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Non-pharmacological Interventions for Adults with Mild Cognitive Impairment and Early Stage Dementia: An Updated Scoping Review

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Abstract

The purpose of this scoping review was to examine the science related to non-pharmacological interventions designed to slow decline for older adults with Mild Cognitive Impairment or early-stage dementia. We reviewed 32 unique randomized controlled trials that employed cognitive training (remediation or compensation approaches), physical exercise, or psychotherapeutic interventions that were published before November 2014. Evidence suggests that cognitive training focused on remediation and physical exercise interventions may promote small improvements in selected cognitive abilities. Cognitive training focused on compensation interventions and selected psychotherapeutic interventions may influence how cognitive changes impact daily living. However, confidence in these findings is limited due methodological limitations. To better assess the value of non-pharmacological interventions for this population, we recommend: 1) adoption of universal criteria for “early stage cognitive decline” among studies, 2) adherence to guidelines for the conceptualization, operationalization, and implementation of complex interventions, 3) consistent characterization of the impact of interventions on daily life, and 3) long-term follow-up of clinical outcomes to assess maintenance and meaningfulness of reported effects over time.

Keywords

Mild Cognitive Impairment; Dementia; Alzheimer’s disease; cognitive rehabilitation; non-pharmacological interventions; behavioral interventions

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1. Introduction

An estimated 5.2 million older adults are suspected to have dementia in the United States (Alzheimer's Association, 2014). Due to aging of one of the largest birth cohorts in United States history, up to 16 million older adults are expected to have dementia by the year 2050 (Alzheimer's Association, 2014). Costs associated with dementia are estimated to exceed $1 trillion USD (in current market value) by 2050 (Alzheimer's Association, 2014). Mild cognitive impairment (MCI) is the state between normal cognitive aging and dementia. Approximately 16% of older adults have MCI (Mitchell and Shiri-Feshki, 2009; Petersen et al., 1999), and these older adults are at high risk of developing dementia. Thus, older adults with MCI are at high risk for disability in daily activities and costly support in the form of caregiver assistance, community resources, and long-term care. Interventions that slow or reverse the decline from MCI to dementia could have a significant impact on individual, familial, and societal burden.

The measure of efficacy of these interventions may best be detected through changes in (or at least maintenance of) cognitive function and the impact of these changes on daily living. Individuals with MCI may have subjective memory complaints and objective evidence of cognitive impairment beyond those expected for their age and education levels. These cognitive impairments may be detected through domain-specific or global measures of cognitive function. The impact of cognitive changes on daily living may be assessed through measures of daily activity performance or quality of life. Despite the common conception that individuals in the early stages of cognitive decline do not have disability in daily activities, evidence suggests that performance of complex cognitively-focused daily activities may be affected, (Rodakowski et al., 2014) and this may have implications for overall quality of life.

Several pharmacological interventions (e.g., donepezil, huperzine A, vitamin E, and cholinesterase inhibitors) have been examined as potential agents for slowing or reversing cognitive decline. However, evidence suggests that these agents do not alter cognitive function outcomes or slow progression to dementia (Birks and Flicker, 2006; Farina et al., 2012; Russ, 2014; Yue et al., 2012). Thus, more recent efforts have focused on non-pharmacological interventions. Non-pharmacological interventions may be promising for a variety of reasons. First, older adults may prefer non-pharmacological strategies to maintain cognitive function and community independence rather than pharmacological strategies that may have adverse side-effects. Second, non-pharmacological strategies have less risk than pharmacological strategies (i.e., low likelihood of contraindications or problems that occur with polypharmacy); therefore, they are likely to be more broadly generalizable.

Non-pharmacological interventions that address cognitive function and the impact of cognitive function on daily living have been widely studied in a variety of clinical populations (e.g., learning disabilities, stroke, traumatic brain injury, dementia) (Chung et al., 2013; Seitz et al., 2012; Skidmore et al., 2014; Young and Amarasinghe, 2010). These non-pharmacological interventions tend to be complex, multimodal interventions, as defined by the Medical Research Council (Craig et al., 2013). Chief among these interventions are cognitive training interventions that can be grossly categorized as either remediation or

compensation approaches (Cicerone et al., 2011). Cognitive remediation approaches attempt to improve cognitive function through focused training and practice (Barnes et al., 2009). Compensation interventions focus on training individuals to maintain independence, safety, or engagement in daily activities through the use of external aids or adapted methods without seeking to improve cognitive functions, per se (Parker and Thorslund, 2007). In addition to cognitive training interventions, physical exercise may also influence cognitive function. Although the data are limited, physical exercise has been associated with improvements in cognitive function healthy older adults (Kelly et al., 2014). Psychotherapeutic interventions have also been examined for their value for helping individuals with cognitive impairments cope with the changes that cognitive impairments bring about in daily life (Simon et al., 2015; Ueda et al., 2013).

While studied in other clinical populations, these interventions have only recently become the subject of interest for older adults with MCI. Recent reviews suggest that cognitive remediation interventions show promise for promoting small improvements in attention, memory, processing speed, and executive functioning (Huckans et al., 2013; Li et al., 2011; Reijnders et al., 2013; Simon et al., 2012). However, given the small magnitude of reported changes in these few reviews, and the lack of reported changes in other reviews (Cooper et al., 2013; Martin et al., 2011; Teixeira et al., 2012), the benefits of these improvements are unclear. Furthermore, the reviews could not comment on the impact of these improvements on everyday life, as the impact was infrequently addressed in the reviewed articles (Huckans et al., 2013, Kurz et al., 2011; Reijnders et al., 2013). The benefits of compensation approaches, physical exercise, and psychotherapeutic interventions also remain unclear (Cooper et al., 2013; Huckans et al., 2013; Simon et al., 2012; Teixeira et al., 2012). Furthermore, many of the reviews combined clinical populations (i.e., health older adults and MCI, or MCI and various stages of dementia) (Kurz et al., 2011; Martin et al., 2011; Reijnders et al., 2013; Thom and Clare, 2011), making it difficult to isolate the benefits of interventions for older adults in the early stages of cognitive decline. The lack of clarity in the findings of these reviews was strongly influenced by state of the science at the time when these reviews were conducted. The purpose of this scoping review is to update and summarize the current state of science addressing non-pharmacological approaches (cognitive remediation, compensation, physical exercise and psychotherapeutic interventions) for adults with MCI and early-stage dementia. We also present specific suggestions to guide future investigations.

