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REVIEW ARTICLE

The Effects of Exercise, Cognitive Intervention and Combined Exercise and Cognitive Intervention in Alder Adults with Cognitive Impairment and Alzheimer's Disease: A literature review

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ABSTRACT

Cognitive impairment is a defining feature of dementia caused by neurodegenerative conditions such as Alzheimer's disease (AD) and cerebrovascular disease. The combination of different protective factors of healthy cognitive aging might be most promising when attempting to delay cognitive decline and preserve cognitive abilities. Particularly, the combination of cognitive and physical activity has attracted increasing interest. But there is no review on the effects of exercise, cognitive intervention, and combined exercise and cognitive intervention in patients with cognitive impairment and AD and it is not cleared what is the best therapeutic intervention for these patients. 26 studies were identified in this review, most studies assessed general cognitive state such as MMSE or ADAS-Cog. Several studies indicated negative results included exercise, cognitive intervention, and combined exercise and cognitive intervention. Combination therapy may be plays an important role in enhancing cognitive function. The mechanisms of benefit from individual and combined physical and cognitive interventions are not clear, it has been postulated that physical and mental activity may therefore have potential to improve cognitive function. More research is needed to study the effect of combined non-pharmacological interventions in older adults with cognitive impairment.

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Ⅰ. Background

Cognitive impairment is a defining feature of dementia caused by neurodegenerative conditions such as Alzheimer’s disease (AD) and cerebrovascular disease. For the person with dementia, memory and other cognitive difficulties can have a major impact on self-confidence and can lead to anxiety, depression and withdrawal from activities, which in turn can make the difficulties seem worse (Bahar-Fuchs, Clare & Woods, 2013). Pharmacological treatment is not satisfactory for patients with dementia. Even though the treated patient may show some cognitive improvement for several months, they show a similar level of cognitive function after 1 year or so, showing the same rate of cognitive decline as untreated patients (Takeda, Tanaka, Okochi, et al., 2012).

Over the past few decades, several lines of scientific evidence and clinical literature have established the beneficial effects of non-pharmacological therapies in enhancing the regenerative power of the brain, thereby promoting additional clinical research in this area (Hindle, Petrelli, Clare, et al., 2013; Olazarán, Reisberg, Clare, et al., 2010; Zec & Burkett, 2008). In humans, cognitive enrichment in the form of educational attainment and occupational status has been shown to induce neuroplasticity that not only strengthens the existing neural networks, but also recruits alternative neural networks to permit normal cognitive functioning in an injured brain (Petrosini, De Bartolo, Foti, et al., 2009). Therefore, numerous studies have investigated the potential of psychological interventions, physical therapy at social interaction at providing an enriched environment, and improving cognition and quality of life patients suffering from brain disorders (Farzana, Ahuja & Sreekanth, 2013).

The most frequently proposed non-pharmacological intervention to implement during the early stages of AD is cognitive intervention (Gardette, Coley & Sandrine, 2010). According to Cochrane review, cognitive rehabilitation is likely to provide some benefit for patients in the short term and in the medium term related to self-rated competence and satisfaction in performing meaningful personal goals, memory capacity and general quality of life (Archer, 2011). On the other hand, Physical exercise in older adults with AD also can contribute positively by attenuating decline in cognitive function (Kirk-Sanchez & McGough, 2014; Hamer & Chida, 2009). A meta-analysis of 16 prospective studies including patients with neurodegenerative diseases found that higher physical activity was associated with a 28% reduction in incident dementia (Zec & Burkett, 2008). More than 3 weeks exercise program have been reported to exhibit stable or improved cognitive health over 5 years (Middleton, Mitnitski, Fallah, et al., 2008). But which intervention is more effective between exercise and cognitive intervention is still lacking (Kueider, Bichay & Rebok, 2014; Snowden, Steinman, Mochan, et al., 2011).

Recently, it has been argued that the combination of different protective factors of healthy cognitive aging might be most promising when attempting to delay cognitive decline and preserve cognitive abilities (Schneider & Yvon, 2013; Bamidis, Vivas, Styliadis, et al., 2014). Several studies have found that a combination of exercise and an enriched environment induces more new neurons and benefits the brain greater than either exercise or an enriched environment alone (Fabel & Kempermann, 2008; Fabel, Wolf, Ehninger, et al., 2009; Olson, Eadie, Ernst, et al., 2006). Particularly, the combination of cognitive and physical activity has attracted increasing interest (Rahe, Petrelli, Kaesberg, et al., 2015). A systematic review showed that combined cognitive and exercise training can be effective for improving the cognitive functions and functional status of older adults with and without cognitive impairment (Law, Barnett, Yau, et al., 2014). A recent RCT also reported that a 12-week strength-balance exercise with computerised cognitive training, would lead to greater improvements in physical and in cognitive performance compared to strength-balance exercise alone (van het Reve & de Bruin, 2014). But there is no review on the effects of exercise, cognitive intervention, and combined exercise and cognitive intervention in patients with cognitive impairment and AD and it is not cleared what is the best therapeutic intervention for these patients.

Therefore, the objectives of this literature review were to: (i) review the evidence for the effectiveness of exercise, cognitive intervention, and combined exercise and cognitive intervention in older adults with cognitive impairment and AD, and (ii) we also discuss potential mechanisms through which intervention may enhance brain health and cognitive function.

Ⅱ. Methods

1. Search strategy

We searched MEDLINE and Google Scholar. The last search was performed in March 16th, 2015.

Search for keywords in MeSH(Medical subject heading; MeSH) with the words ‘AD, dementia, MCI, exercise training, cognitive intervention, combined exercise and cognitive intervention’. All databases were restricted to those published in English between January 1st, 2000 and February 28th, 2015.

