There are emerging calls to investigate the benefits of combining interventions. Eight studies were identified and were assessed as medium to high quality. Study characteristics were identified to promote fidelity of future studies. Combined training can improve cognitive functions and functional status. More well-designed studies with active control group comparison are needed.
Title: Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A Systematic Review

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Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A Systematic Review

Abstract

Global concern on the potential impact of dementia is mounting. There are emerging calls for studies in older populations to investigate the potential benefits of combining cognitive and exercise interventions for cognitive functions. The purpose of this systematic review is to examine the efficacy of combined cognitive and exercise training in older adults with or without cognitive impairment and evaluate the methodological quality of the intervention studies. A systematic search of Cinahl, Medline, PsycINFO, ProQuest, EMBASE databases and the Cochrane Library was conducted. Manual searches of the reference list from the included papers and additional internet searches were also done. Eight studies were identified in this review, five of which included a cognitively impaired population and three studies included a cognitively healthy population. The results 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. However, limited evidence can be found in populations with cognitive impairment when the evaluation included an active control group comparison. Further well-designed studies are still needed to explore the potential benefits of this new intervention paradigm.

Keywords: Systematic review, Cognitive impairment, Healthy older adults, Combined intervention, Dual-task exercise
1. Introduction

The increasing prevalence of cognitive impairment with age intensifies the potential impact upon global health and health care. It has been projected that there will be 7.7 million new cases of dementia each year, implying a new case of dementia every 4 seconds (WHO and ADI, 2012). The World Health Organization (WHO) has urged global efforts to take a serious focus on the potential impacts of dementia on the societal and health care systems worldwide. Individuals with mild cognitive impairment (MCI) are at high risk of progressing to Alzheimer’s diseases and other dementias, with reported conversion rate of 50% in 2-3 year (Amieva et al., 2004) and even up to 60%-100% in 5 to 10 years (Morris et al., 2001; Petersen et al., 2004). Addressing the lack of pharmacological treatment for individuals with MCI (Alzheimer’s Association, 2013), it is critical to explore the potential effects of non-pharmacological interventions.

The benefits of exercise on cognition are widely recognized (Cotman and Berchtold, 2007; Kramer and Erickson, 2007; van Praag, 2009). Animal studies have consistently shown exercise increases cell proliferation and neurogenesis in the dentate gyrus of the hippocampus (Fabel et al., 2003; Kronenberg et al., 2006), an important brain area for learning and memory. Exercise regulates a number of growth factors such as brain-derived neurotrophic factor (BDNF), which plays a crucial role in neuroprotection and synaptic plasticity (Adlard et al., 2005; Vaynman et al., 2004); insulin-like growth factor 1 (IGF-1), which promotes neuronal growth and improves cognitive performance (Cotman and Berchtold, 2002; Liorens-Martin et al., 2010); vascular endothelial growth factor (VEGF), which stimulates angiogenesis and
vasculogenesis (Tang et al., 2010; Zhang et al., 2013) and promotes brain ischemic tolerance (Zhang et al., 2011). Furthermore, exercise reduces inflammatory cytokines and oxidative stress, which suggests anti-inflammatory and antioxidant effects on the brain (Pervaiz and Hoffman-Goetz, 2011; Santin et al., 2011).

Colcombe et al. (2006) also found that exercise correlates with an increase in brain volume over the frontal, parietal, and temporal cortices in humans. Studies also have shown that exercise can promote cerebral blood flow which enhances neurogenesis and improves learning (Farmer et al., 2004; van Praag et al., 2005), as well as promotes cardiovascular fitness and therefore reduces peripheral risk factors (e.g. hypertension) for cognitive decline (Cotman et al., 2007; Pereira et al., 2007).

Whilst the uniqueness of exercise-induced effects to enhance brain health and cognitive functions through multiple routes is evident, results of intervention studies on single exercise intervention are disappointing (Busse et al., 2009; Etnier et al., 2006). A recent systematic review showed that strong evidence to support the effects of exercise interventions on cognitive functions of older adults is still lacking (Snowden et al., 2011).

It has been proposed that exercise has to occur in the context of a cognitively challenged environment in order to be effective for inducing neural and cognitive benefits rather than exercise alone (Fabel and Kempermann, 2008; Fabel et al., 2009). Studies also 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 and Kempermann, 2008; Fabel et al., 2009; Olson
et al., 2006). An animal study reported significant improvements in cognitive ability when combined physical and cognitive training was undertaken (Langdon and Corbett, 2012). A combination of exercise and cognitive interventions, either sequentially or simultaneously, appears to have the potential effect to maintain or improve cognitive functions (Langdon and Corbett, 2012; Schaefer and Schumacher, 2011). Indeed, there are emerging calls for studies in older populations to investigate the potential benefits of combined cognitive and physical interventions to accomplish an optimal outcome (Amoyal and Fallon, 2012; Kraft, 2012; Rebok et al., 2008; Thom and Clare, 2011).

The aims of this review were: (1) to assess the efficacy of combined cognitive and exercise training to improve cognitive functions in older adults with and without cognitive impairment; (2) to examine the methodological quality of the included studies; and (3) to summarize the latest results on combined cognitive and exercise training in older adults with or without cognitive impairment.

For the purpose of this review, combined cognitive and exercise interventions are structured interventions that combine cognitive training and exercise, either conducted in sequence or simultaneously under dual-tasking paradigms. Cognitive training are defined as structure repeated practice on tasks with an inherent problem, using standardized tasks targeting specific cognitive domains and/or teaching strategies and skills in order to optimize cognition and functioning (Clare and Woods, 2003; Martin et al., 2006). Exercise is defined as a form of physical activity that is planned, structured and repetitive over an extended period of time, with the purpose to improve fitness, performance or health (Casperson et al., 1985).
2. Methods

2.1 Search Strategies

A systematic computer-based search of Cinahl, Medline, PsycINFO, ProQuest, EMBASE databases and the Cochrane Library was conducted for the time period between January 1995 and June 2013. The following search terms were used: (combine* interventions OR rehabilitation OR dual-task OR multi-modal) AND (exercise OR physical activity OR resistance training OR endurance training) AND (cognitive training OR cognitive-motor OR mental) AND (cognitive impairment OR cognit* OR dement* OR Alzheimer*). The search was limited to publications in English. All reference lists in selected journal articles were further screened and additional internet searches using the same search terms were conducted on Google Scholar to identify additional potentially relevant articles.