2. Methods

We searched PubMed, PsycINFO, EMBASE, and Cochrane Database of Systematic Reviews for randomized, controlled clinical trials examining non-pharmacological interventions for improving cognitive function, activities of daily living, or quality of life for individuals with MCI or early-stage dementia. We tested and refined the initial search strategy in PubMed with subsequent translations into PsycINFO and EMBASE search languages. We implemented searches with controlled vocabulary in each database supplemented with free-text searching in keywords and titles. Database specific conventions such as mapping and use of multiple search fields and filters, customized the strategy for implementation in each individual database. A randomized clinical trials publication filter

was applied to locate studies evaluating non-pharmacological interventions with MCI. English language and age filters (middle-aged and elderly) were then applied to all search results. For the purposes of this review we excluded studies that focused on adults below the age of 60, adults with moderate or more severe dementia (MMSE≤20), or caregivers or family members as the primary target of intervention. We also excluded studies that did not examine cognitive function or activities of daily living as a primary or secondary outcome. Studies identified through the search were screened for inclusion and exclusion by examining the title of the manuscript, the abstract, and the text. Two authors (JR and ES) completed screening, and compared included and excluded studies. Discrepancies were discussed and resolved. A total of 33 articles met criteria. These articles were based on 32 distinct studies; 1 study used the same sample but reported different outcomes in two separate manuscripts. Therefore, we combined findings from these two publications to represent the single study. All studies were published in peer-reviewed journals.

We extracted data pertaining to the study sample, content of the experimental and control interventions, primary and secondary outcomes, and results including within and between subject effects. A meta-analysis for this particular review was not considered informative due to the wide variations in intervention methods and outcomes assessed. Results are summarized descriptively.

3. Results

Table 1 summarizes the selected studies. With a few exceptions, studies recruited fairly small samples. Table 2 summarizes sample characteristics. Table 3 describes intervention characteristics, primary and secondary outcomes, and major findings from each of the selected studies. Reviewed articles are marked with an asterisk in the reference section.

3.1. Participant Characteristics

Across the 32 studies, participants were recruited from a variety of settings, including university-based research centers, community-based centers or outreach, and clinical practices. Participants were generally 70 years of age or older. There were more female and male participants, and, if race was reported, the majority of the samples consisted of White participants. On average, participants in these studies completed 12 years of education.

3.2. Intervention Characteristics

Interventions in the reviewed studies could be classified as addressing one or more of the following three themes: cognitive training interventions (either remediation or compensation), physical exercise interventions, and psychotherapeutic interventions. Most of the reviewed studies (n=22) examined cognitive training interventions, either alone (Barnes et al., 2009 Boripuntakul et al., 2012, Buschert et al., 2011; Buschert et al., 2012; Carretti et al., 2013, Finn & McDonald, 2011; Gaitan et al., 2013; Greenaway et al., 2013; Jean et al., 2010; Jelcic et al., 2012; Kurz et al., 2012; Kwok et al., 2011; Moro et al., 2012; Olchik et al., 2013; Rozzini et al., 2007; Tappen and Hain, 2014; van Paasschen et al., 2013; Zhuang et al., 2013) or in combination with psychotherapeutic interventions (interpersonal therapy, cognitive-behavioral therapy, coping strategies) (Bottino et al. 2005; Rapp et al.

2002; Troyer et al., 2008; Tsolaki et al., 2011). Cognitive training interventions addressed either remediation (via stimulation or memory training exercises such as attention focusing exercises, mnemonics, or procedural memory cues) (Barnes et al., 2009; Boripuntakul et al., 2012; Buschert et al., 2011; Buschert et al., 2012; Carretti et al., 2013; Finn & McDonald, 2011; Gaitan et al., 2013; Jean et al., 2010; Jelcic et al., 2012; Moro et al., 2012; Olchik et al., 2013; Rozzini et al., 2007; Tappen and Hain, 2014; Troyer et al., 2008; Tsolaki et al., 2011; van Paasschen et al., 2013; Zhuang et al., 2013) or compensation (via external memory aids or adaptive strategies) (Bottino et al., 2005; Greenaway et al., 2013; Jelcic et al., 2012; Kurz et al., 2012; Rapp et al., 2002; Tsolaki et al., 2011). They were delivered in various formats, including individual sessions (Barnes et al., 2009; Boripuntakul et al., 2012; Carretti et al., 2013; Finn & McDonald, 2011 Greenaway et al., 2013; Jean et al., 2010; Jelcic et al., 2012; Kurz et al., 2012; Kwok et al., 2011; Moro et al., 2012; Rozzini et al., 2007; Tappen and Hain, 2014; van Paasschen et al., 2008; Zhuang et al., 2013) and group sessions (Bottino et al., 2005; Buschert et al., 2011; Buschert et al., 2012; Olchik et al., 2013; Rapp et al., 2002; Troyer et al., 2008; Tsolaki et al., 2011). They also incorporated various methods such as traditional training or cognitive stimulation activities (Boripuntakul et al., 2012; Buschert et al., 2011; Buschert et al., 2012; Carretti et al., 2013; Gaitan et al., 2013; Greenaway et al., 2013; Jean et al., 2010; Jelcic et al., 2012; Kurz et al., 2012; Kwok et al., 2011; Moro et al., 2012; Olchik et al., 2013; Rapp et al., 2002; Tappen and Hain, 2014; Troyer et al., 2008; Tsolaki et al., 2011; van Paasschen et al., 2008) and computer-based cognitive stimulation activities (Barnes et al., 2009; Finn & McDonald, 2011 Gaitan et al., 2013; Rozzini et al., 2007; Zhuang et al., 2013). Among the 22 studies that examined some form of cognitive training (either alone, or in combination with psychotherapy), 10 studies compared cognitive training to non-active control interventions (e.g., no treatment, waitlist) (Boripuntakul et al., 2012; Finn & McDonald, 2011; Kwok et al., 2011; Moro et al., 2012; Olchik et al., 2013; Rapp et al., 2002; Rozzini et al., 2007; Tsolaki et al., 2011; van Paasschen et al., 2013; Zhuang et al., 2013), and 12 studies compared cognitive training to active control interventions that did not specifically provide cognitive training (e.g., readings, education, usual treatment) (Barnes et al., 2009; Bottino et al., 2005; Buschert et al., 2011; Buschert et al., 2012; Carretti et al., 2013; Greenaway et al., 2013; Kurz et al., 2012; Olchik et al., 2013; Rozzini et al., 2007; Tappen and Hain, 2014; Troyer et al., 2008; van Paasschen et al., 2013). [N.B. Three studies compared cognitive training to both non-active and active control conditions (Olchik et al., 2013; Rozzini et al., 2007; van Paasschen et al., 2013]. Three additional studies compared two cognitive training interventions (Gaitan et al., 2013; Jean et al., 2010; Jelcic et al., 2012).

