention (Barban et al., 2016; Buschert et al., 2011, 2012; Jeong et al., 2016; Rojas et al., 2013) and three studies combined cognitive and physical interventions (Hagovská & Olekszyová, 2016; Fotini Kounti et al., 2011; Styliadis et al., 2015). The duration of the interventions ranged from 20 (Buschert et al., 2012; Hagovská & Olekszyová, 2016; Kounti et al., 2011) to 48 sessions (Rojas et al., 2013), and from 30 (Hagovská & Olekszyová, 2016) to 120 minutes per session (Buschert et al., 2012; Rojas et al., 2013). The cognitive interventions included: orientation, reminiscence, multisensory, strategies in daily life, external aids, training in specific cognitive functions, physical leisure activities, visuomotor coordination and spatial processing and metacognition and cognitive self-efficacy. PT included: visuomotor, and verbal-kinetic tasks, active movements, walking, balance training, fine motor skills, aerobic exercise, resistance exercise flexibility trainings and exergaming.

Seven studies adjusted the difficulty of the tasks depending on individual performance (Barban et al., 2016; Buschert et al., 2011, 2012; Hagovská & Olekszyová, 2016; Jeong et al., 2016; Fotini Kounti et al., 2011; Styliadis et al., 2015), whereas no information was retrieved regarding this aspect in the other study (Rojas et al., 2013).

3.2.4. Control group type

There were some differences regarding the type of control group (CG) used. Four studies included an active CG, which involved participants in different activities than the IG (Buschert et al., 2012; Hagovská & Olekszyová, 2016; Jeong et al., 2016; Styliadis et al., 2015). On the other hand, four studies had a passive CG, that did not modify their routine (Barban et al., 2016; Fotini Kounti et al., 2011; Rojas et al., 2013; Styliadis et al., 2015). It should be highlighted that the study of Styliadis et al. (2015) included both types of CG.

3.2.5. Measured outcomes

The intervention modalities ("simultaneous cognitive" and "cognitive and physical") and the domains of results contemplated in the quantitative analysis can be observed in Figure 2. All the studies evaluated global cognition using the MMSE, as it was an inclusion criterion. Additionally, different specific cognitive domains were also assessed in several studies, as Figure 2 shows.

3.3. Effects of multicomponent interventions on MCI

3.2.3.1. Global cognition

Baseline Mini Mental State Examination (MMSE) scores ranged from 25.3 (Jeong et al., 2016) to 28.1 points (Buschert et al., 2012) in the IG (Table 1).

Four studies showed significant post-intervention differences in MMSE scores between the IG and CG (Barban et al., 2016; Buschert et al., 2012; Hagovská & Olekszyová, 2016; Kounti et al., 2011). In addition, two studies demonstrated significant pre-post changes within the IG (Buschert et al., 2012; Styliadis et al., 2015). No statistically significant differences in global cognition measured by MMSE were found in the rest of the studies (Jeong et al., 2016; Rojas et al., 2013) (Table 2). Comparing the results obtained in the two types of interventions, the physical plus cognitive interventions obtained improvements in all studies, while only two of the four cognitive-based intervention studies obtained improvements. On the one hand, in physical plus cognitive interventions the differences between groups ranged from 0.48 to 1.41 points, and on the other hand, in the cognitive-only interventions the difference between groups was within 0.1 and 0.92 points. Moreover, one study based on cognitive-only interventions showed no positive improvements in the follow-up at 28 months; in fact it showed changes in one of two groups only in the follow-up at 15 months (Buschert et al 2012).

Moreover, studies included additional assessments of general cognitive function using the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog Scale) (Table 2). One study found significant differences in ADAS-Cog between groups after the intervention (Jeong et al., 2016) and the other study at the 15- and 28-month follow-ups (Buschert et al., 2012).

3.2.3.2. Specific cognitive functions

Table 2 describes the post-intervention and follow-up data from specific cognitive functions. From the four studies that assessed memory, three studies showed significant improvements in memory at the end of the intervention (Barban et al., 2016; Buschert et al., 2012; Jeong et al., 2016) which remained enhanced at the follow-up in two studies (Buschert et al., 2012; Jeong et al., 2016). One study observed this effect between groups (Kounti et al., 2011). Buschert et al., 2012 demonstrated post-intervention benefits in the IG for the immediate and delayed memory; however at 15- and 28-month follow-ups

They found benefits only in the immediate memory. Similarly, Jeong et al. (2016) found differences favoring the IG regarding prospective memory after training and follow-up, and Barban et al. (2016) showed improvements on verbal memory in the IG in contrast to the CG.

Attention was analyzed in four studies (Barban et al., 2016; Buschert et al., 2012; Kounti et al., 2011; Rojas et al., 2013). Kounti et al. (2011) were the only one that were able to find differences between groups after the intervention; the IG score was higher than the CG in short-term and the speed of the test of everyday attention.

Executive function was one of the most examined variables, as it was included in five different studies (Barban et al., 2016; Buschert et al., 2012; Jeong et al., 2016; Kounti et al., 2011; Rojas et al., 2013). Despite the high number of interventions focused on the improvement of this parameter, no statistically significant differences between groups were observed in any of these studies.

The language was also assessed by two studies, with contradictory results (Kounti et al., 2011; Rojas et al., 2013). On the one hand, Kounti et al., 2011 were unable to find differences between groups by the end of the intervention, whereas the IG in the study of Rojas et al., 2013 experienced an improvement in two of the three language tests that they completed.

Visuospatial abilities were assessed by two studies (Kounti et al., 2011; Rojas et al., 2013). Rojas et al. (2013) did not find any effect of their intervention regarding this variable. On the other hand, Kounti et al., 2011 evaluated both the visuospatial abilities and visuospatial constructive abilities, resulting in no differences between groups in visuospatial constructive abilities, but finding positive effects for the IG in their visuospatial abilities.

3.2.3.3. Secondary variables

ADL was assessed by two studies (Jeong et al., 2016; Kounti et al., 2011) and one study described the IADL (Rojas et al., 2013). Only the study of Kounti et al. (2011) found significant differences on ADL performance favouring the IG at the end of the intervention (Table 2).