2.2 Inclusion/exclusion Criteria and Selection Process

As recommended in the Cochrane Handbook of Systematic Review of Interventions, two reviewers (LL and FB) independently screened the titles and abstracts to identify relevant articles and potentially relevant studies. Disagreements between the reviewers about inclusion were resolved through discussion (Higgins and Green, 2011). 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) sample population: older adults (aged 60 and older) with or without cognitive impairment/decline or dementia but no mental or neurological disorders other than
dementia, such as stroke or major depression; (3) intervention: combined cognitive and exercise training; and (4) outcome: cognitive functions assessed using neuropsychological tests as primary or secondary outcomes. Articles were excluded if they were: (1) non-intervention studies; (2) theoretical articles or descriptions of treatment approaches; (3) review articles; (4) unpublished studies, abstracts or dissertations; (5) articles without adequate specification of interventions; (6) non-peer reviewed articles and book chapters; and (7) non-English language articles. Multicomponent intervention studies which did not distinguish the contribution of combined cognitive and physical exercise component on the effects were also excluded.

2.3 Data Extraction and Analysis

Data were extracted using a data extraction form for the description of methodology and important trial characteristics including study populations, intervention type, training delivery, volume of training, outcome measures, and follow-up. This review focused on a description of the studies and their results, and on qualitative synthesis of the findings. However, Cohen’s d effect sizes (Cohen, 1988) for cognitive and functional outcomes at pre- and post-intervention were derived on the basis of reported statistics. The standard effect sizes were calculated by dividing the mean score differences of the combined intervention and control groups in each study by the pooled estimate standard deviation for the two groups. When means and standard deviations were not available, effect sizes were computed from the reported P-value or F-values reported in the study (Thalheimer and Cook, 2002). The 95% confidence intervals (CIs) were also derived to compare groups before and after the intervention. (Practical effect size calculator retrieved March 9, 2013 from

Practical effect size calculator retrieved March 9, 2013 from
http://gunston.gmu.edu/cebcp/EffectSizeCalculator/d/means-and-standard-deviations.html). Effect sizes were interpreted as small, \( d = 0.20 \); medium, \( d = 0.50 \); or large, \( d = 0.80 \) (Cohen, 1988).

2.4 Quality Assessment

Methodological quality of the included studies was independently assessed by 2 reviewers (LL and FB) using a 13-item checklist modified from the Delphi list (Verhagen et al., 1998), the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003) and the “Design-specific criteria to assess for risk of bias” by the Agency for Healthcare Research and Quality (AHRQ) (Viswanathan et al., 2012). Any disagreements identified between the two reviewers were resolved by a third reviewer (MY) as a final decision. Details of the quality checklist and the rating criteria are presented in Appendix 1.

All items on the list applied to both RCT and non-RCT. A quality score ranging from 0 to 13 was calculated for each study. The scale is only used to provide a quantitative reference of the degree/likelihood that the reported methodology and results of the included studies are approaching free of bias. As a summary on quality, a study was defined as: (1) High quality when presenting a positive score on 10 or more items; (2) Medium quality when presenting a positive score on 7-9 items and (3) Low quality when presenting a positive score on <7 items (<50% of the maximum attainable score) (Verhagen et al., 2007; Viswanathan et al., 2012).

3. Results
3.1 Study Selection

A summary of the selection process is illustrated in Figure 1. The initial database search identified a total of 572 potentially relevant citations with 73 from Cinahl, 41 from Medline, 230 from PsycINFO, 35 from ProQuest, 89 from EMBASE and 104 from Cochrane Library. After excluding duplicated articles, 474 citations were left. All titles and abstracts were screened according to the inclusion/exclusion criteria described and 461 articles were discarded.

The common reasons for exclusion of articles were the following: the interventions were not combined exercise and cognitive intervention (80), they were not intervention studies or were reviews/theoretical articles (158), they did not include the target population under this review (213), and did not include cognitive outcomes (10). Full texts of 13 articles were retrieved from the initial database search and carefully examined. Cross-referencing led to three more articles and the internet search using the same search terms identified three more articles. A total of 19 articles were finally retrieved for full text screening.

After further screening with the inclusion/exclusion criteria, 11 articles were discarded as four articles used exercise only or did not use combined exercise and cognitive interventions (Burgener et al., 2008; Heyn, 2003; Komai and Yamada, 2012; Onor et al., 2007); three were on-going studies (Gates et al., 2011; Gillette-Guyonnet et al., 2009; O’Dwyer et al., 2007); one did not include cognitive outcomes (Doi et al., 2013); two were a second paper reporting a data set from the same study (Coelho et al., 2013; Fabre et al., 1999); and one did not distinguish the effects of the combined cognitive and physical training in the study (Shatil, 2013). A total of eight studies were therefore included for this review.
3.2 Study Characteristics

Of the eight studies reviewed, three studies (1 RCT and 2 non-RCTs) included a population of cognitively healthy older adults (Fabre et al., 2002; Legault et al., 2011; Oswald et al., 2006). Four studies (2 RCT and 2 non-RCTs) included a population of people with cognitive impairment including dementia (Schwenk et al., 2010), Alzheimer’s disease (AD; Coelho et al., 2012) and mild cognitive impairment (MCI; Kounti et al., 2011; Suzuki et al., 2012). One RCT included a population of people with cognitive complaints (Barne et al., 2013).

Cognitive complaints have been found to be associated with decreased performance in objective memory and executive function tests (Rouch et al., 2008). Neuroimaging studies have also shown people with subjective cognitive complaints have structural brain changes similar to persons with mild cognitive impairment and different from those of healthy people (Saykin et al., 2006; van der Flier et al., 2004). Therefore, for this review, the identified study which included a population with cognitive complaints (Barne et al., 2013) was reported under the studies with cognitively impaired population. Tables 1 and 2 illustrate the intervention characteristics of the reviewed studies in cognitively healthy populations and older adults with cognitive impairment respectively. Table 3 and 4 illustrate the study characteristics as reported by outcome measures and effect sizes of the reviewed studies.

3.3 Participants and settings

3.3.1 Studies with cognitively healthy participants
The number of cognitively healthy people (total 480) in the studies varied from 32 (Fabre et al., 2002) to 375 (Oswald et al., 2006). The mean age of the study populations ranged from 61.9 (Fabre et al., 2002) to 79.5 (Oswald et al., 2006) years. Only one study performed cognitive screening using the modified Mini-mental Status Examination (modified MMSE) at baseline (Legault et al., 2011). One study was conducted in France, one in Germany and one in United States.

3.3.2 Studies with cognitively impaired participants
The number of people with cognitive impairment (total 322) varied from 27 (Coelho et al., 2012) to 126 (Barnes et al., 2013). The mean age of the study populations ranged from 67.8 (Kounti et al., 2011) to 82.3 (Schwenk, et al., 2010) years. Four studies used the Mini-mental Status Examination (MMSE) score as a baseline measure of cognitive function, with an average score of 22.5 ranging from 15.4 (Coelho et al., 2012) to 29.6 (Kounti et al., 2011). One study used the modified MMSE score with a mean score of 94.4 (Barnes et al., 2013). One study was conducted in Germany, one in Brazil, one in Greece, one in United States and one in Japan.

