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A combination of cognitive training and physical exercise for elderly with the mild cognitive impairment

A systematic review

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Abstract

Purpose – The purpose of this paper is to conduct systematic reviews on Indonesian papers, to examine the most recent evidence of the efficacy of the combination of cognitive training and physical exercise, and to make recommendations in order to improve prevention, care and treatment services in elderly patients with mild cognitive impairment (MCI).

Design/methodology/approach – The databases of Cochrane, Medline, NIH (US National Library Medicine), ProQuest, EbscoHost, Clinical Key, EMBASE, Medical Librarian (TWE) in Ovid, Science Direct, Scopus, The Lancet Global Health, PubMed, Emerald, Indonesian National Library, Google Scholar, Google Indonesia, and Garuda Portal were systematically searched using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to obtain empirical papers published between June 1976 and January 2018.

Findings – Out of the 3,293 articles collected, 10 were included in this analysis. The result of this combined meta-analysis compares the combination therapy group (cognitive therapy and physical exercise) with a control group. It shows that the control group was likely to experience MCI 1.65 times more often than the combination therapy group. According to the result acquired from the synthesized meta-analysis, the control group experienced MCI 1.65 times higher than the combination therapy. The finding is proven to be statistically significant (95% CI = 1.42–1.93).

Research limitations/implications – The research considers only English and Indonesian articles.

Practical implications – It is important to explore the most effective training characteristics in a special combined intervention differentiated by the duration, frequency, intervention, type and combination mode. There is a need for further investigation that focuses on the physiological mechanisms underlying the positive effects, by inserting a more comprehensive neuro-imaging measurement to assess specifically the domain that benefits in terms of cognitive functions and molecular markers. Finally, exploratory

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studies are definitely required, which will specifically examine maintenance and treatment effects as well as derive theoretical explanations related to the interventions and predictors.
Social implications – A combination of cognitive training and physical exercise intervention may improve the global health or cognitive functions.
Originality/value – A combination of cognitive training and physical exercise has been found to improve prevention, care and treatment services in elderly patients with MCI. There is an increase in value in comparison to the study of Karssemeijer, which considered five Indonesian articles.

Keywords Elderly, Systematic review, Mild cognitive impairment, Cognitive training and physical exercise, Indonesia
Paper type Review

Introduction

The population of elderly people (individuals ⩾ 60 years old) throughout the world is increasing rapidly. In 2015, 48 percent of the people in the world were aged ⩾ 60 years since 2000. It is predicted that by 2050, the number of elderly patients will be three times higher[1]. It is projected that the number of elderly people in the world will increase by 21 percent in the next 50 years. The elderly population in developing and developed countries will increase by 140 and 51 percent, respectively[1, 2]. The growth rate of the elderly population in the Asia-Pacific region, like the global population, is increasing faster than it has in the past. The Asia-Pacific region is located near the Western Pacific Ocean, containing much of East Asia as well as Southeast Asia, and it includes Australia, New Zealand, Pakistan, Indonesia, Malaysia, Philippines, Japan, India, Singapore, People's Republic of China, Thailand, Sri Lanka, South Korea, Hong Kong SAR and Chinese Taipei[2, 3].

Among Asian countries, the difference in the prevalence of mild cognitive impairment (MCI) is greater than fivefold. Along with the elderly population, the prevalence of MCI is also increasing among developed and developing countries. The rapid demographic changes due to the aging population in low- and middle-income countries establish a priority, which is the need to identify the people at risk of developing dementia, at earlier stages, in order to target and implement preventive interventions. Because MCI is an intermediate phase between normal ageing-related cognitive decline and dementia, the identification of MCI can play an important role in early intervention, prevention and development of proper and effective treatments[4].

Cognitive impairment is a common problem in the elderly. The likelihood of developing MCI is directly associated with increasing age, with an occurrence rate of approximately 21.5–71.3 per 1,000 person-years in senior citizens. MCI rates range from 3 percent to as high as 42 percent in general population studies and from 6 to 85 percent in clinical settings. The MCI conversion rate to dementia is about 10 percent per year, which increases to 80–90 percent after approximately six years. It is estimated that a new case of dementia is added every 7 s. The prevalence of dementia developing in the elderly population is between 1 and 2 percent per year. In 2018, the World Alzheimer Report estimated that more than 50m people are living with dementia worldwide, and this number will be more than triple, 152m, by 2050[4]. The total estimated worldwide cost of dementia will rise to US$2 trillion by 2030[4, 5].