The mood was also assessed by two studies (Buschert et al., 2012; Jeong et al., 2016). Both studies analyzed changes between and within groups at several time points, but no effect of the intervention on the participant's mood was observed.

Four studies analyzed QoL (Buschert et al., 2012; Hagovská & Olekszyová, 2016; Jeong et al., 2016; Rojas et al., 2013). Two of them showed significant differences between groups post-training in favour of the IG, Jeong et al. (2016) through cognitive interventions and Hagovská & Olekszyová, (2016) through CT and PT (Table 2).

3.2.3.4. Results of Meta-Analysis

Figure 3 shows the pooled effects of the interventions on different cognitive variables. It should be highlighted that the results show a high degree of homogeneity in all variables, excepting the language domain, which was only assessed by two studies.

Overall, cognitive, and physical interventions showed a statistically significant potential to improve global cognition (combined *Hedge's g* (95% CI): -0.249 (-0.431-0.067)), but such differences did not appear when analyzing specific cognitive functions, such as memory, attention, executive functions, or language.

Additional analyses regarding the secondary variables (ADL, mood, and QoL) failed to find a positive combined effect of the interventions on these parameters, which can be checked in Figure 4. In the case of the QoL, the tests were close to statistical significance, and the results from the different interventions were rather heterogeneous.

3.2.3.5. Methodological quality assessment in Individual Studies

The risk of bias assessment for all included studies is summarized in Table 3M. Overall, our analysis indicates that six studies had good methodological quality (PEDro scale 6-7/10) (Barban et al., 2016; Buschert et al., 2012; Buschert et al., 2011; Hagovská & Olekszyová, 2016; Jeong et al., 2016; Styliadis et al., 2015) and two studies presented fair methodological quality (4-5/10) (Kounti et al., 2011; Rojas et al., 2013). Analyzing the most common issues in the different studies, it highlights that in three studies the concealed allocation does not appear, in none of the studies the participants were blinded, in six studies the professionals who carried out the interventions were not blinded, in two studies the professionals who carried out the evaluations were not blinded, in five studies there were more than 15% dropouts and in six studies the analysis of results by intention to treat was not performed.

4. DISCUSSION

Progress in understanding cognition and related cognitive functions and the mechanisms underpinning learning could facilitate the development of more effective approaches to enhance cognitive functioning in MCI. The aim of this systematic review and meta-analysis was to evaluate the current evidence regarding the efficacy of MNPI based in two components (simultaneous cognitive or cognitive and physical) for older adults with MCI. The main findings of this review are that all the interventions improve at least one component of cognition, and that global cognition was improved when considering the pooled effect of all studies.

Regarding global cognition, five studies in our review obtained improvements in global cognition measured by MMSE. Previous studies also showed a significant difference between groups in global cognition using two-component MNPI. More specifically, these differences were found by one (of five) study in Bruderer-Hofstetter et al. (2018); two (of five) studies in Fitzpatrick-Lewis et al. (2015); three (of four) studies in Ge et al. (2018) and in six (of eight) studies in Yang et al. (2020) that combined cognitive and physical interventions. This evidence reinforces the results found in our meta-analysis which showed a positive pooled effect of the MNPI on global cognition. Most of our selected studies were based on CT and PT interventions; nevertheless, in this review we have also considered two simultaneous cognitive components. Although we were not able to detect significant differences by subgroups (cognitive and cognitive and physical), in both cases improvements were obtained. However, in these studies we have included a few numbers of participants; therefore, we have an important limitation to obtain significant conclusions. The mean age of the participants included in our review was similar to previous reviews, but their educational level was lower, and the intervention durations were generally shorter. Despite these differences, we found significant results regarding global cognition. Similarly, MNPI that combined cognitive and physical interventions are more effective at improving cognitive function than exercise alone (Suzuki et al., 2013) and they can impact the brain's cognitive reserve (Jeong et al., 2021). While physical intervention preserves neuronal structural integrity and brain volume (hardware), cognitive intervention strengthens the functioning and plasticity of neural circuits (software), supporting cognitive reserve (Cheng, 2016). Cognitive and physical intervention may contribute to neuroplasticity through two pathways for brain and cognitive aging (Casaletto et al., 2020) and may be more effective than the single components (Bamidis et al., 2015; Bherer, 2015; Lauenroth et al., 2016; Pieramico et al., 2014; Zhu et al., 2016) and reducing AD incidence (Pieramico et al., 2014). It is important to maintain a high cognitive reserve as reduces the risk of developing dementia, which can be achieved primarily through participation in mentally stimulating activities (Valenzuela & Sachdev, 2006). Cognitive reserve can improve cognition and cognitive functions in older adults (Clare et al., 2017; Lavrencic et al., 2018). Cognitive reserve is influenced by the risk of diagnostic conversion and the rate of cognitive impairment (Van Loenhoud et al., 2019) and therefore the baseline global cognitive function (Bamidis et al., 2015; Chuang et al., 2022). In reference to the cognitive and physical training interventions, the dose, the variety of activities, the motivation and the enjoyment could be crucial factors to design novel interventions, which are more efficient than unimodal interventions (Küster et al., 2017).

Our results agree with Sherman et al. (2017), who described that multicomponent training or interventions targeting multiple domains improve cognition by prompting recruitment of alternate neural processes and supporting primary networks to meet task demands simultaneously. In fact, they found that the effect of training on MMSE performance in MCI patients compared to controls was small and significant (Hedges'g = 0.216; 95% CI [0.076, 0.356]) (Sherman et al., 2017). In agreement with our study, Mewborn et al. (2017) performed a comprehensive meta-analysis in which they included 97 individual studies that used different modalities of cognitive interventions with healthy older adults and patients with MCI (Mewborn et al., 2017). Despite the elevated heterogeneity, the overall result was that cognitive interventions were effective for increasing the global cognition in comparison to the CG (Hedges' g: 0.298; CI95%: [0.248-0.347]). It should be highlighted that qualitatively greater effect sizes were found in participants with MCI (g = 0.336) in contrast to healthy older adults (g = 0.314).