Far fewer studies examined physical exercise or psychotherapeutic interventions. Of the 6 studies that examined physical exercise interventions, 4 studies examined aerobic exercise alone (Baker et al.; 2010, Nagamatsu et al., 2012; Scherder et al., 2005; van Uffelen et al., 2008), 1 in combination with balance and dual-task training (Suzuki et al., 2012), and 1 study examined strength and balance training plus a home safety program (Wesson et al., 2013). The frequent rationale for the physical exercise programs was improved physical health, with the suggestion that cognitive or other functional benefits may follow. Psychotherapeutic interventions used interpersonal therapy (n=1) (Burns et al., 2005), coping strategies (n=1) (Stanley et al., 2013), or mindfulness training (n=1) (Wells et al.,

2013a; Wells et al., 2013b). These interventions were designed to promote healthy adaptation to cognitive changes. Finally, one study examined a combination of physical exercise (taiji) and psychotherapy (cognitive-behavioral therapy) (Burgener et al., 2008).

3.3. Primary and Secondary Outcomes

A diversity of measures was used to assess the benefits of non-pharmacological interventions for addressing changes in cognitive function and the impact of these changes on daily living. Measures of cognitive function were either domain specific or global in nature. Measures of specific cognitive abilities often aligned with hypothesized targets of intervention (e.g., assessments of memory after memorization training). Specific cognitive abilities measured were verbal fluency, verbal learning, immediate and delayed memory, attention, information processing speed, and psychomotor speed. The most commonly used global measures of cognitive function were the Mini Mental State Examination (Folstein et al., 1975) and the Alzheimer's Disease Assessment Scale-cognitive domain (Rosen et al., 1984).

Approximately 50% of the studies measured the impact of cognitive changes on daily living as a primary or secondary outcome (Bottino et al., 2005; Burns et al., 2005; Buschert et al., 2012; Finn & McDonald, 2011; Gaitan et al., 2013; Greenaway et al., 2013; Jean et al, 2010; Kurz et al, 2012; Nagamatsu et al, 2012; Stanley et al., 2013; Tappen and Hain, 2014; Troyer et al., Tsolaki et al., 2008; van Paasschen et al., 2013; Wells et al., 2013a; Wells et al., 2013b; Wesson et al., 2013). Measures addressed daily activity performance, self-efficacy, and quality of life. Daily activity performance measures included the Interview for Deterioration of Daily Activities (Teunisse and Derix, 1997), Bayer ADL Scale (Hindmarch et al., 1998), and caregiver report (Bottino et al.). Self-selected goal attainment was measured with the Canadian Occupation Performance Measure (Law et al., 1990; van Paasschen et al., 2013). The impact of memory on daily activities was measured with the Memory Failures in Everyday Memory (Gaitan et al., 2013; Sunderland et al., 1984). One study measured self-efficacy for daily activities (Greenaway et al., 2013). Quality of life was assessed with the Quality of Life-Alzheimer's Disease measure (Buschert et al., 2011; Buschert et al., 2012; Greenaway et al., 2013; Kurz et al., 2012; Stanley et al., 2013; Thorgrimsen et al., 2003; Wells et al., 2013a; Wells et al., 2013b). Other studies used task specific indices (i.e., use of a schedule reminder) (Jean et al., 2010) or measures of feasibility and safety of the intervention (Wells et al., 2013a).

Two additional categories of outcomes emerged even though they were not the focus of our review. Several studies examined the benefits of non-pharmacological interventions for mental health in older adults with MCI (Burgener et al., 2008; Burns et al., 2005; Finn & McDonald, 2011; Gaitan et al., 2013; Kurz et al., 2012; Rapp et al., 2002; Rozzini et al., 2007; Stanley et al., 2013; van Paasschen et al., 2013; Wesson et al., 2013). In addition, a few studies examined changes in neurochemistry markers or fMRI activation (Baker et al., 2010; Boripuntakul et al., 2012; Nagamatsu et al., 2012; van Paasschen et al., 2013; Wells et al., 2013b).

3.4 Intervention Effects

For clarity, only statistically significant differences are reported in the following sections. Examining the reviewed studies, the benefits of cognitive training for addressing cognitive function among older adults with MCI are unclear. The majority of studies examining cognitive training (20 of 22) focused on improvements in cognitive function as the primary or secondary outcome (Barnes et al., 2009; Boripuntakul et al., 2012; Bottino et al., 2005; Buschert et al., 2011; Buschert et al., 2012; Carretti et al., 2013; Finn & McDonald, 2011; Gaitan et al., 2013; Greenaway et al., 2013; Jean et al., 2010; Jelcic et al., 2012; Kwok et al., 2011; Moro et al., 2012; Olchik et al., 2013; Rapp et al., 2002; Rozzini et al., 2007; Tappen and Hain, 2014; Troyer et al., 2008; Tsolaki et al., 2011; Zhuang et al., 2013). Statistically significant between group differences in cognitive function favoring the cognitive training group were reported in 12 of the 20 studies (Barnes et al., 2009; Bottino et al., 2005; Buschert et al., 2011; Finn & McDonald, 2011; Gaitan et al., 2013; Jelcic et al., 2010; Kwok et al., 2011; Moro et al., 2012; Rapp et al., 2002; Tappen and Hain, 2014; Troyer et al., 2008; Tsolaki et al., 2011), but the between group differences were generally modest. Notably, intervention effects on cognitive function, when detected, were generally attributed to remediation (and not compensation) approaches. Furthermore, these effects were for the most part detected in indices of working memory and delayed memory. Finally, studies that combined cognitive training with some form of psychotherapeutic approach (i.e., social engagement, stress management) (Bottino et al., 2005; Rapp et al., 2002; Troyer et al., 2008; Tsolaki et al., 2011) all demonstrated small improvements in cognitive function (compared to active and non-active controls), suggesting that multimodal approaches may enhance cognitive training. However, given small magnitude of improvements in cognitive function across studies, it is difficult to conclude at this time that cognitive training interventions are robustly effective in influencing cognitive function in older adults with MCI.

Among the 9 studies that focused on the impact of cognitive changes on daily living (Bottino et al., 2005; Buschert et al., 2012; Finn & McDonald, 2011; Gaitan et al., 2013; Greenaway et al., 2013; Jean et al., 2010; Kurz et al., 2012; Tsolaki et al., 2011; van Paasschen et al., 2013), within group improvements in performance of activities of daily living were detected in 3 studies (Greenaway et al., 2013; Jean et al., 2010; Tsolaki et al., 2011). Each of these studies included compensatory training and self-efficacy training. Between group differences were detected in only 2 studies (Kurz et al., 2012; van Paasschen et al., 2013). First, Kurz and colleagues provided compensatory training in external memory aids, and detected statistically significantly greater improvements in self-reported quality of life, but not in independence with daily activities, when training was compared to treatment as usual. Second, Van Paaaschen and colleagues demonstrated superior goal-attainment through task-specific compensatory training, compared to a relaxation intervention and a no treatment control. In both cases, the reported effect sizes were relatively small.