Several risk factors that increase the development of MCI are chronic treatments, such as in chronic obstructive pulmonary disease, depression and diabetes mellitus, as well as lifestyle factors[6]. These are more likely to be experienced by males with the Apolipoprotein E Allele, or with other risk factors in their family history that predispose them to cognitive impairment and vascularization, such as hypertension, hyperlipidemia, coronary artery disease and stroke[7]. The strongest correlation is age related, among the elderly[5, 8]. A study on multimorbidity and development of MCI found that four or more participants with chronic conditions, especially two or more in combinations such as hypertension and hyperlipidemia, coronary artery disease and osteoarthritis, had the highest MCI risk. Due to the high prevalence of dementia and its significantly heavy burden on society, it is not surprising that recent healthcare initiatives are mostly intended to help the elderly deal with memory problems. Although some treatments, both pharmacological and non-pharmacological, may provide symptomatic improvement to patients with dementia and Alzheimer's disease, they do not entirely stop the disease[4, 9].

Consequently, finding ways to help the increasing numbers of the elderly population with neurocognitive impairment, such as MCI or Alzheimer-type dementia (AD), has become a major issue and challenge for public health officials. The WHO has established the prevention and control[10] related to the development of prevention strategies for AD as an international priority, with prevalence rates projected to increase by more than 75 percent in the next quarter century. In real terms, it means that approximately 115m elderly people throughout the world are likely to suffer from AD/dementia by 2050, with the most significant increases proportionally to be found in the less-developed countries. This report is the result of a study conducted by international experts on Alzheimer's disease[11, 12]. At the national level, a National Strategy and National Action Plan for Elderly Health is vitally important, providing the elderly with health counseling, consisting of concrete steps that can be sustainably implemented[13].

Systematic review and meta-analysis show that the combination of cognitive training and physical exercise has potential benefits and a positive effect on the cognitive functions of elderly patients with MCI or dementia. This functional benefit suggests a strategy that emphasizes the combination of cognitive training and physical exercise[14]. Karssemeijer *et al.* reported a number of implications: the necessity of combining different interventions, multi-group designs (a combination of cognitive training and physical exercise, single physical exercise, single cognitive training and control groups to distinguish the contribution of intervention components), studies aiming at exploring the characteristics of the most effective training in combined intervention by making specific objectives, including exploration (related to duration, frequency, type and combination), and studies focusing on investigating the underlying physiological mechanisms of positive effects by incorporating more comprehensive neuropsychological measurements and molecular markers as the result. In addition, the studies conducted to measure the long-term effects must indicate a basic understanding of the possible treatment effects[14]. The study objective was to continue the systematic review developed by Karssemeijer *et al.*[14], to carry out systematic reviews in Indonesian papers and to obtain strong evidence of the combined efficacy of cognitive and physical exercise interventions in the cognitive functions of elderly patients with MCI.

Method

This method involves a systematic review and meta-analysis. It summarizes the results of available carefully designed healthcare studies (controlled trials) and provides a high level of evidence about the effectiveness of healthcare interventions. Judgments may be made about the evidence in order to give informed recommendations for healthcare. These reviews are complicated and depend largely on what clinical trials are available, how they were carried out (the quality of the trials) and the health outcomes that were measured. Reviewing authors pool numerical data (which describe the effects of the various treatments) through a process called meta-analysis. Then the authors assess the evidence for any benefits or risks resulting from those treatments. With this method, systematic reviews are able to effectively summarize the existing clinical research on a topic. This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in accordance with the current guides in systematic review and meta-analysis of randomized trials[15–17].