We have not found differences in specific cognitive functions, ADL, and mood. In the QoL, the tests were close to statistical significance. This could be due to the methodological diversity, and the fact that the number of participants is probably too small, which may cause a lack of statistical power and therefore an increased difficulty to obtain significant results. Jacobs et al. (1995) found that MCI patients showed a decline in cognitive functions such as memory, executive function or attention compared to healthy senior people (Jacobs et al., 1995); which could have caused the lack of significant differences within our review. However, previous systematic reviews have identified different effects of two-component MNPI. Yang et al. (2020), found benefits regarding memory and executive functions in five (of seven) studies and a decrease in the depressive mood in one study (of four) (Yang et al., 2020). Additionally, Lipardo et al. (2017) found improvements in memory in all three papers included in their review but were unable to find any study that reported benefits in executive function (Lipardo et al., 2017). Ge et al. (2018) found benefits in two (of five) studies regarding memory, two (of eight) studies regarding attention, three (of seven) papers which assessed executive functions analyzing CT in combination with different therapies including PT. Conversely, they did not find improvements in ADL or QoL (Ge et al., 2018). Ozbe et al. (2019) were able to find positive results in only one study (of six) in ADL and QoL (Ozbe et al., 2019).

Bruderer-Hofstetter et al. (2018) gathered information about the effects of different cognitive and physical interventions on cognitive variables in patients with MCI, and summarized their results in a network meta-analysis (Bruderer-Hofstetter et al., 2018). Despite finding positive results in some individual studies, the pooled results showed that no intervention was effective to improve global cognition or different components such as language, memory, attention, executive functions, or instrumental ADL. However, the combined results for each type of intervention were obtained from a maximum of three different individual studies with a total of 216 participants. This may partially explain the differences found with our study regarding global cognition.

Besides, it should be considered that the methodological quality of individual studies is not good in all studies. Because of this, the internal and external validity of several studies included in the meta-analysis has decreased, which it may affect the generalization of the obtained results. All in all, it should be considered for future randomized controlled trials to take into account the importance of concealed allocation, the professionals who administer the intervention and those who carry out the evaluations. Avoiding dropouts through strategies to improve adherence to intervention programs and attempting to perform intention-to-treat analysis should be encouraged.

5. LIMITATIONS

The conclusions drawn from this review must be considered in the context of some limitations.

The limitations of this study are similar to other meta-analysis in MCI (Lipardo et al., 2017; Sherman et al., 2017). There were a small number of studies, and a limited number of studies in each category (simultaneous cognitive or cognitive and physical interventions) with relatively small sample sizes, which may hinder the generalizability of our results. It can be argued that there is a wide range of interventions included and a diverse number of instruments used to measure cognitive functions, but those were attempted to be minimized by the categorization of the interventions and the use of a single tool to assess global cognition, such as the MMSE. Two studies (Rojas et al., 2013; Styliadis et al., 2015) included in this review did not indicate results comparing groups, and did not offer data to be able to perform the quantitative analysis. Besides, one of them (Styliadis et al., 2015) only offered data on global cognition. In addition, the MMSE is just a screening tool and that in general, independent from the results of this study, or improvement by intervention, still clinical and neuropsychological supervision is needed (Mitchell, 2017).

6. CONCLUSIONS

Our findings support that MNPI based on two components "simultaneous cognitive" and "cognitive and physical" might be a beneficial option for people with MCI to improve their global cognition. Moreover, there is evidence from some studies that the effects of the intervention can be maintained at the follow-up. Our results are promising and can be critical to the development of efficient interventions. More RCTs should be conducted in the future to explore MNPI based on two components ('simultaneous cognitive' and 'cognitive and physical'). Moreover, there is no studies that evaluate the potential effects of CS combined with PT or CR combined with PT. Future research should examine whether multicomponent interventions incorporating two components can obtain improvements in different cognitive measures, maintenance these effects (Bamidis et al., 2015), or can reduce incidence of dementia (Cheng, 2018.) in older adults that living in the community and present different cognitive levels (Mao et al., 2021). Future trials should aim for high quality by recruiting large sample sizes and ensuring a low risk of bias (using randomization and ensuring allocation concealment), as suggested by some authors (Yang et al., 2020). Thus, more precise estimates of effect sizes could be obtained. Additionally, future research may examine the effectiveness of interventions on specific cognitive aspects such as memory, as has been found to be more compromised in people with MCI (Klekociuk et al., 2014).

Credit author statement

Isabel Gómez Soria: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - Original Draft, Project administration **Jorge Marin-Puyalto:** Formal analysis, Investigation, Data curation, Writing - Original Draft **Patricia Peralta-Marrupe:** Investigation, Resources, Writing - Review & Editing **Eva Latorre:** Writing - Review & Editing, Supervision **Estela Calatayud:** Conceptualization, Investigation, Data curation, Writing - Review & Editing, Supervision