From the reviewed studies, it is difficult to comment on the relative benefits of different types of cognitive training interventions for older adults with MCI. Only 3 of the reviewed studies compared one form of cognitive training to another. Jelcic and colleagues demonstrated that a remediation-focused cognitive training program, using lexical semantic stimulation, resulted in improved verbal memory scores compared to unstructured

stimulation combined with compensation-focused training in external memory aids (Jelcic et al., 2012). However, best practices for remediation remain unclear. Jean and colleagues demonstrated that errorless learning and errorful learning of face-name associations yielded similar improvements on the trained task, with no between group differences (Jean et al., 2010). Gaitan and colleagues compared computer-delivered cognitive training, traditional cognitive training (i.e., paper and pencil activities), and a combination of computer-delivered and traditional cognitive training. The three groups did not differ with respect to cognitive function change scores. However, the group that participated in the combination program demonstrated better decision making on the Iowa Gambling Task (Gaitan et al., 2013). These findings might be attributed to the amount of training provided in the combination group, rather than the type of training.

Considering the findings from all studies examining cognitive training interventions, it appears that remediation may be more likely to improve selected cognitive abilities than compensation. This is logical given the compensation focuses on teaching individuals to adapt to changes in their cognitive function, rather than addressing cognitive abilities per se. Furthermore, amount of training may have a stronger impact on outcome than the type of training, although this requires additional investigation. The persistence of small improvements in cognition over time, particularly in the face of cognitive decline is unclear. Long-term follow-up with study participants may be required to ascertain whether there are benefits over time. Moreover, the benefits of small improvements in cognitive abilities for improving daily living are unclear.

With regard to physical exercise interventions, 5 of the 6 studies examined the benefits of aerobic exercise for improving cognitive function (Baker et al., 2010; Nagamatsu et al., 2012; Scherder et al., 2005; Suzuki et al., 2012; van Uffelen et al., 2008). All 5 studies reported statistically significant between group differences in cognitive function change scores favoring aerobic exercise relative to control, but the improvements in cognitive function attributed to aerobic exercise were small in these studies. Baker and colleagues detected greater improvements in measures of executive functions when comparing aerobic exercise to stretching (Baker et al., 2010). Scherder and Suzuki and their colleagues reported greater improvements in measures of processing speed, working memory and fluency, when comparing aerobic exercise to stretching and education (Scherder et al., 2005; Suzuki et al., 2012). Van Uffelen and colleagues demonstrated greater improvements in measures of processing speed for women (not men) in the walking group compared to women in the low intensity activity group (van Uffelen et al., 2008). In this last study, the authors reported only moderate adherence to the program, which may have contributed to small effect sizes. None of these studies examined the impact of aerobic exercise on daily living. The sixth study examined the benefits of a multi-modal physical exercise program incorporating strength and balance training in addition to an occupational therapist delivered home-safety intervention (Wesson et al., 2013). Cognitive function benefits were not assessed, but improvements in daily activity performance were noted in the treatment group over time. Whether the improvements were due to remediation through physical exercise or compensation is not clear.

The studies that examined psychotherapeutic interventions as a sole intervention (n=3) (Burns et al., 2005; Stanley et al., 2013; Wells et al., 2013a; Wells et al., 2013b) reported no significant changes in cognitive function, either within or between groups. Given that the focus of psychotherapeutic approaches is typically compensatory, teaching individuals to learn adaptive skills to support daily living, lack of improvement in cognitive functions is not surprising. Of interest, however, is whether these interventions reduce the negative impact of cognitive changes, as measured by mood and quality of life. Two of the three studies examined mood as the primary outcome (Burns et al., 2005; Stanley et al., 2013), and reported mixed outcomes. Stanley found between group differences for anxiety (favoring mindfulness training over treatment as usual; Stanley et al., 2013), and Burns did not find mood-related between group differences (Burns et al., 2005). All 3 studies examined impact on daily life, but only Stanley and colleagues found significantly greater improvements in quality of life attributed to training in psychosocial coping and self-monitoring compared to treatment as usual (Stanley et al., 2013). As mentioned previously, compensatory cognitive training interventions when offered in concert with psychotherapeutic interventions are associated with statistically significant but small changes in cognitive function (Bottino et al., 2005; Rapp et al., 2002). We only reviewed one study that examined the combined benefits of or physical exercise (taiji) and psychotherapy (cognitive behavioral therapy) (Burgener et al., 2008). Burgener and colleagues reported small improvements in a global measure of cognitive function that were greater in the multi-modal group than the educational control group. In addition, more substantive improvements in balance and physical function, relative to educational control. Impact on daily living was not assessed. Collectively, these studies suggest that psychotherapeutic interventions show promise, but require additional investigation before we can draw strong conclusions about the benefits for older adults with MCI.

4. Discussion

The current state of science examining non-pharmacological interventions for changing (or, at least, maintaining) cognitive function and the impact of these changes on daily living for individuals in the early stage of cognitive decline produces mixed results. A scoping review of the current literature suggests that cognitive training interventions have been the most widely studied, but that physical exercise and psychotherapeutic interventions have been investigated as well. In general, some evidence suggests that cognitive training focused on remediation has been associated with significantly greater improvements in selected cognitive abilities, but the magnitude of improvements is small. The same can be said for physical exercise interventions. One may argue that these small improvements could be meaningful, as small improvements or even maintenance of cognitive function over time, may be valuable in the face of potential cognitive decline. However, before we can support this conclusion, we must first assess the long-term maintenance of these improvements. Cognitive training focused on compensation, as well as selected psychotherapy approaches, show promise for addressing the impact of cognitive changes on daily living. However, confidence in these findings is limited due to several limitations in the studies performed to date. These limitations point to several directions for future investigations examining

potential interventions to slow or reverse functional decline in older adults with MCI or early-stage dementia.

While many agree that identifying and studying older adults at the early stages of cognitive decline hold particular clinical and scientific importance, a universal definition of “early stage” with consistent application across the world of specified criteria remains elusive. Several definitions have existed over time, including questionable dementia, possible incipient dementia, isolated short-term memory loss, amnestic dementia, and mild neurocognitive disorder. The term Mild Cognitive Impairment, while widely used in medicine, research, and education has been defined in a variety of ways (Petersen, 2004; Portet et al., 2006; Winblad et al., 2004). Among the studies we reviewed, MCI was the most commonly used classification, but diagnostic criteria varied from study-specific clinical criteria to using recommendations of an international consensus committee (Winblad et al., 2004). We must acknowledge that given the historical variations in the definition of MCI and “early stage” it is possible that we unintentionally excluded important studies that may have contributed to this review.

Perhaps given the relatively “new” focus on early stages of cognitive decline, it is not surprising that the preponderance of studies that we examined contained fairly small and poorly defined samples. This may be due to the fact that it is difficult to identify and recruit individuals at the early stages of cognitive decline when “early intervention” may be considered. Many older adults in the early stages of cognitive decline may not be aware of subtle changes in their cognition, and therefore may not seek intervention. Furthermore, primary care providers and community agencies that interact with older adults may not notice these subtle cognitive changes if they aren’t looking for them. These realities, added to the aforementioned disparities in definitions and criteria for identification, impede identification and referral of older adults with early stages of cognitive decline. Community outreach through senior centers, libraries, or other locations pertaining to cognitive health literacy may empower older adults to seek services that could support them in the quest to maintain cognitive function and community independence. Education and training of primary care providers and community agencies to improve recognition and screening for early stages of cognitive decline may also improve awareness.