Collecting strategy

Relevant papers were searched from online databases, including Cochrane, Medline, NIH (US National Library Medicine), ProQuest, EBSCOhost, Clinical Key, EMBASE, Medical

Librarian (TWE) in Ovid, Science Direct, Scopus, The Lancet Global Health, PubMed, Emerald, Indonesian National Library, Google Cendekia, Google Indonesia and Garuda Portal. These databases were systematically searched using PRISMA guidelines to obtain empirical papers published between June 2017 and January 2018. This continues the methodology previously established by Karssemeijer *et al.*, which covers June 1976–May 2017, as well as Indonesian articles and empirical papers published before 2018.

Searches were also conducted on two bibliographical lists of papers from two Indonesian Universities (Universitas Sebelas Maret, Surakarta and Universitas Gajah Mada, Yogyakarta), to obtain additional articles using these keywords: Dementia OR cognitive impairment OR Alzheimer AND cognitive training OR memory training OR cognitive stimulation OR resistance training AND physical exercise OR brain game OR exercise OR combined intervention term multimodal OR combined OR cognitive-motor OR dual-task AND elderly OR oldest OR adult people AND randomized control trial (RCT). The tracked articles using keywords still relevant to the theme include memory therapy for elderly; brain exercise for elderly; brain exercise for elderly cognitive functions; memory exercise for elderly; and therapy and elderly cognitive function. The following keywords would assist you to acquire extra Indonesian articles: *terapi terhadap memori pada lansia; latihan kognitif dan senam cegah pikun atau senam otak atau brain game dan cegah pikun atau daya ingat atau memori atau fungsi kognitif atau demensia dan lanjut usia atau lansia pdf*. During the collection process, the researchers set the inclusion criteria on the basis of the main characteristics of research or the PICOS approach: population: elderly > 60 years old; intervention: combination training; comparison: a control group with health education; and outcome: MCI with MMSE and MoCA.

Inclusion criteria and selection process

The criteria set in this research collection include elderly aged $\geqslant 60$ years old; a combination of cognitive training and physical exercise (brain games exercise); 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. MMSE screening was conducted to measure each elderly patient's cognitive functions; the research design was either a randomized controlled trial; and the empirical English articles were published between May 2017 and February 2018, and those in the Indonesian language were published before February 2018. Two reviewers (IU and IB) screened the title/abstract, full text or partial text. Any disagreement or discrepancy found during the reviews was then discussed with the third reviewer (RS), who was also the advisor, and the findings were adjusted accordingly after gaining consensus.

Intervention and result measurement

The articles that were included in the analysis are limited to those using the RCT method, specifically with the presence of a group that received the combined intervention of cognitive training and physical exercise. If the RCT consisted of two or more intervention groups (such as only cognitive training and only physical exercise), then the data used for analysis were taken from the combined intervention and control group. Global cognitive function is evaluated with global cognitive screening instruments as the primary result measurement. All quantifiable results should have been measured both at the beginning of the study and immediately after the intervention period. The appropriate and qualified author team was contacted and requested to provide the lost data if an inadequate report was found.

Bias risk

Selected articles for deeper discussion were then examined with the Cochrane risk-of-bias tool[13]. In total, six domains were assessed, including random sequence generation (selection bias), allocation concealment, blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome (attrition bias), selective reporting (reporting bias) and other biases. Meanwhile, the rating was categorized into three options: low-risk bias, high-risk bias or unclear risk bias in each domain. The bias risk was independently assessed by two researchers (IU and IB), and they reviewed the full text. Any resulting difference was then discussed with the third researcher (RS) until a consensus of all researchers was reached. The bias risk total assessment was based on the assessment of all domains. The results of bias risk assessment were discussed among all authors.

Research validity

The research validity was assessed on the basis of the conceptual framework used, research design, and the predetermined research implementation plan. The research validity assessment was conducted using a checklist mutually developed with the advisor, revised based on the trial results, and validated by the advisor (RS). The conceptual framework domain was assessed on the basis of expertise and empirical validity. The research design was assessed with regards to the data collection design (instrumental and method validity, instrumental utilization reliability, subjects and units of analysis), data processing (the utilization of descriptive and inferential statistics) and data interpretation (validity related to the specified moderator's treatment toward the confounding variables' treatment and external validity). The research implementation was assessed on the basis of the implementation dependability of data collection, data processing and data interpretation of the premediated study design.