IRB protocol/human subjects approval

Not applicable

7. DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

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Study (Autor, year)	Country Setting	Professionals that administered the intervention	Subtype MCI (Criteria)	N (male/female)	Mean age (years)	Education level (years)	Mean MMSE baseline	Intervention group	Control group	Follow-up	PEDro score
Simultaneous cognitive interventions											
Buschert et al. (2011, 2012)	Germany (Memory Clinic of the Alzheimer)	Instructor	aMCI Single and multiple domain (Petersen)	24 GI 12 (6/6) *GC 12 (6/6)	71.8 (8.6) 70.7 (5.7)	12.3 (3.6) 13.3 (2.2)	28.1 (1.5) 26.8 (1.5)	**CS and CT** Group 10–12 participants 120 min/session 6 months 20 sessions	*** Social interactions and paper-pencil exercises focusing on isolated cognitive functions.** 6 meetings 60 min 6 months	8, 15 and 28 months	7
Rojas et al. (2013)	Argentina (Memory Clinic of a public general hospital)	Two experienced neurophysiologists	MCI All subtypes (Petersen)	30 GI 15 (9/6) CG 15 (8/7)	72 (14.3) 76.9 (7.1)	10.5 (3.8) 10.5 (3.8)	27.5 (2.3) 27.1 (2.1)	**CS and CT** 120 min/session Twice/week 6 months 48 sessions	Received routine treatment. with monthly consultations with their doctor	6 months	4
Jeong et al. (2016)	South Korea (Clinics for memory Decline)	Trained health professionals (clinical neuropsychologist, occupational therapist, and regular nurses)	aMCI (Petersen)	224 CGI: 71 (21/50) *HCI: 77 (27/50) *CG: 76 (35/41)	70.8 (6.9) 68.5 (8.5) 71.6 (6.5)	9.5 (4.8) 11.1 (4.1) 8.8 (4.4)	25.3 (2.5) 25.9 (2.5) 25.9 (2.4)	**GCI** **CT (Memory training) and CR** Group 5 subjects 90 min/session Twice/week 3 months 44 sessions	***HCI** Completed daily homework. materials 30-min 12 weeks ***CG** Educational booklet regarding lifestyle for dementia prevention	3 and 6 months	6
Barban et al. (2016)	Italy, Greece, Norway, and Spain (Medical centers)	Trained cognitive therapist	aMCI (Petersen)	106 Arm A⁻ 46 (25/21) Arm B⁺ 60 (31/29)	74.4 (5.7) 72.9 (6)	9 (4.3) 11 (4.7)	27.3 (2.1) 28.1 (1.4)	**CCT and CS (Reminiscence therapy)** 60-min sessions Twice/week 3 months 24 sessions	No intervention	3 and 6 months	7
Cognitive and physical interventions											
Kounti et al. (2011)	EEUU (Alzheimer day center)	Expert psychologists trained in cognitive rehabilitation	MCI (Petersen)	58 GI 29 (6/23) GC 29 (6/23)	70.5 (7.5) 67.8 (7.3)	9.6 (4.7) 7.8 (3.8)	28 (1.6) 27.3 (1.8)	**CT and PT (kinetic exercises)** Group 5 participants 90 minutes/session Once/week 5 months 20 sessions	No intervention	5 months	5

Styliadis et al. (2015)	Greece (Community dwelling, day care centers, clinical centers, and hospitals)	**CT** Psychologist. **PT** Physiotherapist, sport experts. physical educators and psychologists	Predominantly aMCI (Petersen)	70 LLM 14 (5/9) *PT 14 (5/9) *CT 14 (5/9) *AC 14 (5/9) PC 14 (5/9)	71.2 (4.5) 70.4 (6.6) 72.7 (6.6) 71.1 (4.4) 67.6 (4)	8.1 (3.1) 6.1 (1.4) 6.1 (3.2) 7.1 (3) 7.3 (2.3)	25.8 (2.1) 26.2 (2.3) 25.1 (3.2) 26.2 (2) 25 (1.8)	**LLM** 10 hours/week **CT** (Greek adaptation of Brain Fitness software) 60 min/session Three to five sessions/week 2 months 24-40 sessions CT: 27.1 ± 5.6 h **and PT Program "FitForAll" (Targeted body flexibility, balance, strength, physical endurance through aerobic training)** 60 min/session Five sessions/week 2 months 40 sessions PT: 25.2 ± 4.9 h	***PT** 5 hours/week **Program "FitForAll"** 26.1 ± 6.8 h ***CT Brain Fitness software** 5 hours/week 24.3 ± 1.9 h ***AC** 5 hours/week Watching documentaries 26.8 ± 4.8 h **PC** No intervention	2 months	6
Hagovská, M., & Olekszyová, Z. (2016)	Slovak Republic (Outpatient Psychiatric Clinic)	**CT** Psychological system **PT** Physiotherapist	aMCI Multiple domain (ICD-9-CM)	80 GI 40 (22/18) *GC 40 (19/21)	68 (4.4) 65.9 (6.2)	GI: 75% received secondary education. GC: 70% received secondary education	26 (2.6) 26. (1.5)	**CT (Attention training, working memory, long-term memory, executive functions, visuomotor coordination and spatial processing)** 30 min Twice/week 2.5 months 20 sessions **and PT (motor exercises and balance training)** 30 min/session Twice/week 2.5 months 20 sessions	* Balance training 30 min daily 10 weeks	2.5 months	7

aMCI: amnestic Mild Cognitive Impairment. GI: Intervention Group. GC: Control Group. GCI: Group-based cognitive intervention; HCI: home-based cognitive intervention; LLM: Combined physical and cognitive training; PT: Physical training; CT: Cognitive Training; AC: Active control; PC: Passive control; CS: Cognitive stimulation; CR: Cognitive rehabilitation; CCT: Computer cognitive training; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; NS: Not specified.

Qualitative variables are expressed as frequencies, whereas continuous variables are expressed as mean (SD).

*Active control condition; [-] Training-Rest; [+] Rest-Training.

arm A: participants began with a training period of about 3 months and then underwent a length- equivalent period of rest; arm B: participants started with the rest followed by the training.

Table 1. Selected features of the included studies.

Study (Autor, year)	Assessment Tool	Outcome Domain (s)	Post-intervention		Follow-up 1		Follow-up 2	
			Experimental group	Between group findings	Experimental group	Between group findings	Experimental group	Between group findings
Simultaneous cognitive interventions								
Buschert et al. (2011, 2012)	**MMSE**	**Global Cognition**	↑	↑	n/a	↔	n/a	↔
	ADAS-cog	Global Cognition	↔	↑		↑		↑
	RBANS							
	. Story Memory	Immediate Memory	↑	↔		↑		↑
	. Story Recall	Delayed Memory	↑	↔		↔		↔
	TMT-A	Attention	↔	↔		↔		↔
	TMT-B	Executive Function	↔	↔		↔		↔
	MADRS	Mood	↔	↔		↔		↔
	QoL-AD	Quality of Life	↔	↔		↔		↔
Rojas et al. (2013)	**MMSE**	**Global Cognition**	↔	n/a	n/a	n/a	n/a	n/a
	BEM 144	Episodic memory	↔					
	BNT	Language	↑					
	SF	Language	↑					
	WASI	Language	↔					
	Similarities and Matrix reasoning	Abstract Thinking	↔					
	Black Design	Visuospatial Abilities	↔					
	TMT-A	Attention	↔					
	TMT-B	Executive Function	↔					
	Digit Span Memory Test	Working Memory	↔					
	. Forward							
	. Backward							
	QoL-AD	Quality of Life	↔					
	IADL (Lawton and Brody)	Instrumental Activities of Daily Living	↔					