In addition to clarifying the definitions of “early stage” cognitive decline, clarification of the conceptualization, operationalization and implementation of non-pharmacological interventions for this population is also needed. For the purposes of summarization, we grossly characterized interventions based on common intervention concepts. However, wide variation existed in the conceptualization and rationale for the interventions across studies, which limits strong conclusions that can be drawn from this literature. By definition, most studies used “complex interventions” or “interventions that contain several interacting components [including] the number and difficulty of behaviors required by those administering and receiving the intervention, … the number and variability of outcomes addressed by the intervention, and the degree of flexibility or tailoring of the intervention permitted.”(Craig et al., 2013, 2). Non-pharmacological interventions, if they are to be beneficial for older adults with cognitive decline, are likely to meet this definition. Therefore, careful conceptualization, operationalization and implementation of these

interventions are critical. The Medical Research Council provides guidance on best practices for developing, piloting, evaluating, and implementing complex interventions (Craig et al., 2013), and should be incorporated into future studies seeking to test potential non-pharmacological interventions for older adults in the early stages of cognitive decline.

In addition to integrating best practices for designing and studying non-pharmacological interventions for this population, it seems important to embrace outcome assessment strategies that more comprehensively assess the potential benefits and long-term outcomes. There is a long-held debate in cognitive rehabilitation research as to the “real world” benefits of improvements in cognition, as detected with task-specific or norm-referenced tests (Simon et al., 2012). Certainly large magnitude of changes (e.g., one standard deviation as defined by norm-referencing or large effect sizes) can be one way to determine “clinically meaningful” change. However, assessment of the impact of changes in cognitive test scores on measures of independence, safety and engagement in daily activities may be another way. This argues for employing best practices in assessing daily activities through performance observation or through well-validated assessments of disability and social engagement (McDonough et al., 2012; Rodakowski et al., 2014). Furthermore, long-term term follow-up, assessing for potential changes in trajectories of cognitive decline may be another way to assess the heuristic value of these interventions.

For the purposes of our review, we focused on outcomes pertaining to changes in cognitive function and the impact of these changes on daily living as target outcomes of non-pharmacological interventions aiming to slow the decline to dementia. That said, some of the reviewed studies focused on additional measures of brain health that, when added to cognitive function, help to address the cacophony of changes that contribute to dementia. Among these measures were indices of mood and physical health, as well as more proximal measures of neurophysiology and neurological connectivity. Mood, specifically, anxiety, appeared to be most strongly influenced by psychotherapy interventions that focused on relaxation (Stanley et al., 2013). Proximal measures of neurophysiology and neurological connectivity appeared to be most strongly influenced by physical activity interventions (Baker et al., 2010). These findings are not surprising given that several studies have demonstrated strong connections between changes in cognitive function and changes in mood in late life. In fact, approximately 50% of older adults with MCI have concurrent depressive symptoms (Apostolova and Cummings, 2008; Gabryelewicz et al., 2004; Monastero et al., 2009). Furthermore, depressive symptoms in late-life are a risk factor for MCI and dementia (Palmer et al., 2010; Rosenberg et al., 2013). Connections between physical health and cognitive health in late-life are also well-established. Cognitive changes have been found to be contributors to limitations in mobility, including among older adults without known neurological disease (Rosso et al., 2013); whereas, increased aerobic activity is associated with improved brain health and cognitive function in health older adults (Erickson et al., 2011). The linkages among cognition, mood, and physical health is likely due to common underlying pathologies that cause general slowing of neurological function, and clinical manifestations in each of these domains (Rosano et al., 2014).

These linkages suggest that it may be possible to identify biomarkers that may be used to identify older adults in the early stages of decline. Once rigorously validated, these

biomarkers may prove to be important measures of change attributed to intervention. For example, recent cross-sectional evidence suggests that there is a relationship between pro-inflammatory cytokines and engagement in productive activities among older adults (Kim and Ferraro, 2014). However, the nature of this relationship is unclear. The elevation of pro-inflammatory cytokines may contribute to reduced engagement productive activities, or reductions in productive activities may contribute to elevation of pro-inflammatory cytokines. Interventions that address one of these factors may influence the other. For example, non-pharmacological interventions that promote increased levels of productive activities (whether through remediation or compensation) may reduce pro-inflammatory cytokines. Investigations focused on these types of questions may clarify the nature of these important biological and behavioral relationships.

Finally, we focused this review on non-pharmacological interventions. However, the synergistic benefits of pharmacological and non-pharmacological interventions may be another promising area of study. Studies for adults with related neurodegenerative disease (e.g., chronic nonpsychotic major depressive disorder) have found that combination therapies can be significantly more effective than medication or non-pharmacological therapy alone (Keller et al., 2000). Three of the reviewed studies (Bottino et al., 2005; Rozzini et al., 2007; Van Uffelen et al., 2008) examined the additive benefits of pharmacological substances (acetylcholinesterase inhibitors, vitamin B) as adjuncts to non-pharmacological interventions (aerobic exercise, cognitive training). Two of these studies reported a statistically significant benefit of the combination of therapies relative to other conditions (Bottino et al., 2005; Van Uffelen et al., 2008). Bottino and colleagues demonstrated slightly better changes in cognitive test scores for individuals who engaged in cognitive training while taking acetylcholinesterase inhibitors relative to acetylcholinesterase inhibitors alone. Van Uffelen and colleagues reported that women (not men) engaged in aerobic exercise (compared to low intensity activity) while taking vitamin B (compared to placebo) demonstrated modestly greater improvements in cognitive test scores relative. Given the size and scope of these two studies, additional investigation may be warranted.

In summary, we conducted a scoping review of literature examining non-pharmacological interventions for older adults in the early stages of cognitive decline. Descriptive summaries of the literature indicate mixed findings with regard to the efficacy of cognitive training focused on remediation and aerobic exercise for improving cognitive function. Cognitive training focused on compensation and psychotherapy show promise for addressing the impact of cognitive changes in the lives of older adults in the early stages of cognitive decline. In general, effect sizes were small. Nonetheless, given variability in the samples, intervention methods, and outcomes measures, strong conclusions about the efficacy of these interventions are difficult to draw. The review identified specific areas for future research.