Results

The research article collection result identity

The PRISMA diagram (Figure 1) indicates the selection of eligible studies, the process of screening, and reasons for exclusion. Two-stage screening, title/abstract and full text, resulted in 28 studies being selected for inclusion in this review. A data extraction table was completed for each eligible study to collect information including the author(s), publication year, country, population, sample size intervention, control and output (PICO) (Table I).

The article collecting process lasted from 28 January to 28 February 2018, and 3,294 articles were obtained from the listed databases – Cochrane: 290 articles, Medline: 742 articles, Indonesian National Library: 12 articles, Clinical Key: 1 article, EbscoHost: 16 articles, ProQuest: 212, EMBASE: 0, Medical Librarian (TWE) in Ovid: Science Direct: 47, Scopus: 1 article, The Lancet Global Health: 1 article, PubMed: 1.935 articles and Emerald: 28 articles, whereas those using Indonesian language collected through LIPI (garuda portal): 2, Indonesian National Library: 0, Google Scholar: 4, Google Indonesia: 5. The screening conducted on the basis of title and abstract found that there were 33 duplicate articles written and published in English, whereas three other articles written in the Indonesian language were duplicates. The procedure that was used in the literature review to find duplicates involved typing the 3,296 titles and publisher sources into an Excel format, followed by sorting the titles alphabetically so that the names of the duplicate titles ended up in consecutive rows. The number of duplicate titles was then counted, and one of the duplicates was then removed. This step weeded out 33 duplicate English-language papers and three Indonesian-language papers. Furthermore, screening the articles for irrelevant topics on the basis of the titles and abstracts eliminated 3,127 English-language articles and five Indonesian-language articles. The remaining 125 English and three Indonesian articles

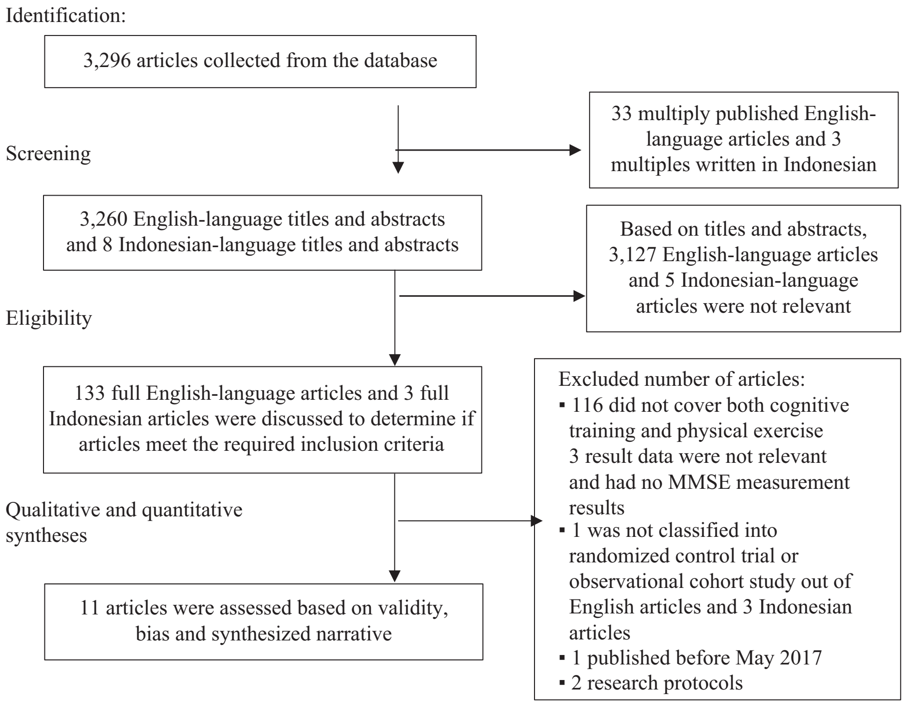

Figure 1.
Flow PRISMA diagram

were then separately examined by two reviewers and screened on the basis of the inclusion criteria. This identified 116 articles that did not include simultaneously conducted cognitive training and physical exercise; 3 that contained irrelevant data with no MMSE measurement results; 1 English-language article and 3 Indonesian-language articles that were not classified into a randomized controlled or observational cohort study; 1 English-language article that was published before May 2017; and 2 articles that were in the form of research protocol. Eventually, an article was obtained, considered to be meeting all critical requirements and eligible to be assessed on the basis of its validity and bias risk, and then narrative analysis was conducted. An overview of the collection process is presented in the PRISMA diagram, which follows Figure 1 and data extraction (Table I).