Study (Autor, year)	Assessment Tool	Outcome Domain (s)	Post-intervention Experimental group	Post-intervention Between group findings	Follow-up 1 Experimental group	Follow-up 1 Between group findings	Follow-up 2 Experimental group	Follow-up 2 Between group findings
Jeong et al. (2016)	**MMSE**	**Global cognition**	n/a	↔	↔	↔	n/a	n/a
	ADAS-cog	Global cognition		↑	↑	↑		
	Story Memory	Logical Memory						
	. Immediate recall			↔	↔	↔		
	. Delayed recall			↔	↔	↔		
	Digit Symbol Test	Executive Function		↔	↔	↔		
	Stroop test- Color reading score	Executive Function		↔	↔	↔		
	Animal Fluency	Executive Function		↔	↔	↔		
	COWAT	Executive Function		↔	↔	↔		
	Digit Span Memory Test	Working Memory						
	. Forward			↔	↔	↔		
	. Backward			↔	↔	↔		
	PMT	Prospective Memory		↑	↔	↑		
	PRMQ	Prospective/retrospective Memory		↔	↔	↔		
	GDS-15	Mood		↔	↔	↔		
	Bayer ADL	Activities of Daily Living		↔	↔	↔		
	QoL-AD	Quality of Life		↑	↔	↔		
Barban et al. (2016)	**MMSE**	**Global cognition**	n/a	↑	n/a	n/a	n/a	n/a
	RAVLT- Delayed	Verbal Memory		↑				
	ROCF - Delayed	Verbal Memory		↔				
	TMT-B	Executive Function		↔				
	TMT-A	Attention		↔*				
	PF	Executive Function		↔				

Study (Autor, year)	Assessment Tool	Outcome Domain (s)	Post-intervention Experimental group	Post-intervention Between group findings	Follow-up 1 Experimental group	Follow-up 1 Between group findings	Follow-up 2 Experimental group	Follow-up 2 Between group findings
Cognitive and physical interventions								
Kounti et al. (2011)	**MMSE**	**Global cognition**	n/a	↑	n/a	n/a	n/a	n/a
	FUCAS	Executive Function		↔				
	WCST	Executive Function		↔				
	1 min TEA	Attention		↑				
	2 min TEA	Attention		↔				
	TEA	Attention						
	. Speed			↑				
	. Switch			↔				
	RAVLT	Verbal Memory						
	. Verbal learning			↔				
	. Delayed verbal recall			↔				
	RBMT- Delayed story recall	Visual Memory		↑				
	ROCFT	Visuospatial Constructive Abilities		↔				
	. Figure recall							
	. Reproduction			↔				
	BNT	Language		↔				
	FAS	Verbal fluency		↑				
	ROCFT-C Figure copy	Visuospatial Abilities		↑				
	FRSSD	Activities of Daily Living		↑				
Styliadis et al. (2015)	**MMSE**	**Global cognition**	↑	n/a	n/a	n/a	n/a	n/a
Hagovská, M., & Olekszyová, Z. (2016)	**MMSE**	**Cognition global**	n/a	↑	n/a	n/a	n/a	n/a
	QoL-AD	Quality of Life		↑				

MMSE: Mini mental state examination; ADAS-cog: Alzheimer's Disease Assessment Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; TMT: Trail Making Test; MADRS: Montgomery Asberg Depression Rating Scale; QoL-AD: Quality of Life-Alzheimer's Disease; BEM 144: Argentine version of the Signoret battery for mnesic efficiency; BNT: Boston Naming Test; SF: Vocabulary from the Wechsler Abbreviated Scale of Intelligence; WASI: Wechsler Abbreviated Scale of Intelligence; GDS15: 15-item version of the Geriatric Depression Scale; PMT: Prospective Memory Test; RMQ: Retrospective Memory Questionnaire; MMQ: Multifactorial Metamemory Questionnaire-Strategy subscale; COWAT: Controlled Oral Word Association Test; PRMQ: Prospective and Retrospective Memory Questionnaire; Bayer ADL: Activities of Daily Living Scale; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey–Osterrieth Complex Figure Test; PF: Phonological verbal fluency; IADL: Instrumental activities of daily living; WCST: Wisconsin Card Sorting Test; FAS: Verbal Fluency Test; FRSSD: Functional Rating Scale of Symptoms of Dementia; FUCAS: Functional Cognitive Assessment Scale; RBMT: Rivermead Behavioral Memory Test; ROCFT-C: Rey-Osterrieth Complex Figure Test and Recognition Trial; TEA: Test of Everyday Attention; VSCA: Visual Spatial Constructive Abilities; DSF: Digit Span Forward test; DSB: Digit Span Backward test.

↑: significant positive effect. ↔: no change. n/a: not applicable. *: Significant group by time interactions. -: Training-Rest. +: Rest-Training

Table 2. Multicomponent intervention based in cognitive intervention and cognitive and physical intervention programs in MCI: Measures and results in analysis qualitative.