A total of 105 abstracts were identified from preliminary searching. Exclusion of 79 studies that did not meet the criteria resulted in a final sample of 26 articles included 10 studies on exercise intervention, 13 studies on cognitive intervention, and 3 studies on combined exercise and cognitive intervention were retrieved for full test screening.

2. Inclusions criteria

Studies were included in this review if they met the following criteria: (1) design: randomized controlled trial (RCT) or non-randomized controlled trial (NRCT); (2) participants: older adults (aged 65 and older) were included who had been diagnosed with a cerebral neurologic disorder such as dementia, mild cognitive impairment (MCI) and AD but no mental or neurological disorders other than dementia, such as stroke or major depression; (3) intervention: alone exercise intervention including aerobic exercise, movement-based exercise and multicomponent exercise or cognitive intervention including cognitive training, cognitive rehabilitation and cognitive stimulation, or combined exercise intervention and cognitive intervention; and (4) outcome: cognitive functions assessed using and neuropsychological tests as primary or secondary outcomes.

3. Exclusions criteria

Articles were excluded if they were: (1) non-intervention studies; (2) review articles; (3) animal studies; (4) unpublished studies, abstracts or dissertations; (5) studies without assessed cognitive function; (6) studies assessed any other interventions (e.g. art therapy, music therapy, physiotherapy et al.) without exercise or cognitive intervention; and (7) non-English language articles.

4. Data synthesis and analysis

All data were presented citation/population, intervention and comparison, study design/length, number of patients, outcome measures and effect size (ES). The ES was calculated according to the following formula:

$$ES = \frac{\text{mean postintervention} - \text{mean preintervention}}{\text{preintervention standard deviation}}$$

ES were interpreted according to Cohen's scale of 'trivial' (<0.20), 'small' (≥0.20 to <0.50), 'moderate' (≥0.50 to <0.80), and 'large' (>0.80) (Cohen J, 1977).

Ⅲ. Research Overview

1. The various types of exercise interventions

Currently, there is no cure for AD (Alzheimer's Association, 2014). However, research has suggested that physical activity and exercise can significantly reduce the risk of developing it (Bherer, Erickson & Liu-Ambrose, 2013). In the recently, a number of intervention studies have investigated the effects of aerobic exercise, movement-based exercise, and multicomponent interventions on cognitive function and brain health in older adults with cognitive impairment and AD. Table 1 shows the characteristics of the various exercise intervention studies.

<Table 1> Characteristics and findings of exercise intervention studies

Citation/ population	Intervention and comparison	Study design/length	N	Outcome measures	Effect size(immediate)*
Arcoverde et al. (2014) 20 dementia	I: a treadmill; 30min/2 times/week/ 60% of heart rate) C: usual care	RCT 16 weeks	I: 10 C: 10	CF: CAMCOG, CDT, MMSE, VF, ST, DS FC: BERG	CAMCOG:1.17 CDT: 0.74 MMSE: 0.84 VF: 0.38 ST: 1.14 DS: 0.45 BERG: 1.04
Baker et al. (2010) 33 MCI	I: a treadmill, stationary bicycle, or elliptical trainer;	RCT 6 months	I: 23 C: 10	CF: Trails B, SCWT, TS, VF, SDM	Trails B: women;0.56/men; 0.70

	45-60min/4d/week/75-85 % of heart rate C: a stretching; below 50% of heart rate			PC: Glucose disposal, HOMA, Cortisol level, BDNF	SCWT: women;0.76/men; 0.05 SDM: women;0.67/men; 0.29 VF: women;0.88/men; 0.28
Vital et al. (2012) 34 AD	I: weight training; 1h/3 times/week C: social gathering group	NRCT 16 weeks	I: 17 C: 17	CF: MMSE, BCB, CDT, VF	No reported
Thurm et al. (2011) 15 dementia	I: multimodal movement intervention; 45 min/2 times/week C: standard care activity group	NRCT 10 weeks	I: 6 C: 9	CF: MMSE, ADAS-Cog, CERAD-Plus, TMT PC: ADFACS	ADAS-Cog: -0.45
Yágüez et al. (2011) 27 AD	I: Brain Gym® movements; 2h and a 30 min break/week C: usual care	RCT 6 weeks	I: 15 C: 12	CF: CANTAB-Expedio	PRT: 0.34 FDR: 0.55 WMT: -0.43
Sung et al. (2006) 36 dementia	I:group music with movement intervention; 30 min/2 times/week C: usual care	RCT 4 weeks	I: 18 C: 18	CF: modified CMAI	-0.68
Vreugdenhil et al. (2012) 40 AD	I: a community-based home exercise: at least 30min/daily if possible C: usual care	RCT 4 months	I: 20 C: 20	CF: ADAS-Cog, MMSE, GDS PC: FR, TUG, SS, BI, IADL, CIBIC-plus	MMSE: 0.20 ADAS-Cog: -0.43 FR: 0.41 TUG: -0.16 SS: 0.64 BI: 0.06 IADL: 0.10 GDS: -0.35
Suzuki et al. (2012) 50 aMCI	I:multicomponent exercise group; 90min/d,2 d/week C: education	RCT 12 months	I: 25 C: 25	CF: MMSE, WMSLM A and B, DS, LVFT, CVFT, SCWT	MMSE: 0.18 WMSLM A: 0.65 WMSLM B: 0.70 DS: -0.01 LVFT: 0.54 CVFT: 0.22 SCWT-Ⅰ: -0.34 SCWT-Ⅲ: -0.34
Rolland et al. (2007) 134 mild to severe AD	I: collective exercise program; 1h/2 times/week C: usual care	RCT 12 months	I: 67 C: 67	CF: NPI, MADRS PC: Katz ADL, 6MS, TUG, MNA	NPI:-0.36 MADRS: -0.07 Katz ADL: 0.39 6MS: 0.57 TUG: 0.38 MNA: -0.19
Nascimento et al. (2012) 20 mild to moderate AD	I: multimodal exercise program; 1h/3 times/week C: usual care	Controlled trial 6 months	I: 10 C: 10	CF: MMSE, NPI PC: Pfeffer	MMSE: no reported NPI: -0.4 Pfeffer: -0.06