3.4 Intervention Duration and Group Comparison
3.4.1 Studies with cognitively healthy participants

Table 1 presents the characteristics of interventions for cognitively healthy older adults. The total time of intervention varied from 38 (Fabre et al., 2002) to 67.5 (Oswald et al., 2006) hours, while the intervention duration ranged from two months (Fabre et al., 2002) to one year (Oswald et al., 2006). Two studies were four-arm controlled trials comparing the combined cognitive and exercise training, single cognitive training, single exercise training and control groups (Fabre et al., 2002; Legault et al. 2011). Fabre et al. (2002) used no treatment control and Legault et al. (2011) used health education control. One study was a six-arm controlled trial comparing combined cognitive and physical training, combined psycho-educational and physical training, single cognitive training, single psycho-educational training, single physical training and no treatment control groups (Oswald et al., 2006).

3.4.2 Studies with cognitively impaired participants

Table 2 presents the intervention characteristics for older adults with cognitive impairment. The total time of intervention varied from 30 (Kounti et al., 2011) to 120 (Suzuki et al., 2012) hours, and the intervention duration ranged from three months (Barne et al., 2013; Schwenk et al., 2010) to one year (Suzuki et al., 2012). One study (Barne et al., 2013) was a four-arm controlled trial comparing the combined mental activity and exercise training; mental activity and exercise control; mental activity control and exercise; and mental activity control and exercise control. Four studies were two-arm controlled trials comparing a single dual task intervention group with a control group, including motor placebo (Schwenk et al., 2010), no treatment (Coelho et al., 2012), waitlist (Kounti et al., 2011) and health education (Suzuki et al., 2012).
3.5 Intervention Programs

3.5.1 Studies with cognitively healthy participants

All three reviewed studies used combined cognitive and physical training sessions in sequence. All interventions were center-based, with one study also including a home-based walking program (Legault et al., 2011). The content of cognitive training included computer-based memory training (Legault et al., 2011); processing speed, attention and memory training (Oswald et al., 2006) or structured multicomponent cognitive training (Fabre et al., 2002). In regards to the exercise sessions, two studies used aerobic exercise (Fabre et al., 2002; Legault et al., 2011); and one study used balance and flexibility training (Oswald et al., 2006).

3.5.2 Studies with cognitively impaired participants

Of the five reviewed studies, four studies used dual-task training within the exercise sessions (Coelho et al., 2012; Kounti et al., 2011; Schwenk et al., 2010; Suzuki et al., 2012). One study used combined cognitive and physical training by including an independent home-based computer cognitive training plus a supervised center-based exercise training (Barnes et al., 2013). Regarding the exercise components, three studies included aerobic and strength training which targeted exercise intensity (Barnes et al., 2013; Coelho et al., 2012; Suzuki et al. 2012); one study included resistance and balance training (Schwenk et al., 2010) and one study included walking and movement-based exercise (Kounti et al., 2011). In regards to the dual-task components, three studies (Coelho et al., 2012; Schwenk et al., 2010; Suzuki et al., 2012) involved performing motor tasks (e.g. walking, throwing/bouncing ball) and concurrent cognitive tasks (e.g. calculation, naming or reacting to verbal command).
One study (Kounti et al., 2011) conducted dual-task training using cognitive-based kinetic exercise with visual and verbal cues (e.g. wreath, boards with letters, balls and rings).

3.6 Outcome measures and intervention effects

3.6.1 Studies with cognitively healthy participants

Table 3 presents the outcomes, key findings and effect sizes of the reviewed studies in cognitively healthy persons. Two studies measured general cognitive functions, with one study reporting significant improvement in the cognitive function composite score, and sustained at five-year follow-up (Oswald et al., 2006). Two studies assessed memory performance, with one study showing a significant effect on the Wechsler Memory Scale (Fabre et al., 2002). One study also included subjective measures of cognitive impairment, functional status and everyday competence (Oswald et al., 2006) and found significant improvements in cognitive impairment (Sandoz clinical assessment geriatrics) at follow-up as well as in functional status (Independent living composite score) at post-intervention and at five-year follow-up. Only one study assessed executive functions but found no effects (Legault et al. 2011).

3.6.2 Studies with cognitively impaired participants

Table 4 presents the outcomes, key findings and effect sizes of the reviewed studies in people with cognitive impairment. Two outcomes, executive functions (in 4 out of 5 studies) and attention/processing speed (in 4 out of 5 studies), were commonly used in the reviewed studies. Two studies reported significant improvements in executive functions from Frontal Assessment Battery and Clock Drawing Test (Coelho et al., 2012) in AD and Rey-Osterrieth Complex Figure Test (Kounti et al., 2011) in MCI.
These two studies also found significant effects on attention/processing speed from Symbol Search Subtest of Wechsler Adult Intelligence Scale III (Coelho et al., 2012) and Test of Everyday Attention (Kounti et al., 2011).

Three studies included measures of Verbal Fluency for language performance, with two studies of MCI finding significant improvements (Kounti et al., 2011; Suzuki et al., 2012). Kounti et al. (2011) and Suzuki et al. (2012) also examined general cognitive functions and both found significant improvements on Mini-mental state examination (MMSE) scores. Three studies assessed memory performance, however only one study of MCI showed significant effects on immediate recall of Wechsler Memory Scale-Revised (Suzuki et al., 2012). One study of MCI also used subjective measure of functional status (Functional Rating Scale of Symptoms of Dementia) which showed significant improvement (Kounti et al., 2011). One study measured dual-task cost (DTC) in participants with dementia and observed significant effect on DTC combined motor-cognitive performance (Schwenk et al., 2010).

3.7 Methodological Quality of included studies

The results of the methodological quality assessment are presented in table 5. The reviewed studies fulfilled 7 to 11 quality criteria out of the maximum of 13 items. Only one RCT (Schwenk et al., 2010) performed a concealed randomization and was the only study that had both rater and subject blinded. However, this was the only one study that did not use intention-to-treat in data analysis. Three RCT (Barnes et al.,
2013; Legault et al., 2011; Suzuki et al., 2012) did not state whether the random allocation was concealed, with two (Legault et al., 2011; Suzuki et al., 2012) did not report the method of random sequence generation. The RCT by Legault et al. (2011) was stated as single-blinded but did not report the party which was blinded. Two RCT (Barnes et al., 2013; Suzuki et al., 2012) and one other non-RCT (Kounti et al., 2011) reported rater-blinded. One study (Oswald et al., 2006) recruited a random sample but the group allocation was not random.