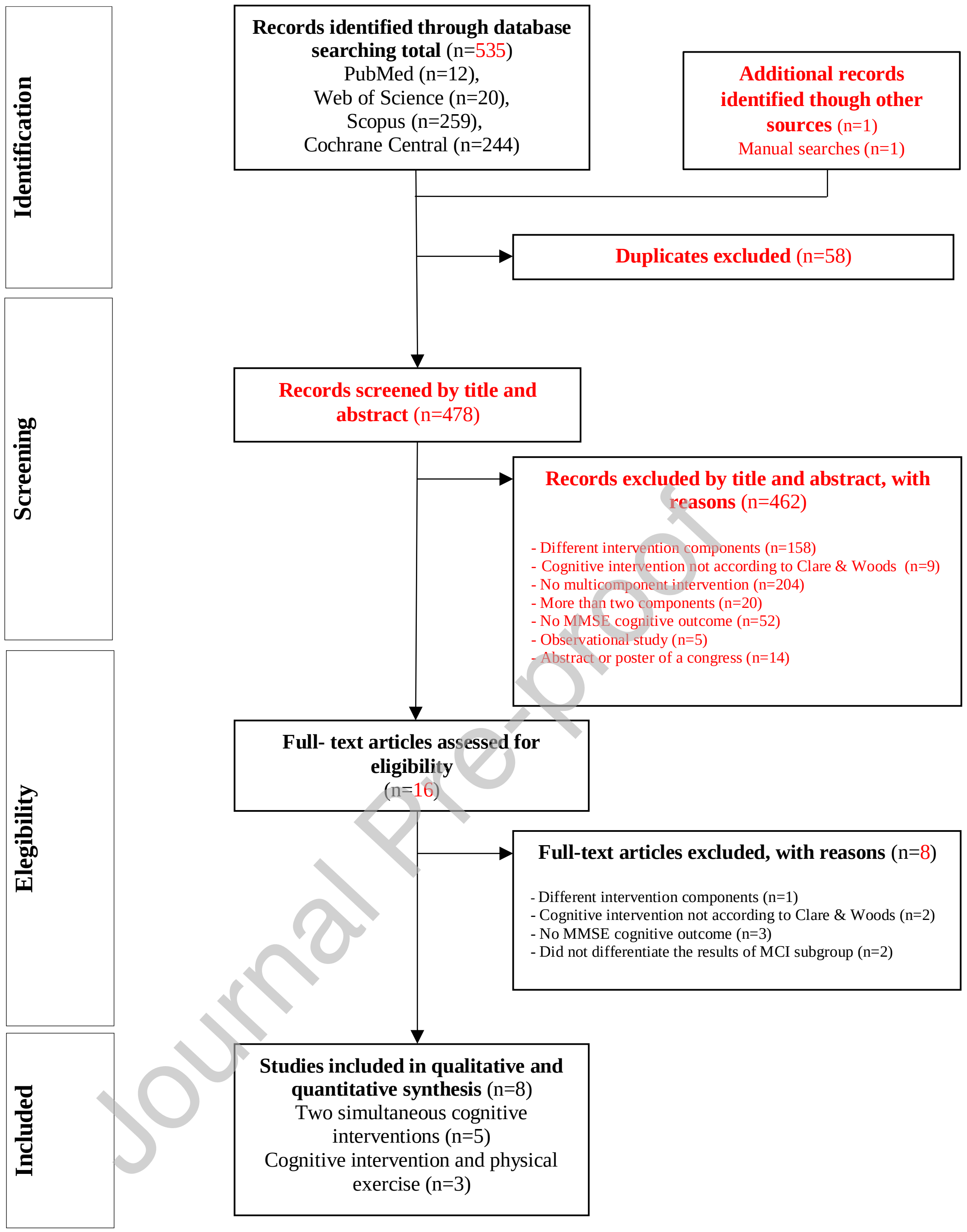
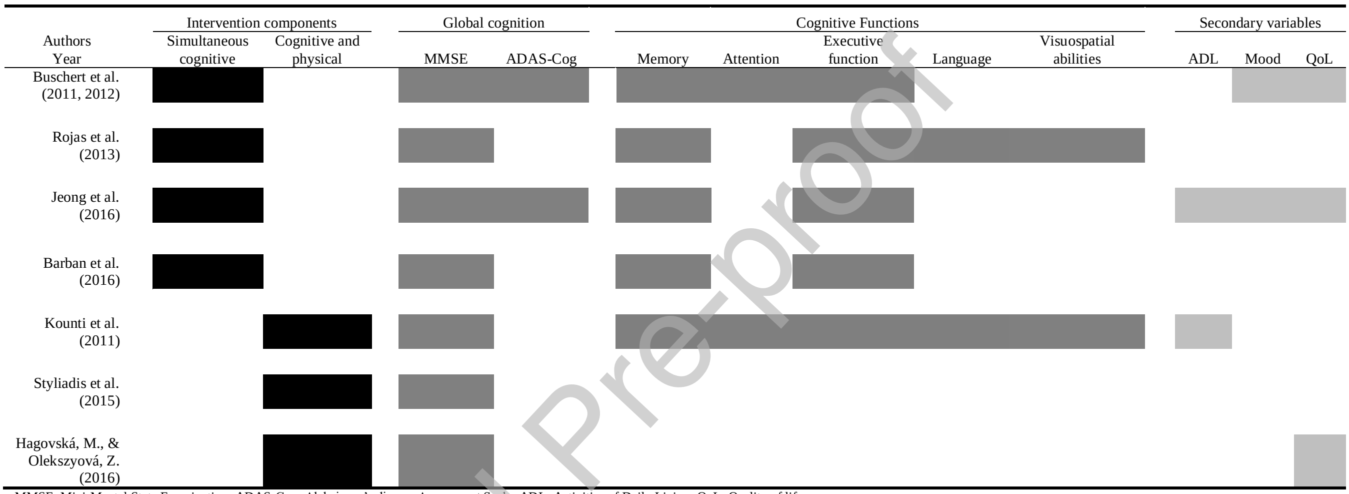


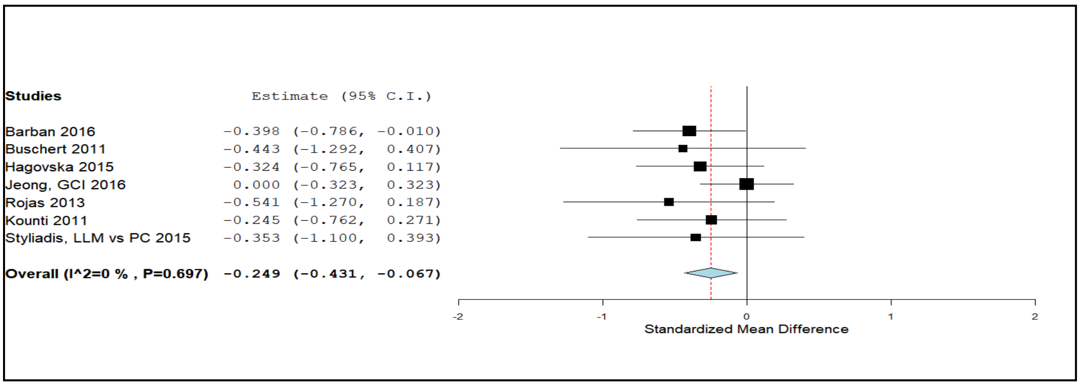
Figure 1. PRISMA diagram of study selection.