Abbreviation: I=intervention; C=comparison; CF=cognitive function; PC=physical capacity; aMCI=amnestic mild cognitive impairment; AD=Alzheimer's disease; CAMCOG=cambridge cognitive examination; CDT=clock drawing test; MMSE=mini-mental state examination; VF=verbal fluency; ST=Stroop test; DS=Digit span; BERG=Berg balance scale; Trails B=trail making test B; SCWT=stroop color and word test; TS=task switching; SDM=symbol digit modalities; HOMA=homeostasis model assessment; BDNF=brain-derived neurotrophic factor; RAVLT=rey auditory verbal learning test; WAIS=Wechsler adult intelligence scale; WASI=Wechsler abbreviated scale of intelligence; BNT=boston naming test; BCB=brief cognitive battery; ADAS-Cog=Alzheimer disease assessment scale-cognitive subscale; CERAD-Plus=the consortium to establish a registry for Alzheimer's disease; ADFACS=Alzheimer's disease functional assessment and change scale; CANTAB-Expedio; the Cambridge neuropsychological test automated battery-Expedio; PRT=pattern recognition test; FDR=false discovery rate; WMT=working memory test; modified CMAI; modified Cohen-mansfield agitation inventory; GDS=geriatric depression scale; FR=functional reach; TUG=timed up and go test; SS=sit-to-stand; BI=barthel index; IADL=instrumental activities of daily living; CIBIC-plus=the clinician's interview-based impression of change plus caregiver input; WLTIR=word list total immediate recall; WLDC=word list delayed recall; DS=digit symbol coding; CDR=clinical dementia rating; BDI=beck depression inventory; PCS=medical outcomes 36-item short form(SF-36) physical component summary; MCS=SF-36 mental component summary; WMSLM=logical memory subtest of the Wechsler memory scale-revised; LVFT=letter verbal fluency test; CVFT=category verbal fluency test; NPI=neuropsychiatric inventory; MADRS=Montgomery-asberg depression rating scale; Katz ADL=the Katz index of activity of daily living disability; 6MS=6-meter walking speed; MNA=mini-nutritional assessment; Pfeffer=the Pfeffer functional activities questionnaire.
*effect sizes are presented in intervention group only.

1.1. The effect of aerobic exercise interventions: RCT

Aerobic exercise RCTs in older adults have demonstrated effects on cognitive performance. Especially, treadmill training had a beneficial effect on the global cognitive function (Arcoverde, Deslandes, Moraes, et al., 2014) and observed for executive control abilities such as selective attention, search efficiency, processing speed, and cognitive flexibility (Baker, Frank, Foster-Schubert, et al., 2010). Arcoverde et al. (Arcoverde, Deslandes, Moraes, et al., 2014) addressed that treadmill training group presented significant improvement in balance and mobility compared to the pharmacological treatment group. On the other hand, a 6 weeks walking intervention was not effective in cognitive function (Baker, Frank, Foster-Schubert, et al., 2010).

1.2 The effect of aerobic exercise interventions: NRCT

One study reported that a 16 weeks weight training found no significant differences associated to the effects of the practice of strength training on memory and cognition in elderly with AD (Vital, Hernández Salma S., Pedroso, et al., 2012).

1.3. The effect of movement-based exercise interventions: RCT

Movement-based interventions combined strengthening, coordination, balance, flexibility, and stamina (Thurm, Scharpf, Liebermann, et al., 2011). One study examined the association between movement-based intervention and cognitive decline (Yágüez, Shaw, Morris, et al., 2011). A short course of 6 weeks of a non-aerobic movement-based intervention improved sustained attention, visual memory and working memory in AD patients. One study reported that group music with movement intervention can be an effective intervention in decreasing agitated behaviours (Sung, Chang, Lee, et al., 2006).

1.4. The effect of movement-based exercise interventions: NRCT

The one studies examined the association between movement exercise intervention and cognitive function. Thurm and colleagues reported that multimodal physical movement training combined strengthening, coordination, balance, flexibility, and stamina of 10 weeks has positive effects on cognitive function in physically very frail nursing home residents with dementia (Thurm, Scharpf, Liebermann, et al., 2011).

1.5. The effect of multicomponent exercise interventions: RCT

The three studies examined the association between multicomponent exercise and cognitive function. Multicomponent exercise includes two or more main types of exercise such as strength training, balance training, flexibility training and aerobic exercise.

One studies conducted a home-based exercise program. Vreugdenhil and colleagues suggest that a community based home exercise program specifically developed for people with dementia is effective in improving functional ability across a number of domains, including cognition, physical function and activities daily living(ADL) (Vreugdenhil, Cannell, Davies, et al., 2011).

Two studies conducted a center-based exercise program. Suzuki and colleagues found that 12 months of multicomponent exercise improved general cognitive function, immediate memory, and language ability in older adults with aMCI relative to the education control group (Suzuki, Shimada, Makizako, et al., 2012). Rolland and colleagues found that a multicomponent exercise program including aerobic, strength, flexibility, and balance, 1 hour twice a week, led to significantly slower decline in ADL score in AD patients living in nursing home than routine medical care. But no effect was observed for behavioral disturbance, depression, or nutritional assessment scores (Rolland, Pillard, Klapouszczak, et al., 2007).

1.6. The effect of multicomponent exercise interventions: NRCT

One study reported that 6 months of a multicomponent exercise intervention is associated with improved neuropsychiatric inventory (NPI) scores of patients with AD and contributes to the attenuation of the impairment in the performance of instrumental activities of daily living in elderly women with AD (Nascimento, Teixeira, Gobbi, et al., 2012).