All the included studies reported eligibility criteria, baseline similarity, same follow-up length, pre-specified outcomes as well as point measures and measures of variability for the primary outcome measures. Seven of the eight studies achieved outcome measures from more than 85% of the participants initially allocated to groups at least at one time point of measures. Main methodological shortcomings or bias identified included no or inadequate randomization, non-concealed allocation, lack of blinding and unclear reliability of outcomes measures in some studies. All studies fulfilled the criteria for 7 or more quality items, with one (Schwenk et al., 2010) meeting 11 out of 13 quality criteria. Therefore, seven of the reviewed studies were considered to be of medium quality and one was assessed as high quality.

[INSERT TABLE 5 ABOUT HERE]

Overall, the results of the reviewed studies in both populations with and without cognitive impairment were conflicting. Among the three studies with cognitively healthy participants, one study found no effects while two studies revealed significant
effects. Fabre et al. (2002) reported a significant effect on memory performance ($d = 1.29$). Oswald et al. (2006) found significant effects, with within-group effect sizes reported, on general cognitive functions ($d_w = 1.14$), subjective rating of cognitive impairment ($d_s = 0.59$) and functional status ($d_f = 0.27$), which were sustained at 5-years follow-up.

Among the five studies with cognitively impaired participants, one study found no effect while four studies reported significant improvements in outcomes including cognitive-motor dual-task cost ($d = 0.99$) in dementia; executive functions ($d = 0.52 – 1.18$) and attention ($d = 0.24 – 1.57$) in MCI and AD; general cognitive functions ($d = 0.11 - 0.63$), language ($d = 0.22 – 0.62$), memory ($d = 0.16$) and subjective rating of functional status ($d = 0.59$) in MCI.

4. Discussion

This systematic review examined the efficacy of combined cognitive and exercise training to improve cognitive functions in older adults with and without cognitive impairment. Eight studies were identified in this review, five of which included a population with cognitive impairment and three studies included a population without cognitive impairment. The paucity of research in this area was obvious, particularly among the wide progressively degenerating cognitive continuum in populations with cognitive impairment (Petersen, 2004). The studies were published within the past ten years (2002 to 2013). This suggests that research to assess the impact of combined cognitive and physical exercise on cognitive functions in older adults is still in its fledgling stage. The identified studies were from a variety of mainly developed countries. The potential benefits of a combined intervention appears to be attracting
the interest of researchers throughout the world however more studies are needed before generalization of reliable evidence can be reached, especially in developing countries.

The results of this 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. Significant improvements were found in two out of the three studies with cognitively healthy populations and in four out the five studies with cognitively impaired populations. The limited number and heterogeneity of the reviewed studies do not enable any firm conclusion to be drawn. Nevertheless, specific study characteristics can be identified in this review that may help to promote intervention fidelity in future studies.

4.1 Comparison and control group design

Appropriate design of the comparison and control groups is important to allow critical investigation on the comparative effectiveness between the specific components of an intervention and other components or common conditions being studied (Hart et al., 2008; Kinser and Robins, 2013).

In cognitively healthy populations, Fabre et al. (2002) found the combined training demonstrated significant improvement in memory compared to either single memory or aerobic training alone. Oswald et al. (2006) showed the combined cognitive and physical training improved general cognitive performance and subjective measures of functional status compared to a no treatment control, and proved more promising than the single training groups. The multi-arm comparison group design in these studies allow a clear comparison between the unique component in the combined intervention
and the common components (single cognitive or exercise training) in the comparison
groups as well as the non-specific components (staff exposure or social contact) in
the control group. This design can greatly strengthen the validity and credibility of the
findings in the studies. Nevertheless, the exposure to interventions varied between the
combined and single interventions.

In a population with cognitive complaint, Barnes et al. (2013) also used a multi-arm
comparison group design and the intervention time were the same among all the
intervention and comparison groups. However, no significant differences were
observed between the intervention and the comparison groups. The authors believed
that both the active- control activities and the placebo-control activities may be
beneficial to the participants and have potential impact on the outcomes. Therefore, a
larger sample size would be required to have adequate power for detecting significant
group differences (Baskin et al., 2003; Hart et al., 2008).

All the other four studies with cognitively impaired populations that used a dual- task
exercise group compared with a control group reported significant findings. It can be
challenged that the improvements observed in the studies may not be attributed to the
interventions or, more precisely, the specific component of the intervention. The use
of a no-treatment group by Coelho et al. (2012) may control for the effects of time
and the effects of repeated testing on outcome measures. The use of a waitlist group
by Kounti et al. (2011) may also control for the effects from an expectancy of
improvement. The use of health education by Suzuki et al. (2012) may further control
for other non-specific treatment effects (e.g. social contact) but the three sessions’
contact time was far less than the 120 hours’ intervention time, which may lead to
ineffective control of the non-specific moderators by the control group (Hart et al.,
2008; Safer et al., 2006). Schwenk et al. (2010) compared the intervention group with a low intensity exercise group. This may allow for a further comparison on the effects from the difference in exercise intensity. Studies have found that moderate intensity aerobic exercise is more effective for improving cognitive function than low intensity exercise (Colcombe and Kramer, 2003), whereas combined aerobic and strength training has a greater effect compared to single mode exercise training (Erickson and Kramer, 2009). A good comparison control should omit the unique intervention component under investigation, while possessing the common ingredients in equal measure (Safer et al., 2006). Although positive findings were reported in all the four studies used dual-task training as intervention, it can still be questionable whether the improvements were all attributed to the dual-task components. An appropriate comparison with the potential beneficial components or moderators is important to validate the differential effects under the investigation. As a result, appropriate activity selection in comparison control and a well-designed comparison group are crucial in future studies on the efficacy of combined interventions.

4.2 Study population screening
Cognitive impairment/dementia may be caused by multiple intertwined pathological factors (Stewart, 2002). Neurodegenerative conditions such as AD and cerebrovascular disease, including subclinical brain injury, silent brain infarction, and clinically overt stroke, are the most common causes of cognitive impairment/dementias in older individuals (Alzheimer’s Disease International 2009; Gorelick et al., 2011). Vascular dementia (VaD) is the second most common form of dementia after AD, accounting for 20-30% of the diseased population (Stewart, 2002). Importantly, there is increasing evidence that vascular pathology frequently co-exists with neurodegenerative pathology and most dementias have both vascular and
neurodegenerative features (Dichgans and Zietemann, 2012; Neuropathology Group, 2001). More than 30% of AD population has been found to have cerebrovascular pathology (Roman, 1999). The pathogenic importance of vascular contributions in cognitive impairment and dementia merits particular attention in diagnosis and screening for study populations.