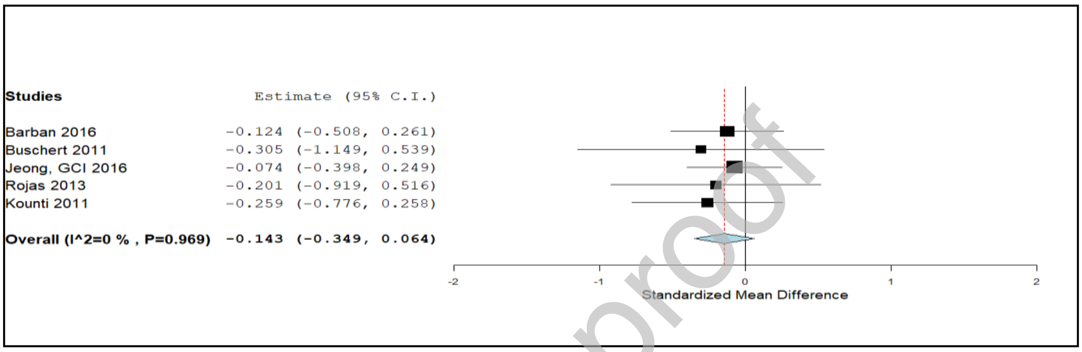
MMSE: Mini-Mental State Examination; ADAS-Cog: Alzheimer 's disease Assessment Scale; ADL: Activities of Daily Living; QoL: Quality of life

Figure 2. Components used in the intervention ("simultaneous cognitive" and "cognitive and physical") and domains of results included in each study.

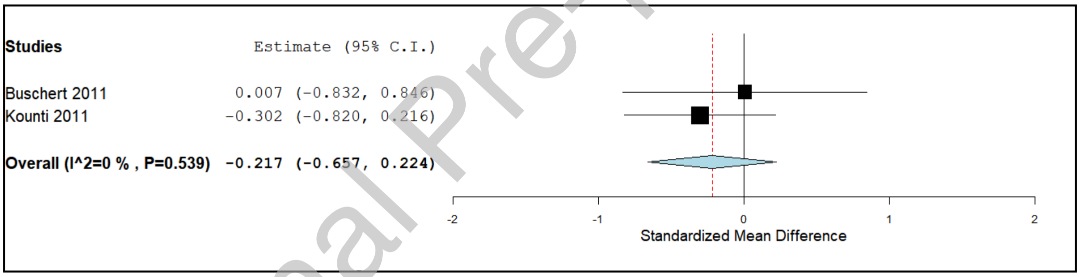
3a


Studies
Estimate (95% C.I.)
Barban 2016 −0.398 (−0.786, −0.010)
Buschert 2011 −0.443 (−1.292, 0.407)
Hagovska 2015 −0.324 (−0.765, 0.117)
Jeong, GCI 2016 0.000 (−0.323, 0.323)
Rojas 2013 −0.541 (−1.270, 0.187)
Kounti 2011 −0.245 (−0.762, 0.271)
Styliadis, LLM vs PC 2015 −0.353 (−1.100, 0.393)
Overall (I^2=0 % , P=0.697) −0.249 (−0.431, −0.067)
-2 -1 0 1 2
Standardized Mean Difference

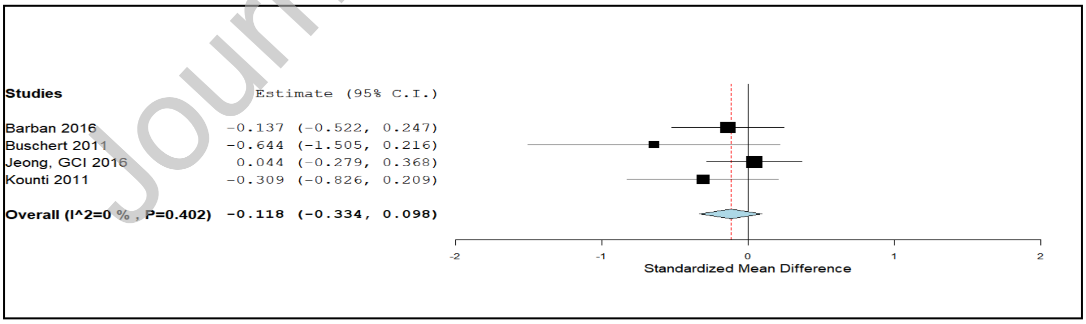
3b


Studies
Estimate (95% C.I.)
Barban 2016 −0.124 (−0.508, 0.261)
Buschert 2011 −0.305 (−1.149, 0.539)
Jeong, GCI 2016 −0.074 (−0.398, 0.249)
Rojas 2013 −0.201 (−0.919, 0.516)
Kounti 2011 −0.259 (−0.776, 0.258)
Overall (I^2=0 % , P=0.969) −0.143 (−0.349, 0.064)
-2 -1 0 1 2
Standardized Mean Difference

3c


Studies
Estimate (95% C.I.)
Buschert 2011 0.007 (−0.832, 0.846)
Kounti 2011 −0.302 (−0.820, 0.216)
Overall (I^2=0 % , P=0.539) −0.217 (−0.657, 0.224)
-2 -1 0 1 2
Standardized Mean Difference

3d


Studies
Estimate (95% C.I.)
Barban 2016 −0.137 (−0.522, 0.247)
Buschert 2011 −0.644 (−1.505, 0.216)
Jeong, GCI 2016 0.044 (−0.279, 0.368)
Kounti 2011 −0.309 (−0.826, 0.209)
Overall (I^2=0 % , P=0.402) −0.118 (−0.334, 0.098)
-2 -1 0 1 2
Standardized Mean Difference