2. The various types of cognitive interventions

Cognitive interventions as a group fall under the broader umbrella of non-pharmacological interventions. Cognitive interventions can be broadly defined as interventions that directly or indirectly target cognitive functioning as opposed to interventions that focus primarily on behavioural (e.g. wandering), emotional (e.g. anxiety) or physical (e.g. sedentary lifestyle) function (Bahar-Fuchs, Clare & Woods, 2013). There are different types of cognition-based interventions have been described. In cognitive intervention, the concepts of cognitive training, cognitive rehabilitation, and cognitive stimulation are the most popular approaches. Cognitive training typically involves guided practice on a set of standardized tasks designed to reflect particular cognitive functions such as memory, attention or problem-solving. Cognitive rehabilitation, originally developed mainly through work with younger brain-injured people but equally applicable to progressive conditions, refers to the rehabilitation of people with cognitive impairments. Cognitive stimulation promotes the involvement in activities that are aimed at a general enhancement of cognitive and social functioning, without specific objectives (Clare, Woods, Moniz Cook, et al., 2003). Table 2 shows the characteristics of the various cognitive intervention studies.

<Table 2> Characteristics and findings of cognitive intervention studies

Citation/ population	Intervention and comparison	Study design/length	N	Outcome measures	Effect size(immediate)
Buschert et al. (2012)	I: a cognitive intervention; 2h/week C: self-study	RCT 6 months	I: 12 C: 12	CF: MMSE, ADAS-Cog, RBANS, TMT,	No reported

24 aMCI				MADRS, QOL: QOL-AD	
Galante et al. (2007) 11 early stage AD	I: a computer exercise; 60min/3 times/week C: aspecific treatment(semi-structured interview on their own life history);60min/3 times/week	RCT 4 weeks	I: 7 C: 4	CF: MMSE, MODA, BWRT, PM, CBT, DCT, RCPM, SVF, PVF, denomination, constuctional apraxia, ideomotor apraxia-right limb and left limb	MMSE: 0.03 MODA: 0.24 BWRT: -0.25 PM: -0.02 CBT: 0.09 DCT: -0.09 RCPM: 0.33 SVF: 0.00 PVF: 0.01 Denomination: 0.00 constructional apraxia: 0.22 ideomotor apraxia right limb: 0.17 ideomotor apraxia left limb: -0.06
Kawashima et al. (2015) 39 mild to moderate dementia	I: a individualized cognitive intervention; 30min/every week day C: usual care	NRCT 6 months	I: 19 C: 20	CF: MMSE, FAB	MMSE: 0.5 FAB: 0.48
Herrera et al. (2012) 22 aMCI	I: computer based memory attention training program; 60min/2 times/week C: stimulating cognitive activities	RCT 12 weeks	I: 11 C: 11	CF: doors recognition subtest, DMS48 test, digit span test, BEM-144 12-word-list recall test, 16-item free and cued reminding test, MMSE-recall of the 3 words, recall of Rey's complex figure/36	doors recognition subtest: set A=0.15, set B=0.18 DMS48 test: 0.029 Forward digit span test: 0.14 BEM-144 12-word-list recall test: 0.20 16-item free and cued reminding test: 0.20 MMSE-recall of the 3 words: 0.19
Barnes et al. (2009) 47 MCI	I: computer-based cognitive training; 100min/day, 5 days/week C: passive computer activities	RCT 6 weeks	I: 22 C: 25	CF: RBANS, CVLT, VF, BNT, CTMT, DF, SS	RBANS: 0.33 CVLT: 0.16 VF: -0.22 BNT: -0.23 CTMT: -0.03 DF: -0.11 SS: 0.85
Tappen et al. (2014) 68 MCI or probable early-stage AD	I: in-home cognitive training program; 1h/week C: the life review group	NRCT 12 weeks	I: 37 C: 31	CF: MMSE, CDR	No reported
Oskoei et al. (2013) 30 MCI	I: NEJATI cognitive rehabilitation; 2.5h/2 times/week/total 12 sessions C: usual care	RCT 6 weeks	I: 15 C:15	CF:MMSE, WMS-O, SCWT,	No reported
Kurz et al. (2012) 189 AD	I: combined 4 established strategies adopted from neurorehabilitation and psychotherapy; 1h/week C: usual care	RCT 3 months	I: 92 C: 97	CF: NPI, WMSRLM, TMT-A,RWT PC: B-ADL, AFIB QOL: DEMQOL, GDS	NPI: 0.02 WMSRLM: 0.08 TMT-A: 0.02 RWT: -0.13 B-ADL: 0.06 AFIB: 0.15 DEMQOL: 0.04 GDS: -0.33
Lee et al. (2009)	I: a SRT program; 25-26min/3 week/24	NRCT 8 weeks	I: 13;very mild AD,	CF: MMSE, BNT, WLMT,	MMSE: 0.15 BNT: 0.11