Among the reviewed studies in populations with cognitive impairment, Suzuki et al. (2012) used the criteria by Petersen et al. (2001) for diagnosis of aMCI population. Kounti et al. (2011) used the criteria of Petersen et al. (2001) and Artero et al. (2006) for multi-domain MCI and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorder Association (NINCDS-ADRDA) for dementia (McKanhnn et al., 1984). Both of these studies performed neuroimaging examination, in addition to neuropsychological tests and medical history, to confirm a diagnosis and reported exclusion of persons with stroke. No information was reported on the pathological nature of cognitive impairment in the population selected. Coelho et al. (2012) did not report on the diagnostic details for the population selection, but used the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria (American Psychiatric Association 2000) for diagnosis of Alzheimer’s disease, which also excluded those with cognitive deficits due to cerebrovascular disease. Barnes et al. (2013) also excluded those with other neurological conditions in their study with a cognitive complaint populations. The diagnosis was based on interview, physician diagnosis and neuropsychological assessment. Indeed, cerebrovascular pathologies, such as stroke, have been found to be typically associated with VaD, (De la Torre, 2002). Studies have shown that cerebral infarcts (covert or overt) are additive with Alzheimer’s disease pathology in that cerebral ischemia worsens the effects of AD on cognitions (Esiri et al., 1999;
Only one study (Schwenk et al., 2010) considered the vascular nature of dementia by including the criteria for the diagnosis of dementia and VaD, based on both the NINCDS-ADRDA (McKanhnn et al., 1984) and the National Institute of Neurological Disorders and Stroke-Association International pour la Recherche en l’Enseignement en Neurosciences (NINCDS-AIREN; Roman et al., 1993). However, the authors did not report on any neuropathology evaluations or methods for operationalization of the screening criteria. Silent infarct also has been found to influence cognition even in normal aging (Vermeer et al., 2003). Nevertheless, in the reviewed studies with cognitively healthy population, no studies addressed or investigated the potential impact of silent vascular contribution to cognition in normal persons.

Studies have shown that the presence of vascular lesions contributes to the severity of cognitive impairment (Snowden et al., 1997; Riekse et al., 2004; Petrovitch et al., 2005). Different subgroups may have different cognitive deficits and responses to treatments associated with the differences in etiologies (Gorelick et al., 2011; Moorhouse and Rockwood, 2008). Identifying the causes of cognitive impairment/dementia is of particular importance in the investigation for effective preventative and treatment strategies (Stephen et al., 2009). Clear identification and report on the specific nature of the study population selected (neurodegenerative, vascular, mixed pathology) will be crucial to facilitate cross study comparison and generalization of study findings.

4.3 Training sequence in combined intervention

The sequence in delivering the cognitive training and exercise training sessions on
combined training may have a potential impact on the intervention outcomes. Legault et al. (2011) found no intervention effects when the physical training was delivered after the cognitive training. Oswald et al. (2006) however found positive intervention effects with the physical training sessions delivered before the cognitive training for half of the intervention period. Animal studies found that exercise promotes neurogenesis in the brain and improves learning (Farmer et al., 2004; van Praag et al., 2005). Neuroimaging studies in populations with cognitive impairment reported that compensatory recruitment of new brain areas were observed during the performance of a demanding task (Reuter-Lorenz et al., 2005; Belleville et al., 2011). Fabel et al. (2009) proposed that the exercise in combined training prepares the potential of the brain for increased neurogenesis upon additional exposure to cognitive enrichment. In a recent animal study on the effects of combined training with positive findings, the physical activity was set to precede the cognitive training or the participants were re-exposed to cognitive training after physical training (Langdon and Corbett, 2012). It appears more favorable to have the exercise sessions delivered before the cognitive training session, in order to better prepare the brain for the compensatory recruitment process in the subsequent cognitive training sessions. Nevertheless, more intervention studies are needed to systematically reveal the potential impacts of training sequence on training outcomes.

4.4 Dual-task component

The high quality RCT by Schwenk et al. (2010) found significant improvement in dual- task performance only under complex dual task conditions. The patients needed to be adequately challenged to reach the effects. It was reported that higher basic DTC were associated with a higher percentage of improvement in DTC. This highlights the
importance of adjusting the level of the training tasks to meet individual capacity in intervention design, thus making optimal use of an individual’s latent potential (Hertzog et al., 2009).

Although the findings from using dual-task intervention are encouraging, the results need to be interpreted with caution. It has been challenged that the similarity of the dual-tasks assigned in the interventions and the assessment tasks may produce a learning effect ultimately affecting the reliability of the outcome results (Pichierri et al., 2011). Therefore, selection of alternative dual-tasks should be considered in future studies using dual-task exercise.

4.5 Intervention period

Suzuki et al. (2012) reported significant group effects on general cognitive function and memory at 6 months which were not demonstrated in the MCI population at 12 months treatment end. The intervention period in the study of Suzuki et al. (2012) was the longest compared to that in other studies (3-5 months) with cognitively impaired participants. A previous meta-analysis has found negative association between the training duration and the cognitive intervention effect on persons with MCI and suggested that studies with longer sessions and longer duration of total sessions would produce smaller effect sizes (Li et al., 2011). As revealed by the study results in this review, an intervention period of three to six months has shown to be more favorable than a longer intervention period in populations with cognitive impairment. Nevertheless, the moderating effect of program duration for cognitively impaired populations may need to be examined in future studies.

4.6 Outcome measure selection
The studies by Suzuki et al. (2012) in amnestic MCI and Barnes et al. (2013) in participants with memory complaints did not find any effects on executive functions. In contrast, the studies by Coelho et al. (2012) in AD participants and Kounti et al. (2011) in MCI participants found significant improvements in executive functions and attention. Impairments in executive functions have been found in people with cognitive complaint (Rouch et al., 2008), amnestic and non-amnestic MCI (Reinvang et al., 2012) and AD (McGuinness et al., 2010). Executive function deficits have consistently been found to predict AD conversion (Ritchie et al., 2001; Tabert et al., 2006) although it remains unclear how executive functions are impaired in amnestic MCI (Bisiacchi et al., 2008; Marshall et al., 2011). Therefore, it is important to include executive functions as one of the intervention outcomes in studies with cognitively impaired populations. Nevertheless, the changes in executive functions could be so subtle that some of the widely used executive function tests may not be sensitive enough to detect the minimal changes (Espinosa et al., 2009; Pickens et al., 2010). Moreover, the diversity of components under the umbrella of executive functions (Miyake et al., 2000) may further complicate the difficulty in assessing executive functions. The approach to use multiple outcome measures, as that in the study by Kounti et al. (2011), may be helpful but care must be taken to balance the assessment burden on the participants (Pickens et al., 2010). The selection of outcome measures with appropriate sensitivity and specificity to the study population should be of primary concern in future studies (Karrasch et al., 2005; Parra et al., 2012).