Participants and characteristics

In sum, 11 articles were obtained that met the requirements of research with RCTs conducted in Nagoya Japan, USA, German, Korea, Spain and Italy (Figure 1). Each of the studies dealt with an elderly population aged 55+ years or with MCI and a combination of cognitive training and physical exercise interventions; each study obtained the effects of patients' cognitive functions and motions with MCI; in specific studies, the control group received health education[18–20], Sham cognitive and sham exercise[12], treatment as usual[21], mock therapy[22], care as usual[23–25], psychosocial support [26]; it obtained the cognitive measurement result using mini mental state examination [19, 20, 23, 27], Alzheimer's Disease Assessment Scale-Cognitive Subscale[12, 21, 28], combined[18, 22, 26]. Exercise and cognitive activity ranged from 30 to 300 min/session, the studies spanned a duration ranging from 8 to 52 weeks and the frequency was in the range of two to five sessions/week.

No.	Study and country	Population	Intervention	Comparison	Outcome
1	Singh *et al.*[12], USA	100 elderly aged 55 or above with MCI	Computer-based multimodal and multidomain cognitive exercises Progressive resistance training (100 min, 2–3 times a week for 26 weeks)	Sham cognitive and sham exercise	Training significantly improves global cognitive function, with maintenance executive and global benefits for 18 months, RR 0, 4
2	Suzuki *et al.*[18], Japan	100 elderly with MCI (average age: 74 years)	Cognitive tasks during exercise (not specified): aerobic exercise, strength and balance training (90 min, twice a week for 26 weeks)	Health education	For 6 interactions, the exercise group showed significantly better mini mental state examination (p 0.04) and logical memory scores ($p = 0.04$), and reduced cortical atrophy of the whole brain (p: 0.05) compared to the control group, RR 0, 31
3	Burgener *et al.*[19], USA	Elderly average age: 77 years	Cognitive exercises (focus on memory enhancement, verbal fluency, visual and spatial learning, verbal comprehension): CT: 90 min/session, bi-weekly, PT: 60 min/session, 3×/wk for 20 weeks	Attention-control educational programs	At 20 weeks, differences between groups were found for mental abilities and self-esteem, stability in depression and physical health, RR 0, 57
4	Shimada *et al.*[20], Italy	308 elderly > 60 years old (average age: 65 years)	Combined physical and cognitive training program with a time of 90 min, 1 week for 40 weeks. They call this "Cognitive Training"	Health education through pamphlet	Differences in cognitive values with MMSE 0.8 points, $p = 0.012$ and differences in the value of Wechsler Memory Scale = Revised = Logical memory II 1.0, p 0.004, RR 0, 22
5	Graessel *et al.*[21], Germany	96 elderly with MCI (average age: 85 years)	Cognitive tasks (not specified) and t is: Cognitive tasks (not specified) and Motor exercises, e.g. Bowling/croquet (120 minutes, 6 times a week for 52 weeks Motor exercises, e.g. bowling/croquet (120 min, 6 times a week for 52 weeks	Treatment as usual	E-ADL-test is a performance test that is suitable for measuring daily life activities because it is easy to use, reliable, valid and well received, RR 0, 72
6	Han *et al.* [22], Korea	64 elderly with MCI (average age: 75 years)	Cognitive training, cognitive stimulation and reality orientation (not specified) and physical therapy (180 min, once a week for 8 weeks)	Mock therapy 3-h sessions per week for 8 weeks	MCET improves cognition, behavior, and quality of life in people with MCI or mild dementia more effective than conventional cognitive enhancement activities. Periodic evaluation at 0, 9, 21 weeks, RR 0, 35
7	Holthoff *et al.*[23], Germany	30 elderly with AD (average age: 72 years)	Changes in direction (forward reverse) and type of training on movement trainer cycling on movement trainer (30 min 3 times a week for 12 weeks)	Care as usual	Patients in the intervention group increased during the intervention and returned to the beginning of performance at week 12 and analysis of reaction time, speed and hand–eye attention revealed improvements only in the intervention group, RR 0, 57