19 AD	times C: no reported		6;mild AD C:-	WLRT, WLRT, IC-story, IC-theme, DR-story, DR-theme, Recognition, BVRTA	WLMT:0.09 WLRT: 0.00 WLRT: -0.36 IC-story: -0.09 IC-theme: -0.03 DR-story: 0.09 DR-theme: 0.15 Recognition: 0.05 BVRTA: 0.10
Han et al., (2014) 10 MCI	I: a self-administered SRT program; 24min/6 times/week C: no reported	NRCT 4 weeks	I: 10 C:-	CF: CERAD; MMSE, CFT, BNT, WLMT, WLRT, WLRT, CPT, CRT, Trails A and B	MMSE: -0.79 CFT: -0.22 BNT: 0.22 WLMT: 0.46 WLRT: 0.45 WLRT:0.17 CPT: 0.2 CRT: 0.23 Trails A: 0.10 Trails B: -0.21
Cipriani et al. (2006) 23 AD,MCI and MSA	I: a NPT software program; 13-45min/4 days/week C: no reported	NRCT 3 months	I: 10;AD, 10;MCI C: 3;MSA	CF: MMSE, PF, SF, VS, Trails A and B, RBMT QOL: GDS, AADL, STAI-X1, STAI-X2, SF-12 PCS, SF-12 MCS	(Results indicated with AD/MCI) MMSE: 0.88/0.5 PF: 0.73/-0.06 SF: -0.03/0.26 VS: 0.10/0.48 Trails A: -0.23/-0.35 Trails B: -0.07/0.47 RBMT: 0.21/0.6 GDS: -0.44/-0.31 AADL:0.08/0 STAI-X1:-0.49/-0.39 STAI-X2: -0.32/-0.52 SF-12 PCS: 0.16/-0.29 SF-12 MCS: 0.02/0.69
Kurz et al. (2009) 28 AD and MCI	I: a cognitive rehabilitation programme; 22h/week C: no reported	NRCT 4 weeks	I: 10;mild AD, 18;MCI,	CF: CVLT, RCF QOL:BADL,BDI	(Results indicated with AD/MCI) CVLT: 2.14/0.78 RCF: 0.23/0.79 BADL: -0.06/-0.6 BDI: -0.41/-0.66
Cove et al. (2014) 59 dementia	I: CST plus carer training and CST; 45min/week C: no CST and no carer training	RCT 14 weeks	I: 17;CSTplus carer training, 21;CST, C: 21	CF: MMSE, ADAS-Cog, QOL: QOL-AD	MMSE: 0.00 ADAS-Cog: 0.00 QOL-AD: 0.03

Abbreviations: I=intervention; C=comparison; CF=cognitive function; PC=physical capacity; QOL=quality of life; aMCI=amnestic mild cognitive impairment; AD=Alzheimer's disease; MMSE=mini-mental state examination; ADAS-Cog= Alzheimer disease assessment scale-cognitive subscale; 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; MODA=Milan overall dementia assessment; BWRT=bisyllabic word repetition test; PM=prose memory; CBT=Corsi's block tapping test; DCT=digit cancellation test; RCPM=Raven's coloured progressive matrices; SVF=semantic and phonemic verbal fluency, PVF=phonemic verbal fluency; FAB=Frontal Assessment Battery at Bedside; BEM-144; Batterie D'efficince Mnesique-144; CVLT=the California verbal learning test; VF=verbal fluency; BNT=boston naming test; CTMT=California trail making test; DF=design fluency; SS=spatial span; CDR= clinical dementia rating; WMS-O=Wechsler memory scale; SCWT=stroop color word test; NPI=neuropsychiatric inventory; WMSRLM=Wechsler memory scale revised logical memory; RWT=Regensburg word fluency test; B-ADL=bayer activities of daily living; AFIB=Aachen functional item inventory; DEMQOL= dementia quality of life scale; GDS=geriatric depression scale; WLMT=word list memory test; WLRT=word list recall test; WLRT=word list recognition test; IC=immediate recall; DR=delayed recall; BVRTA= the Benton visual retention test A; CERAD; the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet CFT=categorical fluency test; CPT=construction praxis test; CRT=construction recall test; MSA= multiple system atrophy, PF=phonemic fluency; SF=semantic fluency; VS=visual search; RBMT= Rivermead behavioral memory test; AADL=advanced activity of daily living; STAI=state anxiety; SF-12 PCS=medical outcomes 36-item short form(SF-36) physical component summary; SF-12 MCS=SF-36 mental component summary; RCF=rey complex figure; BDI= Beck Depression Inventory; CST; cognitive stimulation therapy.
*effect sizes are presented in intervention group only.

2.1. The effect of cognitive intervention: RCT

One study reported that long-term effects of a 6-month cognitive intervention in aMCI on cognitive and noncognitive function and the impact on conversion rate to AD in an early treatment group compared to a group receiving an 8-month time-lagged intervention (Buschert, Giegling, Teipel, et al., 2012). In the other hand, a 4-week short-term cognitive intervention did not improve cognitive function only it has delayed the continuous progression of cognitive impairment in AD (Galante, Venturini & Fiaccadori, 2007).

2.2. The effect of cognitive intervention: NRCT

One study reported that statistically significant improvement in MMSE and an improvement trend on FAB scores after 6 months cognitive intervention (Kawashima, Hiller, Sereda, et al., 2015).

2.3. The effect of cognitive training: RCT

Three studies were performed with computer-based cognitive training in older adults with cognitive impairment and AD. Herrera and colleagues reported that a 12-week computer-based memory-attention training program improved episodic recall, one of the memory components in the core cognitive impairment in MCI patients at risk of converting to AD (Herrera, Chambon, Michel, et al., 2012). But a 6-week computer-based cognitive training was not statistically significant between the intervention and control groups (Barnes, Yaffe, Belfor, et al., 2009). One study reported that a 12-week, 24-session, in-home cognitive training significantly improved face-name recognition, making change more quickly, greater accuracy in balancing a checkbook, and remembering the simpler (cued by a visible envelope) of the tasks to do when timer goes off (Tappen & Hain, 2014).

2.4. The effect of cognitive training: NRCT

There is no reported NRCT study about the effect of cognitive cognitive training.

2.5. The effect of cognitive rehabilitation: RCT

The two studies examined the association between cognitive rehabilitation and cognitive function. Oskoei and colleagues reported that a 6-week cognitive rehabilitation computer program significantly improved the percentage of changes and the calculated size of selective attention between experimental and control group (Oskoei AS, Nejati V & Ajilchi B, 2013). Kurz and colleagues reported that a 3-month cognitive rehabilitation was not significantly improved treatment-related differences regarding patient or carer-rated quality of life, patients' behavioral disturbance, or patients' cognitive ability (Kurz, Thöne-Otto, Cramer, et al., 2012).