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Table 1

Study Characteristics

	Number of studies
Clinical population	
Mild Cognitive Impairment (or similar condition)	20
Early Alzheimer's Disease	8
Both of the above	4
Intervention method	
Cognitive training interventions	17
Physical exercise interventions	6
Psychotherapeutic interventions	3
Multimodal interventions	6
Comparison group(s)	
Non-active control	12
Active Control	13
Active Treatment	7
Cognitive function as primary or secondary outcome	
Yes	28
No	4

Table 2

Sample Characteristics

Author (Year)	Population	Sample Size	Gender, Race	Mean Age (years)	Mean Education (years)
Baker (2010)	Amnestic Mild Cognitive Impairment	Intervention (n=19)	Male, 47.4% White, NR	Men 70.9 ± 6.7, Women 65.3 ± 9.4	NR
		Control (n=10)	Male, 50% White, NR	Mean 70.6 ± 6.1, Women 74.6 ± 11.1	NR
Barnes (2009)	Mild Cognitive Impairment	Intervention (n=22)	Male, 59.1% White, NR	74.1 ± 8.7	16.8 ± 3.2
		Control (n=25)	Male, 60.0% White, NR	74.8 ± 7.2	16.6 ± 2.9
Boripuntakul (2012)	Mild Cognitive Impairment	Intervention (n=5)	Male, 40.0% White, NR	77.6 ± 6.1	9.0 ± 5.2
		Control (n=5)	Male, 40.0% White, NR	78.4 ± 5.0	12.4 ± 3.0
Bottino (2005)	Early-stage Alzheimer's disease	Intervention (n=6)	Male, 16.7% White, NR	74.7 ± 7.0	7.5 ± 4.0
		Control (n=7)	Male, 42.9% White, NR	72.9 ± 6.3	8.6 ± 3.7
Burgener (2008)	Early-stage dementia	Intervention (n=24)	Male, 54.2% White, NR	77.9 ± 7.9	16.2 ± 3.7
		Control (n=19)	Male, 52.6% White, NR	76.0 ± 8.1	15.4 ± 3.9
Burns (2005)	Early-stage dementia	Intervention (n=20)	Male, 50.0% White, NR	73.9 ± 13	NR
		Control (n=20)	Male, 55.0% White, NR	77.7 ± 16	NR
Buschert (2011)	Amnestic-mild cognitive impairment or early-stage Alzheimer's Disease	aMCI: Intervention (n=12)	aMCI: Male, 50.0% aMCI: White, NR	aMCI: 71.8 ± 8.6	aMCI: 12.3 ± 3.6
		aMCI: Control (n=12) Early stage AD: Control (n=7)	aMCI: Male, 50.0%, White, NR; Early AD: Male, 42.9%, White, NR	aMCI: 70.7 ± 5.7 Early AD: 74.2 ± 9	aMCI: 13.3 ± 2.2 Early AD: 13.6 ±6.5
Buschert (2012)	Amnestic-mild cognitive impairment	Intervention (n=12)	Male, 50.0% White, NR	71.8 ± 8.6	12.3 ± 3.6
		Control (n=12)	Male, 50.0% White, NR	70.7 ± 5.7	13.3 ± 2.2
Carretti (2013)	Amnestic-mild cognitive impairment	Intervention (n=10)	Male, 60.0% White, NR	71.8 ± 2.2	6.5 ± 2.8

Author (Year)	Population	Sample Size	Gender, Race	Mean Age (years)	Mean Education (years)
		Control (n=10)	Male, 40.0% White, NR	70.6 ± 2.6	7.2 ± 3.3
Finn (2011)	Mild cognitive impairment	Intervention (n=8)	Male, 37.5% White, NR	69.0 ± 7.7	13.3 ± 2.2
		Control (n=8)	Male, 62.5% White, NR	76.4 ± 6.5	12.0 ± 2.8
Gaitan (2013)	Mild cognitive impairment and early-stage Alzheimer's Disease	Intervention (n=23)	Male, 65.2% White, NR	74.9 ± 4.9	4.8 ± 3.8
		Control (n=16)	Male, 25% White, NR	76.0 ± 6.6	3.9 ± 3.2
Greenaway (2013)	Amnestic-mild cognitive impairment	Intervention (n=20)	Male, 40.0% White, 90%	72.7 ± 6.9	16.4 ± 2.8
		Control (n=20)	Male, 38.0% White, 85%	72.3 ± 7.9	16.4 ± 2.8
Jean (2010)	Amnestic-mild cognitive impairment	Intervention (n=11)	Male, 36.0% White, NR	68.6 ± 9.2	14.5 ± 3.2
		Control (n=11)	Male, 45.0% White, NR	68.6 ± 5.9	14.6 ± 4.2
Jelcic (2012)	Early-stage Alzheimer's disease	Intervention (n=20)	Male, 10.0% White, NR	82.9 ± 3.6	6.7 ± 2.9
		Control (n=20)	Male, 25.0% White, NR	81.8 ± 5.5	8.3 ± 3.6
Kurz (2012)	Early-stage dementia	Intervention (n=100)	Male, 50.0% White, NR	72.4 ± 8.6	12.8 ± 3.1
		Control (n=101)	Male, 62.4% White, NR	75.0 ± 7.1	12.2 ± 3.0
Kwok (2011)	Mild cognitive impairment	Intervention (n=14)	Male, 35.7% White, NR	85.8 ± 4.9	≥ 12 years, 14.3%
		Control (n=17)	Male, 6.3% White, NR	72.4 ± 8.6	≥ 12 years, 11.8%
Moro (2012)	Amnestic-mild cognitive impairment	Intervention group A (n=15)	Male, NR White, NR	73.3 ± 6.9	8.9 ± 4.4
		Intervention group B (n=15)	Male, NR White, NR	68.5 ± 8.7	11.1 ± 2.8
Nagamatsu (2012)	Probable mild cognitive impairment	Intervention group A (n=30)	Male, NR White, NR	75.6 ± 3.6	≤12 years: 13.9%
		Intervention group B (n=28)	Male, NR White, NR	73.9 ± 3.4	≤12 years: 10.4%