4.7 Visual-spatial component

Kounti et al. (2011) was the only study that used dual tasks with visual-spatial stimuli. Studies have found that both MCI and AD patients show deficits in visual spatial function (Iachini et al., 2009; Possin, 2010) which is also one of the predictors of
conversion to dementia of persons with MCI (Amieva et al., 2004; Griffith et al., 2006). Indeed, visual spatial function is a very important cognition in everyday functioning, for instance, navigating a car safely in driving or searching the routes in a new environment. Subtle declines in this ability would impose a great impact on everyday livings in elderly populations (Alescio-Lautier et al., 2007; Iachini, et al., 2009; Possin, 2010). Studies have found that visual spatial ability can be trained through practice (Jaeggi et al., 2008; Wright et al., 2008). Therefore, including visual spatial components in interventions as well as in outcome measures are highly recommended in future studies.

4.8 Generalization of training effects

Training effects can reflect real benefits and practical values of an intervention only if the results of the intervention can be generalized to other non-trained tasks, settings and sustained over time (Boelen et al., 2011; Glasgow et al., 2003). Previous cognitive training studies have shown improvements in training-related outcomes but limited generalization to non-trained tasks (Noack et al., 2009; Simon et al., 201). The generalizability of the intervention results to everyday functioning is regarded as an important implication of success (Glasgow et al., 2003; Lambert et al., 2010).

In the reviewed studies with a cognitively healthy populations, Legault et al. (2011) assessed the impact of combined training on non-trained cognitive domain (executive function) but found no significant effects. Oswald et al. (2006) reported positive generalization of the intervention effects in functional status and emotional status, which was also sustained over time at 5-year follow up. However, the assessment tools involved were non-standardized subjective ratings.
In populations with cognitive impairment, all of the five reviewed studies used neuropsychological assessments to assess training-related cognitive domains including attention, language and executive functions. Only Kounti et al. (2011) also included the Functional Rating Scale of Symptoms of Dementia (FRSSD) and the Functional Cognitive Assessment Scale (FUCAS) to assess functional status, and found positive post-intervention effects for FRSSD, which is an informant-report rating. Nevertheless, traditional psychometric tests have been challenged for not being able to adequately reflect older adults’ functioning in a real everyday context where the demands may be different to that in a test environment (Law et al., 2012; Marsiske and Willis, 1995). More ecologically validated tests should be included to examine the practical translation of intervention effects.

The ability to maintain independent living in the community is of particular importance for most elderly adults (Mack et al., 1997). Studies have shown that persons with cognitive impairment have difficulties in daily functioning, especially in complex everyday tasks that rely heavily on memory and reasoning (Aretouli and Brandt, 2010; Péres et al., 2006). This imposes a potential impact on the safety and quality of life of the person with cognitive impairment (Gauthier et al., 2006; World Health Organization and Alzheimer’s Disease International, 2012). It will be of utmost importance for future intervention studies to include ecological tests and investigate the generalizability of training effects to real world functional outcomes.

Overall, more well-designed studies, with special attention to comparison control and population screening, outcome selection, training sequence, intervention period and generalizability of outcomes, are still needed to reveal the differential effects of combined cognitive and exercise training especially in older population with cognitive
impairments. In the absence of a cure for cognitive impairment or dementia, further research efforts are needed to explore the potential benefits of this new intervention paradigm to help delay, and possibly reverse the progression of cognitive impairment.

4.9 Limitations

Limitations of this review should be noted. The limited number and heterogeneity of the reviewed studies did not allow critical analysis of the results for different groups of populations with cognitive impairment. Further, the search terms were limited to title, abstract and keywords to constrain the magnitude of the search yield to a manageable size and only citations published in English were included in this review. These restrictions may limit coverage of all potential studies under this topic. Moreover, initial study screening with title and abstract may lead to further limited cover of possible intervention identification although full text would be drawn for examination whenever a decision could not be judged by screening with title and abstract.

5 Conclusion

Results of the present review showed that studies with cognitively healthy populations revealed significant benefits of combined cognitive and exercise interventions on general cognitive functions, memory and functional status compared to active control groups. Studies with cognitively impaired populations also showed significant improvements in general cognitive functions, memory, executive functions, attention and functional status in persons with MCI and AD or dementia, but lack comparison with active control groups.

In conclusion, combined cognitive and exercise training can be effective for
improving the cognitive functions and functional status of older adults with and without cognitive impairment. However, limited evidence can be found in populations with cognitive impairment when the evaluation includes an active control group comparison. More well-designed studies are required before one can draw any firm conclusion on the efficacy of the combined cognitive and exercise intervention in older adults.
Conflicts of Interest:

We declare that there are no conflicts of interest.