2.6. The effect of cognitive rehabilitation: NRCT

The spaced retrieval training (SRT) study, a method of learning and retaining target information by recalling that information over increasingly longer intervals, examined the association between cognitive rehabilitation and cognitive function. Lee and colleagues are reported that a 8-week SRT significantly increased the patients' retention span up to 24 min in patients with very mild and mild AD. But SRT did not have a signiticant effect on the patients' performances on the cognition test and the comprehensive verbal and visual episodic memory tests (Lee, Park, Jeong, et al., 2009). Han and colleague also reported that a 4-week SRT program significantly improved word list memory test (WLMT) scores (Han, Oh, Yoo, et al., 2014).

On the other hand, a 4-week cognitive rehabilitation improved memory. Cipriani and colleagues reported that a 4 days per week/4-week computer-based rehabilitation program improved cognitive performances both AD and MCI group. Especially, AD group significantly improved in memory (short-term, long-term, verbal, and visual one), perception (perceptual recognition and identification) and attention (both spread and divided one). Differently from the AD group, MCI patients significantly improved in working memory and psychomotor learning, but did not reach great improvement in the area of perception. The control group had no significant improvement at all (Cipriani, Bianchetti & Trabucchi, 2006). Kurz and colleagues reported that a 4-week cognitive rehabilitation programme included activity planning, self-assertiveness training, relaxation techniques, stress management, use of external memory aids, memory training, and motor exercise significantly improved activities of daily living, mood, verbal and nonverbal episodic memory in MCI patients. In contrast, patients with mild dementia exhibited a non-significant increase in verbal memory but no other changes. MCI patients allocated to the waiting list control condition showed a significant re-test effect on verbal episodic memory, but no improvement of everyday activities or mood (Kurz, Pohl, Ramsenthaler, et al., 2009).

2.7. The effect of cognitive stimulation: RCT

One study reported that once weekly cognitive stimulation therapy did not improve cognition, quality of life or the quality of the caregiving relationship (Cove, Jacobi, Donovan, et al., 2014).

2.8. The effect of cognitive stimulation: NRCT

There is no reported NRCT study about the effect of cognitive stimulation.

3. The various types of combined exercise and cognitive interventions

There are some evidences to support the effectiveness of combined exercise and cognitive intervention in older adults with cognitive impairment and AD. Table 3 shows the characteristics of the various combined exercise and cognitive intervention studies.

<Table 3> Characteristics and findings of combined exercise and cognitive intervention studies

Citation/ population	Intervention and comparison	Study design/length	N	Outcome measures	Effect size(immediate)*
Fiatarone Singh et al., (2014) 100 MCI	I: active physical training(high intensity progressive resistance training) plus active cognitive training(computerized, multidomain cognitive training);60-100min/2-3days/week C: sham physical training(seated calisthenics)plus sham cognitive training(watching videos/quizzed)	RCT 6 months	I: combined;27, physical training;22, cognitive training;24 C: 27	CF: ADAS-Cog, WAIS-Ⅲ, COWAT, animal naming, WMS-Ⅲ, BVRT-R,SDMT PC: B-IADL	ADAS-Cog: -0.33
Coelho et al. (2013) 27 AD	I: motor activities and cognitive tasks; 1h/3 times/week C: regular daily activity	NRCT 16 weeks	I: 14 C: 13	CF: FAB, CDT, symbol search-sub test of WAIS-Ⅲ	FAB: 1.31 CDT: 0.36 Symbol: 0.94
de Andrade et al. (2013) 30 AD	I: a multimodal exercise intervention; 1h/3 times/week C: usual care	NRCT 16 weeks	I: 14 C: 16	CF: MMSE, MoCA, CDT, FAB, symbol search-sub test of WAIS-Ⅲ, QOL: GDS	MoCA: 0.60 CDT: 0.33 FAB: 1.10 symbol search: 0.83

Abbreviations: I=intervention; C=comparison; CF=cognitive function; PC=physical capacity; QOL=quality of life; MCI=mild cognitive impairment; AD=Alzheimer's disease; ADAS-Cog=Alzheimer's disease assessment scale-cognitive subscale; WAIS-=Wechsler adult intelligence scale; COWAT= Controlled Oral Words Association Test; WMS-Ⅲ=Wechsler memory scale Ⅲ; BVRT-R=Benton visual retention test-revised; SDMT=symbol digit modalities test; B-IADL=bayer activities of daily living; FAB=frontal assessment battery; CDT=clock drawing test; MMSE=mini-mental state examination; MoCA=Montreal cognitive assessment; GDS=geriatric depression scale.
*effect sizes are presented in intervention group only.

3.1. The effect of combined exercise and cognitive intervention: RCT

One studies examined the isolated and combined effects of exercise and cognitive intervention. Fiatarone Singh and colleagues reported that 2-3 days/week for 6 months of high intensity exercise improved the primary outcome of global cognition, as well as executive function and verbal/constructional memory in older adults with MCI. Cognitive training had no significant effects on global function, individual tests, or any cognitive domains other than memory, and it attenuated memory domain decline during the period of active training only. Combined training unexpectedly significantly reduced the benefits of isolated exercise program on executive and global function (Fiatarone Singh, Gates, Saigal, et al., 2014).

3.2. The effect of combined exercise and cognitive intervention: NRCT

Two studies investigate the effect of a 16-week multimodal exercise intervention on frontal cognitive function in patients with AD. Coelho and colleagues reported that the patients in the intervention group significantly increased the scores in frontal cognitive variables included abstraction organization, motor sequencing, behavior self-control and attention, frontal assessment battery and symbol search subtest. Control group worsened significantly in frontal cognitive functions, particularly in planning, organization and motor sequencing (Coelho, Andrade, Pedroso, et al., 2013). de Andrade and colleagues reported that not only improved frontal cognitive function but also improved functional capacity such as greater lower limb strength, better gait, and greater flexibility (de Andrade, Gobbi, Coelho, et al., 2013).