Table I.
Summary source

(*continued*)

No.	Study and country	Population	Intervention	Comparison	Outcome
8	Rabipour *et al.*[24], Italy	113 elderly with MCI (average age: 75 years)	Cognitive training with stimulation in social interaction given two materials each: CT, 120 min/session, 3×/wk; PT, 60 min/session, 3×/wk for 7 months	Care as usual	Improves cognitive status and indicators of brain health on MCI subjects, RR 0, 37
9	Santos *et al.*[25], Brazil	79 elderly with MCI average age: 75 years)	Computer-assisted cognitive training and cognitive stimulation (not specified) and strength and balance training, walking 300 min/session, 2×/wk for 12 weeks	Care as usual	This multidisciplinary rehabilitation program was beneficial for patients with mild AD and CIND. However, patients with moderate dementia did not benefit from the intervention, *p* 0, 021
10	Olazarán *et al.*[26], Spain	172 elderly with MCI / AD (average age: 75 years)	Cognitive exercises (focus on memory, attention, executive functions, language, visuospatial abilities) and psychomotor exercises 210 min/session, 2 ×/weeks for 52 weeks	Psychosocial support	Patients in the intervention group maintained cognitive status at 6 months, whereas patients in the control group had significantly decreased. At 12th month, there is an increase in affective status in the experimental group, 75%; control group, 47%; p 0.017), RR 0, 75
11	Venturelli *et al.*[27], Italy	40 elderly with AD (average age: 84 years)	Aerobic, cognitive stimulation with reality orientation method, combined aerobics and CT and standard treatment groups (60 min, 5×/week for 12 weeks)	Care as usual	The effects of AE + CT on SDS and cortisol levels and the lack of effects of CT alone indicate the effectiveness of exercise-based treatment in SDS, suggesting the possible dysregulation of the hypothalamic–pituitary–adrenal axis underlying SDS, RR 0, 77

Notes: MCI, mild cognitive impairment; MMSE, mini mental state examination; AD, Alzheimer's disease; CT, cognitive training; ADL, activities of daily living; AE, Aerobic exercise; SDS, sundowning syndrome); MCET, multimodal cognitive enhancement therapy; E-ADL-Test, The Erlangen Test of activities of daily living; CIND, cognitive impairment without dementia

Table I.

Bias risk

The results of bias risk assessed 11 articles about the combination of the resulting effect with a systematic study of the relationship of how the combination of cognitive training and physical exercise may affect cognitive functions. Karssemeijer *et al.*[14] and Shimada[20] identified that ten of those reviewed articles held some methodological limitations. Using Cochran's bias risk instruments resulted in several considerations: there were four articles that labelled the bias without explaining how a random sequence evaluation was obtained; there were seven articles that did not explain the concealment techniques used at the research location; there were nine articles that had high risks of bias between the respondents and the personnel involved in providing intervention or control (blinding participant/personnel); there was an article that did not explain the evaluation or the way the research result was obtained; there were two articles that had high risks of bias because the research results were not fully reported (incomplete outcome data); and there was one article that did not explain the possibility of other biases. These are presented in Table II.

Research validity

The validity of the study was assessed according to the conceptual framework, research design and research implementation. All papers indicated empirical validity in the formulation of a research conceptual framework. In addition, the reported results show that the expert validity through the use of the neuropsychological evaluation battery theory[27] and neurological functioning and regeneration guided theory[19] may be considered as a mediator and validate the content related to the intervention. All papers used a cluster randomized trials design[12, 18–27].

The combination effect

The result of combined meta-analysis shows the heterogeneity (I2) of this meta-analysis is more than 50 percent, so we calculated the relative risks (RRs) using a random-effects model. Only one paper did not have RRs value: Santos *et al.*[25]. Therefore, the meta-analysis was carried out on ten articles and Santos *et al.*[25] was excluded. The analysis compared the combination therapy group (cognitive therapy and physical exercise) with the control group. These results are presented in Figure 2.