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Table 1. Intervention characteristics of studies in cognitively healthy populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Total Intervention Hours (h)</th>
<th>Control/ Comparison (total hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabre, et al., 2002</td>
<td>Non-RCT</td>
<td>N = 32; France</td>
<td>Supervised group Combined Aerobic (AT) &amp; Mental training (MT)</td>
<td>38 h</td>
<td>CG: No training, but meeting for leisure activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG/CG/CG<em>1/CG</em>2: 8</td>
<td>AT: brisk walking and/or jogging (intensity determined by ventilation threshold</td>
<td></td>
<td>CG*1: Aerobic training (AT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>/8/8/8/8</td>
<td>2x/week for 60 min/ session for 2 months</td>
<td></td>
<td>CG*2: Mental training (MT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Age (years):</td>
<td>MT: eight themes: perceptive activities, attention, intellectual structuration,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG/CG1/CG<em>1/CG</em>2:</td>
<td>association and imagination, language, spatial marks, temporal marks and associa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>61.9/65.7/65.4/67.5</td>
<td>ted recruiting. 1x/week; 90 min/ session for 2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMSE score: not conducted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG*1: No training</td>
<td>CG*: Comparison group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG*2: Cognitive training (CT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG*3: Physical training (PT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG*4: Combined Psy T + PT (67.5 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG: Intervention group; CG: Control group; CG*: Comparison group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMSE: Mini-Mental State Examination</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Intervention characteristics of studies in cognitively impaired populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Total Intervention Hours (h)</th>
<th>Control/Comparison (total hours)</th>
</tr>
</thead>
</table>
| Barnes, et al., 2013     | RCT (Rater-blind) | N = 126; older adults with memory complaints; USA                           | Independent Home-based + center-based supervised class  
Combined Mental Activity (MA-I) & Aerobic Exercise (Ex-I)  
MA-I: independent computer-based training at home for visual and auditory processing 12 weeks; 60 min/day; 3 days/week  
Ex-I: aerobic & strength training 12 weeks; 60 min/day; 3 days/week | 72 h                        | CG: Mental activity (MA-I) & Exercise control (Ex-C; stretching, toning) (72 h)  
CG*1: Aerobic exercise (Ex-I) & Mental activity control (MA-C; DVD educational lecture) (72 h)  
CG*2: Exercise control (Ex-C) & Mental activity control (MA-C) (72 h) |
| Coelho, et al., 2012     | Non-RCT           | N = 27; Alzheimer’s disease (AD); Brazil                                    | Supervised group  
Multimodal Dual-task exercise: Strength/resistance training, moderate intensity aerobic capacity/balance training. motor activities (bouncing ball, walking, exercise with weights); plus simultaneous cognitive tasks (naming/words generation or reacting to verbal command) 16 weeks; 3x/week; 90 min/session | 48 h                        | CG: No intervention                                                                               |
| Kounti, et al., 2011     | Non-RCT (Rater-blinded) | N = 58; mild cognitive impairment; Greece                                   | Supervised group  
Dual- task kinetic exercise: visual-active movement, visual-walking, visual-balance, visual-fine motor, auditory-free movement 20 sessions, 1x/week; 90 min/session | 30 h                        | CG: Wait-list control                                                                              |
Table 2 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Diagnosis</th>
<th>Country</th>
<th>IG/CG</th>
<th>Mean Age (years)</th>
<th>MMSE Score</th>
<th>Intervention</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwenk, et al., 2010</td>
<td>RCT</td>
<td>61</td>
<td>Dementia</td>
<td>Germany</td>
<td>26/35</td>
<td>80.4/82.3</td>
<td>21.0 ± 2.9/21.7 ± 2.9</td>
<td>Supervised group</td>
<td>48 h</td>
<td>CG: Motor placebo group; low intensity exercise including flexibility exercise, calisthenics, and ball games while sitting (24 h)</td>
</tr>
<tr>
<td>Suzuki, et al., 2012</td>
<td>RCT</td>
<td>50</td>
<td>Amnestic mild cognitive impairment</td>
<td>Japan</td>
<td>25/25</td>
<td>76 ± 7.1 years</td>
<td>26.8 ± 1.8/26.6 ± 1.6</td>
<td>Supervised group</td>
<td>120 h</td>
<td>Health education; 3 sessions over 12 months</td>
</tr>
</tbody>
</table>

IG: Intervention group; CG: Control group; CG*: Comparison group
MMSE: Mini-Mental State Examination
Table 3: Study Characteristics and results of studies in cognitively healthy populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Outcome Measures of interest</th>
<th>Significant between-group effects</th>
<th>Effect Sizes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabre, et al., 2002</td>
<td>N = 32</td>
<td>Combined Aerobic (AT) &amp; Mental training (MT)</td>
<td>Post-intervention 2 months</td>
<td>BEC 96 questionnaire, Wechsler memory scale (WMS)</td>
<td>(compared to CG &amp; CG*) 0 +</td>
<td>$d = -0.66 (-1.67 – 0.34)$ $d = 1.29 (0.21 – 2.36)$</td>
</tr>
<tr>
<td>Legault, et al., 2011</td>
<td>N = 73</td>
<td>Combined Cognitive (CT) &amp; Physical training (PT)</td>
<td>Post-intervention 4 months</td>
<td>Executive functions &amp; Memory Composite Score, Executive functions Composite Score, Episodic Memory Composite Score</td>
<td>0</td>
<td>Data not available for calculation</td>
</tr>
<tr>
<td>Oswald, et al., 2006</td>
<td>N = 375</td>
<td>Combined Cognitive (CT) &amp; Physical training (PT)</td>
<td>Post-intervention 12 months; FU 5 years</td>
<td>Cognitive Function Composite Score, Sandoz clinical assessment geriatrics SCAG, Independent Living Composite Score, Everyday competence, Emotional Status</td>
<td>(compared to CG) + / + at FU 0 / + at FU + / + at FU 0 +/- at FU</td>
<td>Data not available for calculation</td>
</tr>
</tbody>
</table>

CG: control group; CG*: comparison group
FU: follow-up; N: number of subjects
+: positive effect for intervention group; 0: no difference between groups
CI: confidence interval
$d$: standard between-group effect size
Table 4: Study Characteristics and results of studies in cognitively impaired populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Outcome Measures of Interest</th>
<th>Significant between-group effects</th>
<th>Effect Sizes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnes, et al., 2013</td>
<td>N = 126; older adults with memory complaints</td>
<td>Combined Mental Activity &amp; Aerobic Exercise</td>
<td>Post-intervention 12 weeks</td>
<td>Rey Auditory Verbal Learning Test (RAVLT) Verbal Fluency (letter &amp; category) Digit Symbol Substitution Test (DSST) Trail Making Test (TMT) Eriksen Flanker Test (EFT) Useful Field of View (UFOV)</td>
<td>0 0 0 0 0 0</td>
<td>$d = 0.35$ ($-0.11 - 0.41$) $d = 0.14$ ($-0.89 - 0.62$) $d = 0.04$ ($-0.79 - 0.72$)</td>
</tr>
<tr>
<td>Coelho, et al., 2012</td>
<td>N = 27; Alzheimer’s disease (AD)</td>
<td>Multimodal Dual-task exercise</td>
<td>Post-intervention 16 weeks</td>
<td>Frontal Assessment Battery (FAB) Clock Drawing Test (CDT) Symbol Search Subtest of WAIS-III (Symbol)</td>
<td>+ +</td>
<td>$d = 1.18$ ($0.37 - 2.01$) $d = 0.96$ ($0.16 - 1.76$) $d = 1.57$ ($0.71 - 2.44$)</td>
</tr>
<tr>
<td>Kounti, et al., 2011</td>
<td>N = 58; mild cognitive impairment</td>
<td>Dual-task kinetic exercise</td>
<td>Post-intervention 20 weeks</td>
<td>Mini-mental state examination (MMSE) Test of Everyday Attention (TEA) Rey Auditory Verbal Learning Test (RAVLT) Rey-Osterrieth Complex Figure Test (ROCFT) Verbal Fluency Test (FAS) Functional Rating Scale of Symptoms of Dementia (FRSSD) Functional Cognitive Assessment Scale (FUCAS) Wisconsin Card Sorting Test (WCST) Wechsler Adult Intelligence Scale-Revised (WAIS-R) Rivermead Behavioral Memory Test (RBMT) Boston Naming Test (BNT)</td>
<td>+ + +</td>
<td>$d = 0.40$ ($-0.12 - 0.92$) $d = 0.08$ ($-0.44 - 0.59$) $d = 0.01$ ($-0.50 - 0.53$) $d = 0.38$ ($-0.14 - 0.90$) $d = 0.17$ ($-0.34 - 0.69$)</td>
</tr>
<tr>
<td>Schwenk, et al., 2010</td>
<td>N = 61; dementia</td>
<td>Dual-task exercise</td>
<td>Post-intervention 12 weeks</td>
<td>DTC Cognitive performance DTC Combined motor-cognitive performance</td>
<td>0 +</td>
<td>Data not available for calculation $d = 0.99$ ($0.39 - 1.59$)</td>
</tr>
<tr>
<td>Suzuki, et al., 2012</td>
<td>N = 50; amnestic mild cognitive impairment</td>
<td>Multicomponent dual-task exercise</td>
<td>Post-intervention 6 months, 12 months</td>
<td>Mini-mental state examination (MMSE) Immediate recall WMS-R Delayed recall WMS-R Digit symbol-coding (DSC) subset WAIS-III Letter verbal fluency test (LVFT) Category verbal fluency test (CVFT) Stroop Color and Word Test (SCWT)</td>
<td>+ at 6 m &amp; 12 m + at 6 m &amp; 12 m + at 12 m</td>
<td>$d = 0.44$ ($-0.44 - 0.67$) $d = 0.09$ ($-0.46 - 0.65$) $d = 0.16$ ($-0.39 - 0.72$) $d = 0.22$ ($-0.34 - 0.77$)</td>
</tr>
</tbody>
</table>