4. Results of reviewed studies

A total of 26 intervention studies fulfilled the inclusion criteria for this review. Most studies assessed general cognitive state and memory has been evaluated subsequently. Not all of the study indicated positive results included exercise, cognitive intervention, and combined exercise and cognitive intervention (table 4).

<Table 4> Results of reviewed studies

	Outcome	Result
Exercise intervention(n=10)		
Arcoverde et al. (2014)	General cognitive state	P
Baker et al. (2010)	Executive function, memory	Executive function : P Memory: N
Vital et al. (2012)	General cognitive state, memory	General cognitive state: N Memory: N
Thurm et al. (2011)	General cognitive state	P
Yágüez et al. (2011)	Attention, memory	P
Sung et al. (2006)	Agitated behaviours	P
Vreugdenhil et al. (2012)	General cognitive state	P
Suzuki et al. (2012)	General cognitive state, memory, processing speed, executive function, verbal fluency	General cognitive state: P Memory: P Processing speed: N Executive function: N Verbal fluency: P
Rolland et al. (2007)	Behavior disturbances	N
Nascimento et al. (2012)	General cognitive state, Behavior disturbances	General cognitive state: N Behavior disturbances: P
Cognitive intervention(n=13)		
Buschert et al. (2012)	General cognitive state, memory	P
Galante et al. (2007)	General cognitive state	N
Kawashima et al. (2015)	General cognitive state	P
Herrera et al. (2012)	Memory	P
Barnes et al. (2009)	General cognitive state	N
Tappen et al. (2014)	General cognitive state, memory, verbal fluency	General cognitive state: N Memory: P Verbal fluency: N
Oskoei et al. (2013)	General cognitive state, memory, attention	General cognitive state: N Memory: N Attention: P
Kurz et al. (2012)	Memory	P
Lee et al. (2009)	General cognitive state, memory	General cognitive state: N Memory: N
Han et al., (2014)	General cognitive state, memory	General cognitive state: N Memory: P
Cipriani et al. (2006)	General cognitive state	P
Kurz et al. (2009)	Memory	Memory: P(MCI patients only)
Cove et al. (2014)	General cognitive state	N

Combined exercise and cognitive intervention(n=3)		
Fiatarone Singh et al., (2014)	General cognitive state, executive function, memory	General cognitive state: N Executive function: N Memory: N (combined group only)
Coelho et al. (2013)	Executive function, attention	Executive function: P Attention: P
de Andrade et al. (2013)	Executive function, attention, memory	Executive function: P Attention: P Memory: N

Abbreviations: P=positive; N=negative

Ⅳ. Considerations and Conclusions

This systematic review investigated the effect of exercise, cognitive, combined exercise and cognitive intervention to improve cognitive functions in older adults with cognitive impairment and AD. 26 studies were identified in this review, most studies assessed general cognitive state such as MMSE or ADAS-Cog. Several studies indicated negative results included exercise, cognitive intervention, and combined exercise and cognitive intervention. In our results, especially, the effect of cognitive intervention is indeterminate. Several systematic reviews found that cognitive training can produce moderate-to-large beneficial effects to MCI subjects on memory-related outcomes. But the number of high-quality RCT remains low, and so further trials must be a priority (Gates, Sachdev, Fiatarone Singh, et al., 2011; Simon, Yokomizo & Bottino, 2012). The studies were published within the past 15 years (2000-2015). We found only 3 combined exercise and cognitive intervention studies. This suggests that research to assess the impact of combined physical exercise and cognitive intervention on cognitive functions in older adults is still in its fledgling stage.

Multiple physiologic mechanisms likely account for neuroprotective and neuroplastic effects of exercise on brain structures (Kirk-Sanchez & McGough, 2014). Many cardiovascular risk factors are associated with cognitive performance and risk for cognitive decline (Grodstein F, 2007). Exercise-mediated physiologic mechanisms include elevated neurotrophin levels, improved vascularization, facilitation of synaptogenesis, mediation of inflammation, and reduced disordered protein deposition (Radak, Hart, Sarga, et al., 2010; Intlekofer & Cotman, 2013). Gates and colleagues suggested that the efficacy of combining progressive resistance training and cognitive training two distinctly different training mechanisms (Gates, Valenzuela, Sachdev, et al., 2011)(figure 1). The mechanisms of benefit from individual and combined physical and cognitive interventions are not clear, it has been postulated that physical and mental activity may therefore have potential to stimulate plasticity of the brain and possibly reduce dementia onset (Intlekofer & Cotman, 2013).