Discussion

Result interpretation

The benefits that illustrate the intervention of physical exercise and combination of cognitive training are likely to enhance the intellectual and physical performance of adults with MCI. Much research on cognitive training has previously been conducted, including cognitive exercises on memory amelioration[19, 26]; fluency in speech, visual and spatial learning, and modulated comprehension[19]; concentration, executive functions, and

Table II.
Summary of bias risk

Bias	High	%	Unclear	%	Low	%
Random sequence generation (selection bias)	0	0	4	36.4	7	63.6
Allocation concealment	0	0	7	63.6	4	36.4
Blinding of participants and researchers (performance bias)	9	81.8	0	0	2	18.2
Blinding of outcome assessment (detection bias)	0	0	1	9.1	10	90.9
Incomplete outcome data (attrition bias)	2	18.2	3	27.3	6	54.5
Selective reporting (reporting bias)	0	0	0	0	11	100
Other bias	0	0	4	36.4	7	63.6

Study or subgroup	log(Risk ratio)	SE	Weight	Risk ratio IV, Random, 95% CI
Burgener *et al.* (2008)	0.57	0.158	9.4%	1.77 [1.30, 2.41]
Fiatarone *et al.* (2014)	0.4	0.14	10.3%	1.49 [1.13, 1.96]
Graessel *et al.* (2011)	0.72	0.103	12.1%	2.05 [1.68, 2.51]
Holthoff (2015)	0.57	0.19	8.1%	1.77 [1.22, 2.57]
Ji won *et al.* (2016)	0.35	0.92	0.7%	1.42 [0.23, 8.61]
Olazaran *et al.* (2004)	0.75	0.111	11.7%	2.12 [1.70, 2.63]
Shimada *et al.* (2017)	0.22	0.057	14.1%	1.25 [1.11, 1.39]
Suzuki *et al.* (2013)	0.31	0.101	12.1%	1.36 [1.12, 1.66]
The brain (2017)	0.37	0.095	12.4%	1.45 [1.20, 1.74]
Venturelli *et al.* (2016)	0.77	0.164	9.2%	2.16 [1.57, 2.98]
Total (95% CI)			100.0%	1.65 [1.42, 1.93]

Heterogeneity: $\tau^2=0.04$; $\chi^2=37.20$, df=9 ($p<0.0001$); $I^2=76\%$
Test for overall effect: $Z=6.37$ ($p<0.00001$)

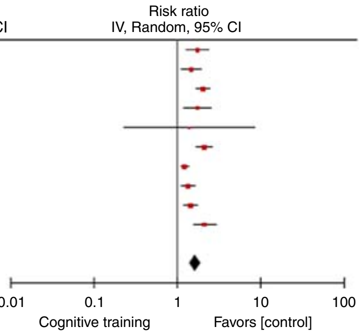

Figure 2.
Forest plot of the risk ratios resulted from the studies included in the meta-analysis

Notes: SE, side effect; CI, confidence interval visuospatial abilities[24], computer-based multidomain and multimodal cognitive exercises [12, 22, 25]; unspecified reality orientation[22, 27]; vague cognitive tasks[18, 21]; changes in direction and type of training[23]; and cognitive training[20]. It also includes physical exercises comprising of Taiji[19], motor exercises, such as bowling/croquet[21], cycling[23], progressive resistance training[12], physical therapy[22], walking[25, 27], psychomotor exercises[26], strength and balance training[18, 25] and aerobic exercise[18, 24].

To correct the variable sizes, a random-effects meta-analysis was utilized. This was used because research illustrated the heterogeneity inherent in the intervention methods such as type, outcome, duration and measures[29]. This technique was also used to examine the standardized mean difference (SMD: 0.32 (0.17, 0.47), by Karssemeijer *et al.*[14], owing to the numerous instruments utilized by the research study. However, the RRs were calculated using a random-effects model. Research analysis indicates that the control group is likely to encounter MCI 1.65 times higher than the combination therapy group, which is statistically significant (RR = 1.65; 95% CI = 1.42–1.93) (Figure 2).