Author (Year)	Population	Sample Size	Gender, Race	Mean Age (years)	Mean Education (years)
		Control (n=28)	Male, NR White, NR	75.1 ± 3.6	≤12 years: 13.9%
Olchik (2013)	Normal cognition (NC) and mild cognitive impairment (MCI)	NC Intervention (n=23)	NC Intervention: Male, 4.3% NC Intervention: White, NR	NC Intervention: 67 ± 6.1	NC Intervention: 13.0 ± 4.6
		MCI Intervention (n=16)	MCI Intervention: Male, 25.0% MCI Intervention: White, NR	MCI Intervention: 70.3 ± 4.3	MCI Intervention: 14.3 ± 4.9
		NC Control1 (n= 20)	NC Control 1: Male, 10.0% NC Control 1: White, NR	NC Control 1: 66.7 ± 5.1	NC Control 1: 14.9 ± 3.9
		NC Control2 (n=22)	NC Control 2: Male, 22.7% NC Control 2: White, NR	NC Control 2: 68.2 ± 6.8	NC Control 2: 12.4 ± 4.5
		MCI Control1 (n=17)	MCI Control 1: Male, 17.6% MCI Control 1: White, NR	MCI Control 1: 72.2 ± 6.3	MCI Control 1: 13.2 ± 5.2
		MCI Control2 (n=14)	MCI Control 2: Male, 14.3% MCI Control 2: White, NR	MCI Control 2: 70.2 ± 5.7	MCI Control 2: 11.2 ± 4.2
Rapp (2002)	Mild cognitive impairment	Intervention (n=9)	Male, 11.0% White, 100.0%	73.3 ± 6.6	≥12 years, 100%
		Control (n=10)	Male, 70.0% White, 90.0%	75.1 ± 7.0	≥12 years, 100%
Rozzini (2007)	Mild cognitive impairment	Intervention 1 (n=15)	Male, NR White, NR	Between 63 and 78	NR
		Intervention 2 (n=22)	Male, NR White, NR	Between 63 and 78	NR
		Control (n=22)	Male, NR White, NR	Between 63 and 78	NR
Scherder (2005)	Mild cognitive impairment	Intervention A (n=15)	Male, 13.3% White, NR	Intervention group A: 84 ± 6.4	Intervention group A: 2.6 ± 1.1
		Intervention B (n=13)	Male: 15.4% White, NR	Intervention group B: 89 ± 2.4	Intervention group B: 2.9 ± 1.1
		Control (n=15)	Male, 6.7% White, NR	Control group: 86 ± 5.1	Control group: 2.7 ± 1.7

Author (Year)	Population	Sample Size	Gender, Race	Mean Age (years)	Mean Education (years)
Stanley (2013)	Early-stage dementia	Intervention (n=16)	Male, 37.5% White, 75.0%	77.6 ± 10.5	12 years: 37.5%
		Control (n=16)	Male, 43.7% White, 56.3%	79.6 ± 9.0	12 years: 56.3%
Suzuki (2012)	Amnestic-mild cognitive impairment	Intervention (n=25)	Male, 52.0% White, NR	75.3 ± 7.5	11.1 ± 2.4
		Control (n=25)	Male, 56.0% White, NR	76.8 ± 6.8	10.8 ± 2.7
Tappen (2014)	Mild cognitive impairment and early-stage Alzheimer's disease	Intervention (n=37)	Male, 59.0% White, NR	80.9 ± 5.5	14.3 ± 3.6
		Control (n=31)	Male, 61.0% White, NR	81.8 ± 5.8	14.1 ± 2.6
Troyer (2008)	Amnestic-mild cognitive impairment	Intervention (n=24)	Male, 45.8% White, NR	76.0 ± 5.6	15.2 ± 3.3
		Control (n=24)	Male, 45.8% White, NR	74.8 ± 7.7	14.3 ± 3.1
Tsolaki (2011)	Mild cognitive impairment	Intervention (n=122)	Male, 22.8% White, NR	68.5 ± 7.0	9.3 ± 4.1
		Control (n=79)	Male, 26.2% White, NR	66.9 ± 8.8	9.0 ± 4.2
van Paasschen (2013)	Early-stage Alzheimer's disease	Intervention (n=7)	Male, 42.9% White, NR	72.6 ± 7.3	10.1 ± 2.5
		Control (n=12)	Male, 33.3% White, NR	75.8 ± 8.7	10.0 ± 1.4
van Uffelen (2008)	Mild cognitive impairment	Intervention 1 (n=77)	Male, 48.1% White, NR	Intervention 1 Men 74.0 ± 2.7 Intervention 1 Women 76.0 ± 2.9	Men, ≤ 12 years 57% Women, ≤ 12 years 64%
		Intervention 2 (n=78)	Male, 56.4% White; NR	Intervention 2 Men 75.0 ± 2.7 Intervention 2 Women 76.0 ± 2.9	Men, ≤12 years 61% Women, ≤12 years 52%
		Control 1 (n=75)	Male, 64% White, NR	Control 1 Men 75.0 ± 2.8 Control 1 women 75.0 ± 2.9	Men, ≤12 years 42% Women, ≤12 years 70%
		Control 2 (n=74)	Male; 55.4% White; NR	Control 2 Men 74.0 ± 2.9 Control 2 Women 76.0 ± 2.9	Men, ≤12 years 34% Women, ≤12 years 82%
Wells (2013a, b)	Mild cognitive impairment	Intervention (n=7)	Male, NR White, NR	73.0 ± 8.0	NR

Author (Year)	Population	Sample Size	Gender, Race	Mean Age (years)	Mean Education (years)
		Control (n=7)	Male, NR White, NR	75.0 ± 7.0	NR
Wesson (2013)	Early-stage dementia	Intervention (n=11)	Male, 54.5% White, NR	78.7 ± 4.2	10.6 ± 2.4
		Control (n=11)	Male, 63.6% White, NR	80.9 ± 5	12.0 ± 4.3
Zhuang (2013)	Mild cognitive impairment and early-stage dementia	Intervention (n=19)	Male, 21.1% White, NR	83.5 ± 7.3	8.6 ± 4.2
		Control (n=14)	Male, 28.6% White, NR	82.6 ± 7.1	6.6 ± 5.4

Note. NR=Not Reported

Table 3

Intervention Characteristics and Study Outcomes

Author (Year)	Intervention	Primary Outcomes	Secondary Outcomes	Statistically Significant Between Group Findings
Baker (2010)	2 groups: **1** High intensity aerobic exercise intervention group **2** Stretching control group	Symbol-Digit Modalities, Verbal Fluency, Stroop, Trail Making B, Task Switching, Story Recall, and List Learning	Fasting plasma levels of insulin, Cortisol, Brain Derived Neurotrophic Factor, Insulin growth factor-I, and B amyloids 40 and 42	Exercise demonstrated modestly larger improvements in Symbol-Digit Modalities and Verbal Fluency relative to control.
Barnes (2009)	2 groups: **1** Computer-based brain games intervention group **2** Passive computer games control group	Repeatable Battery for Assessment of Neuropsychological Status (total score)	RBANS Index, California Verbal Learning Test- II, Controlled Oral Word Association Test, Boston Naming Test, California Trail Making Test and Design Fluency test from the Delis- Kaplan Executive Function Scale, Spatial Span Test	Among the outcomes, computer-based brain games demonstrated larger improvements in only Spatial Span Test compared to control based on reported effect sizes.
Boripuntakul (2012)	2 groups: **1** Cognitive training intervention group **2** No treatment control group	Memory, Attention, Executive Functions - Logical memory Part I and II, Digit Span, Trail Making A and B	Neurochemistry biomarkers, the myoinositol/creatine (mI/Cr) ratio	No between group analyses were reported.
Bottino (2005)	2 Groups: **1** Cognitive training intervention group **2** Routine treatment group Both groups received pharmacotherapy	Mini-Mental State Examination, CDR, and Cognitive Subscale of the Alzheimer's Disease Assessment Scale	Vocabulary and Block design subtests from Wechsler Intelligence Revised Scale, Forward and Backward Digit Span from Wechsler Memory Revised Scale, Trails Making Test A and B, Verbal Fluency Semantic, Boston Naming Test, Fuld Object Memory Evaluation; Caregivers completed Hamilton Anxiety Scale and Montgomery-Asberg Depression Rating Scale	Cognitive training demonstrated modestly larger improvements in Mini-Mental State Examination and Backward Digit Span scores relative to control.
Burgener (2008)	2 groups: **1** Taiji exercises, cognitive-behavioral therapies, support intervention group **2** Educational control group	Mini-Mental State Examination, Single Leg Stance, Berg Balance Scale, and CIRS	Geriatric Depression Scale, Rosenberg's Self-Esteem Scale	At the mid-point in follow-up (20 weeks), the multimodal intervention group demonstrated higher Mini-Mental State Examination scores and self-esteem than the attention control.
Burns (2005)	2 groups: **1** Psychodynamic interpersonal therapy intervention group	Cornell Scale for Depression, Mini-Mental State Examination	Bristol ADL Scale	No between group differences were found.