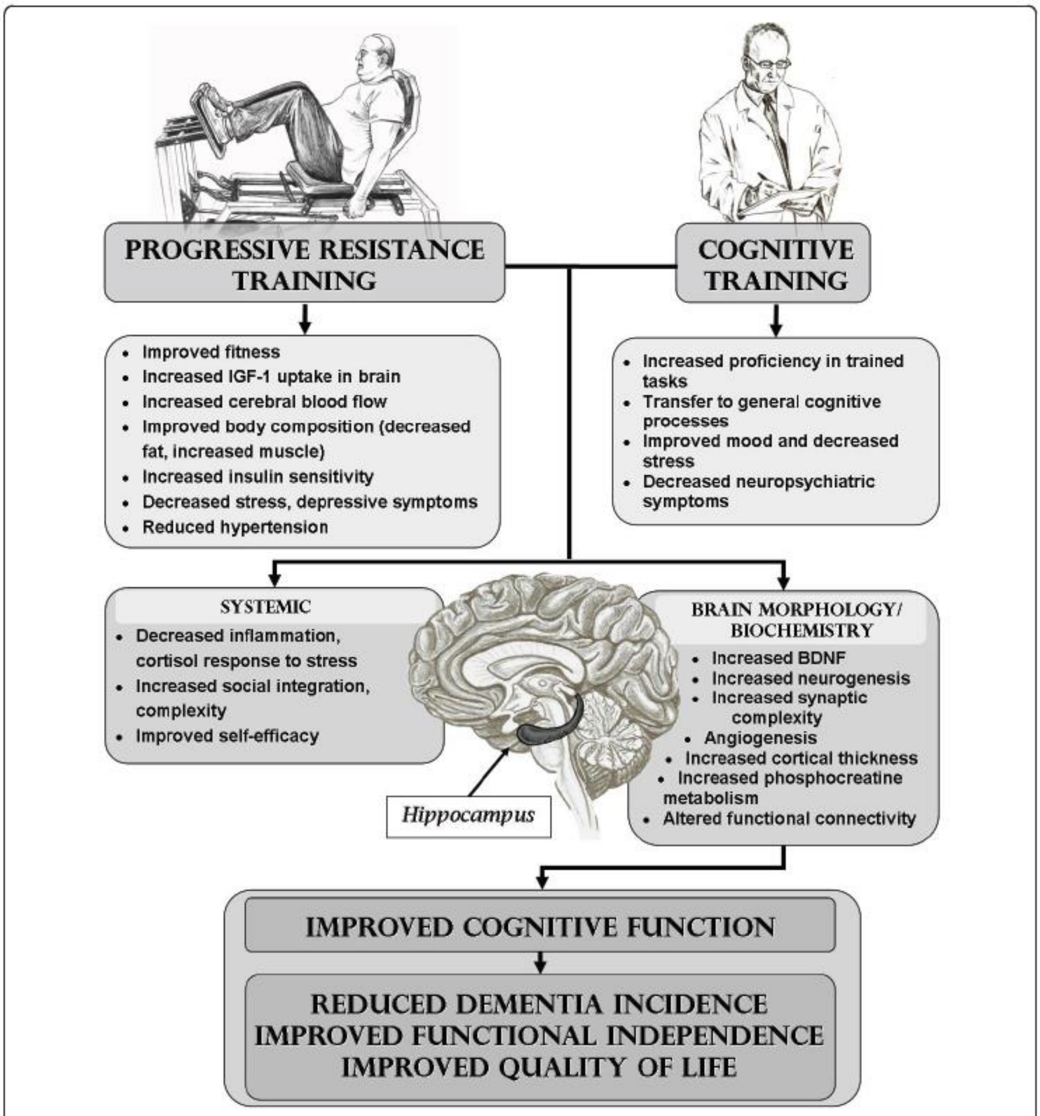

Figure 1 Theoretical model of mechanisms linkage between progressive resistance training, cognitive training, and cognitive and functional outcomes. BDNF = brain-derived neural growth factor IGF-1 = insulin-like growth factor-1.

<Figure 1> the mechanisms of combined exercise and cognitive intervention
source: Gates, Valenzuela, Sachdev, et al.(2011)

In the other hand, practically, the difference in effectiveness between single and multi-task interventions might be explained by people with dementia having difficulty performing dual tasks (Petterson, Olsson & Wahlund, 2007). Tappen and colleagues reported that participants were afraid of falling and needed considerable assistance with ambulation, or stopped walking when they were asked a question (Tappen, Williams, Barry, et al., 2002). The systematic review and meta-analysis by Pendlebury and Rothwell indicated that the poststroke dementia (PSD) prevalence rates range from 7%-41%; the lower percentage appearing in population-based studies of first-ever stroke patients, and the higher in hospital-based studies of recurrent stroke in which prestrike dementia was included (Melkas, Jokinen, Hietanen, et al., 2014). There are serious barriers to the assessment and treatment for patients with limited exercise capacity such as PSD. Standard treadmill testing can be difficult for any older adult with conditions limiting walking and is especially difficult in stroke survivors who have impairments in lower extremity strength and coordination (Potempa, Braun, Tinknell, et al., 1996). The exercise intervention is need to be well tolerated and safe in not only PSD patients but also very older adults with AD.

There are many non-pharmacological treatments not only cognitive intervention such as cognitive training, cognitive rehabilitation, or cognitive stimulation for older adults with cognitive impairment and AD. To facilitate the better management of cognitive impairment, recent attention has focused on the use of complementary and alternative medicine (CAM), together with Oriental and traditional medicines (Cooper, 2004). Kim and colleagues reported that the effect of CAM on cognitive function in AD although systematic review is small sample size (Kim, Cho, Lee, et al., 2015). But to the best of our knowledge, there is no study about combined physical exercise and CAM intervention for improved cognitive function.

Law and colleagues reported that combined cognitive and exercise interventions significantly improved general cognitive functions, memory, executive functions, attention and functional status in persons with MCI and AD or dementia. Studies with cognitively healthy populations also revealed significant benefits of combined cognitive and exercise interventions on general cognitive functions, memory and functional status compared to active control groups (Law, Barnett, Yau, et al., 2014). Environment enrichment takes into the account the crucial role played by the complex interaction between genetic factors and environmental modifiers in the etiology and progression of brain and psychiatric disorders (Burrows, McOmish & Hannan, 2011). Combination therapy may be play an important role in enhancing cognitive function. It is unclear the effectiveness of multicomponent cognitive interventions such as combined cognitive intervention and CAM, or combined exercise intervention and CAM, and also comparison between those strategies.

In conclusion, the beneficial effects between exercise, cognitive intervention, and combined exercise and cognitive intervention in enhancing cognitive function still not remain to be satisfactorily explained. But these results offer more invenstigation of combined exercise and cognitive intervention. More research is needed to study the effect of combined non-pharmacological interventions in older adults with cognitive impairment.

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