The interpretation of results and comparison with the previous systematic review studies

This paper is the second meta-analysis research examining the combined effects of cognitive training and physical exercise intervention on the cognitive functions of elderly people with MCI or dementia, after the report by Karssemeijer *et al.*[14] and the systematic review previously by Law *et al.*[30], which investigated the combined intervention cognitive benefits for elderly patients with cognitive impairment. Out of the five research studies, three show a significant improvement in global cognitive function, memory, executive function or attention. Those three studies use RCT, whereas the other two studies compare the results with the active control group[30].

This report is similar to that conducted by Zhu *et al.*[31] with 20 intervention studies involving 2,667 participants. The results also show that the effect size for the combined intervention compared with the control group is 0.29 (random-effect model, $p = 0.001$). When compared with physical exercise alone, the combined intervention may have a larger effect on the overall effect size (0.22, $p < 0.01$), whereas no significant difference is found between the combined intervention and the cognitive intervention. The effect of the combined intervention is moderated by the participants' age, frequency of intervention and setting. Other findings also suggest that the combined intervention shows that there are benefits compared with the control group and physical exercise group, yet the evidence is still lacking to prove that an advantage exists when comparing combined intervention with the cognitive intervention[31].

The systematic review was updated by Levin, Netz and Ziv[32], relating the effectiveness and efficacy of the combined cognitive training and physical exercise intervention piloted throughout the world, which concluded that the combined interventions may significantly increase the numbers of physical, motor and cognitive outcomes when compared to a single exercise intervention. Cognitive training and physical exercise are considered to be the best intervention strategy. Multi-component exercise training is found to be beneficial to improve both walking and processing speed, whereas the combination of cognitive–physical training is considered most beneficial for psychomotor speed, processing speed, attention and multitasking[32].

Systematic review and meta-analysis recently reported by Karssemeijer *et al.*[14] realized that the combined cognitive and exercise intervention potentially has cognitive benefits for elderly people with MCI or dementia. Through RCT, the efficacy of the combined intervention is proven because the combined activity group shows significantly higher scores on the MMSE (the difference is > 0.8 point with *p*, 0.25, 012). Thus, the identification of individual predictors for more beneficial results is highly important, in order to personalize the multimodal intervention.

In conclusion, choosing the proper results measurement system will be highly important in future research. The utilization of more comprehensive neuropsychological assessments is required to identify the most beneficial cognitive function domains resulting from the combined intervention. A long-term investigation is definitely required to determine the effect of activities related to the prevention or delay of AD cases.

Implications for further research

From the explanations of sequential development on the systematic review of the combined intervention effect from June 1976 to January 2018, some recommendations can be made. First, it is necessary to determine and calculate whether the effect of combined activity is associated with the prevention or delay of AD in elderly people with MCI. Next, a multi-arm research design is necessary, including combined cognitive training and physical exercise, single physical exercise, single cognitive training, and control groups in order to differentiate the contributions from various components of the intervention methodologies. Additionally, it is important to explore the most effective training characteristics in a special combined intervention differentiated by the duration, frequency, intervention, type and combination mode. There is also a need for further investigation, which focuses on the physiological mechanisms underlying the positive effects, by inserting a more comprehensive neuro-imaging measurement to assess specifically the domain that benefits in terms of cognitive functions and molecular markers. Finally, exploratory studies are definitely required, which will specifically examine maintenance and treatment effects as well as derive theoretical explanations related to the interventions and predictors[14, 20, 31, 33].

Conclusion

A combination of cognitive training and physical exercise intervention may improve the global health or cognitive functions of elderly patients. Because there are various methods, intervention types and sample sizes, a careful interpretation of the results is certainly required. However, method limitations demonstrate the importance of using combined interventions to help delay the development of MCI or dementia. A solid research design of multi-arm RCT including long-term follow-up assessments is definitely needed in order to investigate the potential advantages of the combined intervention method when compared to single interventions in elderly people with MCI or dementia, including extensive neuropsychological assessments to obtain further insights related to the different domain effects and demonstrate efficacy, in conjunction with the other theories that explain the relationship between intervention and prediction. A systematic review and empirical research are certainly required in future studies.

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