N: number of subjects; DTC: dual-task cost
$d$: standard between-group effect size; CI: confidence interval
+: positive effect for intervention group; 0: no difference between groups
<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization Method</th>
<th>Concealed Allocation</th>
<th>Eligibility Criteria</th>
<th>Baseline similarity</th>
<th>Assessor blinded</th>
<th>Care provider blinded</th>
<th>Subject blinded</th>
<th>Valid reliable measures</th>
<th>Same follow-up length</th>
<th>Outcome from &gt; 85% subjects</th>
<th>Pre-specified outcomes</th>
<th>Data presentation</th>
<th>Intention to-treat</th>
<th>Sum Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnes, et al., 2013</td>
<td>Yes (computer generated sequence)</td>
<td>Unclear (not stated)</td>
<td>Yes (stated)</td>
<td>Yes (baseline characteristics presented)</td>
<td>Yes (stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear (not stated)</td>
<td>Yes (reference stated)</td>
<td>Yes (stated)</td>
<td>Yes No (21% drop-off reported)</td>
<td>Yes Yes (mean standardized changes &amp; confidence intervals)</td>
<td>Yes Yes (stated)</td>
<td>Yes (stated)</td>
<td>9</td>
</tr>
<tr>
<td>Coelho, et al., 2012</td>
<td>No (assigned)</td>
<td>No</td>
<td>Yes (stated)</td>
<td>Yes (baseline characteristics presented)</td>
<td>Unclear (not stated)</td>
<td>No</td>
<td>Yes (reference stated)</td>
<td>Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (mean &amp; SD)</td>
<td>Yes Yes (completer comparison)</td>
<td>Yes (stated)</td>
<td>Yes (stated)</td>
<td>8</td>
</tr>
<tr>
<td>Fabre, et al., 2011</td>
<td>No (randomly assigned)</td>
<td>No</td>
<td>Yes (stated)</td>
<td>Yes (baseline characteristics presented)</td>
<td>Unclear (stated)</td>
<td>No</td>
<td>Yes (reference stated)</td>
<td>Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (mean &amp; standard error)</td>
<td>Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Kounti, et al., 2011</td>
<td>No (assigned)</td>
<td>No</td>
<td>Yes (stated)</td>
<td>Yes (complete baseline comparison)</td>
<td>Yes (stated)</td>
<td>No</td>
<td>No</td>
<td>Yes (data &amp; reference stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (mean &amp; SD)</td>
<td>Yes Yes (stated)</td>
<td>Yes (stated)</td>
<td>7</td>
</tr>
<tr>
<td>Legault, et al., 2011</td>
<td>Unclear (method of random sequence generation was not stated)</td>
<td>Unclear (not stated)</td>
<td>Yes (stated)</td>
<td>Yes (baseline characteristics presented)</td>
<td>Unclear (stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear (stated reference without information)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (mean &amp; SD; mean change &amp; SE)</td>
<td>Yes (stated)</td>
<td>Yes (stated)</td>
<td>7</td>
</tr>
<tr>
<td>Oswald, et al., 2006</td>
<td>No (stated)</td>
<td>No</td>
<td>Yes (stated)</td>
<td>Yes (baseline characteristics presented &amp; with adjustment in analysis)</td>
<td>No (stated)</td>
<td>Unclear (not stated)</td>
<td>Unclear (not stated)</td>
<td>Yes (reference stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (z-score mean &amp; SD; effect size d)</td>
<td>Yes (stated)</td>
<td>Yes (stated)</td>
<td>11</td>
</tr>
<tr>
<td>Schwenk, et al., 2010</td>
<td>Yes (numbered container)</td>
<td>Yes (by independent person)</td>
<td>Yes (stated)</td>
<td>Yes (stated baseline and completer baseline comparison)</td>
<td>Yes (stated)</td>
<td>No</td>
<td>Yes (reference stated)</td>
<td>Yes (data reported)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (mean &amp; SD)</td>
<td>Yes Yes (completer analysis)</td>
<td>Yes (stated)</td>
<td>Yes (stated)</td>
<td>9</td>
</tr>
<tr>
<td>Suzuki, et al., 2012</td>
<td>Unclear (method of random sequence generation was not stated)</td>
<td>Unclear (not stated)</td>
<td>Yes (stated)</td>
<td>Yes (baseline characteristics presented)</td>
<td>Yes (stated)</td>
<td>No</td>
<td>No</td>
<td>Yes (reference stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (stated)</td>
<td>Yes Yes (group mean difference &amp; confidence intervals)</td>
<td>Yes (stated)</td>
<td>Yes (stated)</td>
<td>9</td>
</tr>
</tbody>
</table>
Figure 1: Selection process of the systemic review

Database yield 572 citations

Duplicate (n = 98)

474 potential citations

Exclude based on title & abstract (n = 461)
- Not combined cognitive-physical intervention (n = 80)
- Not intervention studies (n = 158)
- Not target participants (n = 213)
- Not include cognitive outcomes (n = 10)

13 citations for full text evaluation

Extra citations (n = 6)
- Manual search (n = 3)
- Internet search (n = 3)

19 citations for full text evaluation

Excluded after full text evaluation (n = 11)
- Not combined cognitive-physical intervention (n = 4)
- On-going studies (n = 3)
- Second paper reporting same data set (n = 2)
- did not include cognitive outcomes (n = 1)
- did not distinguish the effects of the combined cognitive and physical training (n = 1)

8 articles included for final review