3e

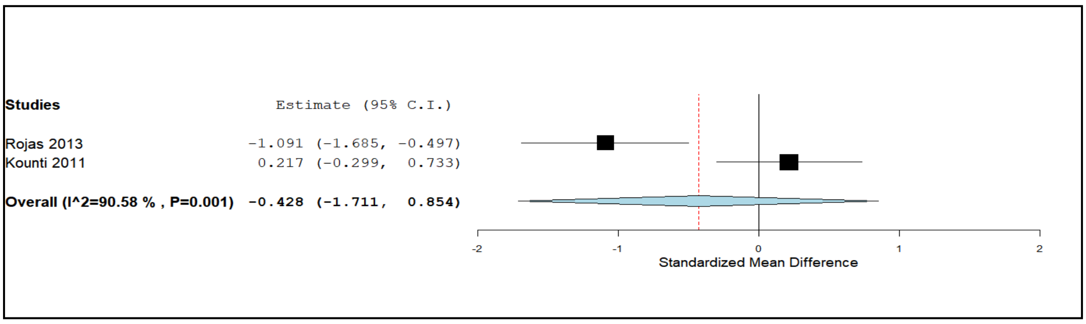
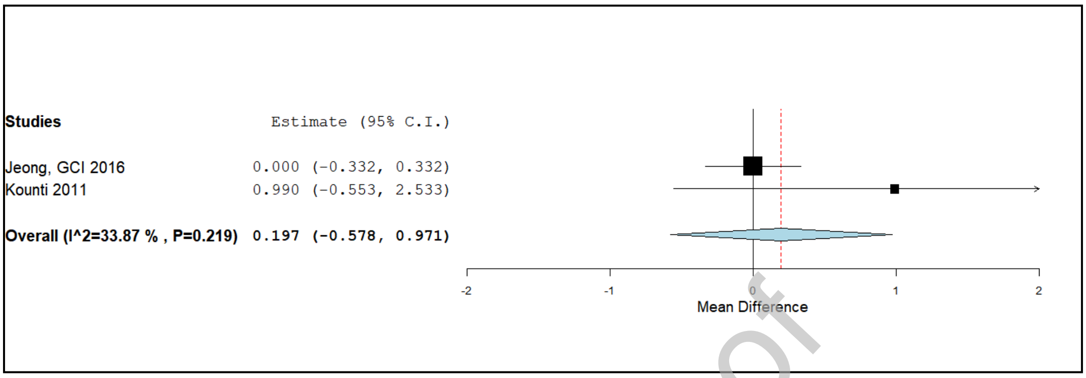
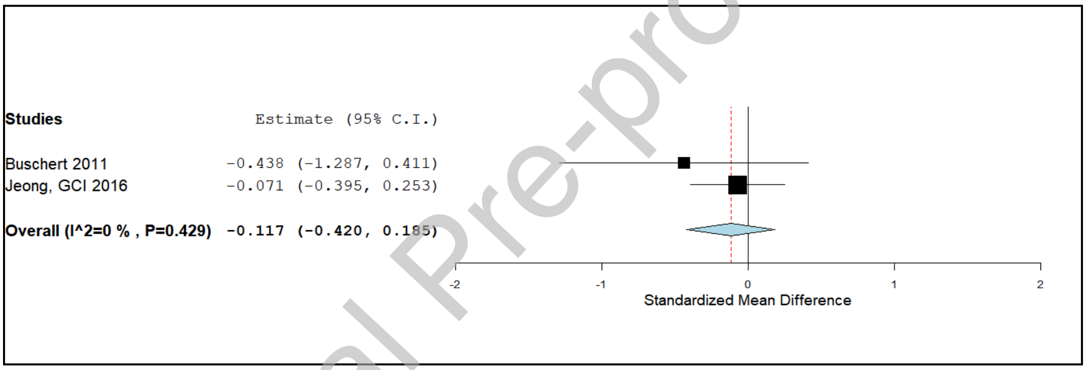

Studies
Estimate (95% C.I.)
Rojas 2013 −1.091 (−1.685, −0.497)
Kounti 2011 0.217 (−0.299, 0.733)
Overall (I^2=90.58 % , P=0.001) −0.428 (−1.711, 0.854)
-2 -1 0 1 2
Standardized Mean Difference

Figure 3. Forest plot of effect sizes (ESs) from seven the studies that assessed global cognition; (3a) from five the studies that assessed memory, (3b) from two the studies that assessed attention (3c) from four the studies that assessed executive functions and (3d) from two the studies that assessed language.

4a



4b



4c

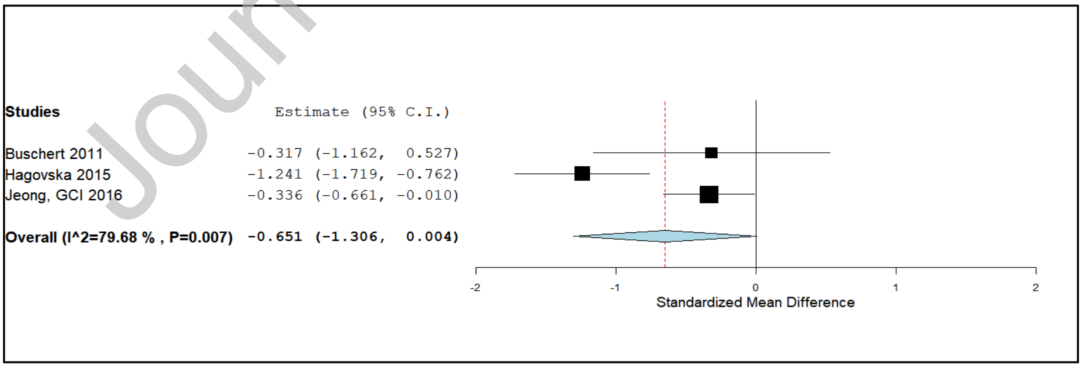


Figure 4. Forest plot of effect sizes (ESs) (4a) from the two studies that assessed ADL, (4b) from the two studies that assessed mood and (4c) from the three studies that assessed QoL.