Author (Year)	Intervention	Primary Outcomes	Secondary Outcomes	Statistically Significant Between Group Findings
	2 No treatment control group			
Buschert (2011)	2 groups: **1** Multicomponent cognitive training intervention group **2** Self-study of exercises control group	Alzheimer's disease assessment scale, Mini-Mental State Examination	Repeatable Battery for the Assessment of Neuropsychological Status, Trail Making Test A and B, Montgomery Asberg Depression Rating Scale	Between group differences were only found for those with aMCI. Cognitive training demonstrated modestly larger improvements in Alzheimer's Disease Assessment Scale and Montgomery Asberg Depression Rating Scale relative to control.
Buschert (2012)	2 groups: **1** Multicomponent cognitive training intervention group **2** Self-study of exercises control group	Mini-Mental State Examination, Alzheimer's Disease Assessment Scale - cognitive domain	Repeatable Battery for the Assessment of Neuropsychological Status, Trail Making Test A and B, Montgomery Asberg Depression Rating Scale, Quality of Life-Alzheimer's Disease scale	No between group differences were found.
Carretti (2013)	2 groups: **1** Working memory training intervention group **2** Educational activities control group	Categorization Working Memory Span Test	Forward and Backward Digit Span, Dot matrix, List recall, Cattell test	No between group analyses were reported.
Finn (2011)	2 groups: **1** Computer-based cognitive training **2** No treatment control group	Cambridge Automated Neuropsychological Test Battery, Paired associates learning, Intra/ extra-dimensional set shifting, Rapid visual information processing	Memory Functioning Questionnaire, Memory Controllability Inventory, Depression Anxiety and Stress Scale	Computer-based cognitive training demonstrated modestly larger improvements in visual sustained attention relative to control.
Gaitan (2013)	2 groups: **1** Traditional in-person cognitive training intervention group **2** Computer-based plus traditional cognitive training intervention group	Digits forward span, Forward Spatial Span, Stroop Test, Digit backward span, Spatial Span backward, List learning, List learning Free Recall List Learning Recognition, and more	Iowa Gambling Task (decision making), Memory failures in Everyday Memory, Geriatric Depression Scale	Computer-based plus traditional cognitive training demonstrated modestly larger improvements in Mini-Mental State Examination Scores, disadvantageous deck, and State-Trait Anxiety Inventory relative to control.
Greenaway (2013)	2 groups: **1** Memory Support System with training intervention group **2** Memory Support System without training control group	Mini-Mental State Examination, Everyday Cognition, Dementia Rating Scale	Adherence, Center for Epidemiological Studies-Depression, Quality of life-AD, Chronic Disease Self-Efficacy Scales	No between group differences were found.
Jean (2010)	2 groups: **1** Errorless cognitive training intervention group	Training Measure	Dementia rating scale, California Verbal Learning Test, Self-Esteem Scale, Mini-Mental State Examination, Multifactorial memory Questionnaire, Rivermead Behavioral memory Test	No between group differences were found.

Author (Year)	Intervention	Primary Outcomes	Secondary Outcomes	Statistically Significant Between Group Findings
	2 Errorful learning cognitive training intervention group			
Jelcic (2012)	2 groups: **1** Lexical semantic stimulation (LSS) intervention group **2** unstructured cognitive stimulation (UCS) control group	Mini-Mental State Examination, Boston Naming Test, Verbal Naming Test, Phonemic and Semantic Fluency, Brief Story Recall, Rey Auditory Learning	Forward Digit Span, Rey-Osterrieth Complex Figure, Stroop Test, Attentive Matrices, Trail Making Test A and B, ROCF Copy, Clock Drawing Test, and instrumental activities of daily living	After Bonferroni correction for multiple comparisons, LSS demonstrated modestly larger improvements Mini-Mental State Examination, Boston Naming Test, Verbal Naming Test, and Story Delayed Recall relative to relative to UCS.
Kurz (2012)	2 groups: **1** Cognitive training intervention group **2** Treatment as usual control group	Bayer-ADL scale	Aachen Functional Item Inventory, Quality of Life in Dementia, Geriatric Depression Scale, Neuropsychiatric Inventory	No between group differences were found.
Kwok (2011)	2 groups: **1** Calligraphy training intervention group **2** No treatment control group	Chinese version of the Mini-Mental State Examination	None listed	Calligraphy demonstrated moderately large improvements in the Chinese Mini-Mental State Examination relative to control.
Moro (2012)	2 groups: **1** Cognitive stimulation intervention group **2** No treatment control group	Auditory Verbal Learning Test	Bell test, Omissions, False recognitions, Listening span test, Story recall, Verbal fluency, Tower of London, Analogies, Stroop test, Trail Making Test A and B	Cognitive stimulation demonstrated modest improvements for immediate and delayed recall, listening span test, story recall, Trail-Making Test A, and verbal span relative to control.
Nagumatsu (2013)	3 groups: **1** Aerobic training (AT) intervention group **2** Resistance training (RT) intervention group **3** Balance and tone control group	Stroop Test	Trail Making Tests, Verbal Digits Tests, memorizing face-scene pairs, Everyday Problems Test, fMRI	RT demonstrated higher Stroop test and associative memory task as well as changes in 3 regions of the cortex relative to control. AT demonstrated improved balance, mobility, and cardiovascular capacity relative to control. No differences were found between experimental conditions.
Olchik (2013)	3 groups: **1** Memory training intervention group **2** Education control group **3** No treatment control group	Verbal Fluency, FAS Verbal Fluency, Rey Auditory Verbal Learning Test, Rivermead Behavioral Memory Test	None listed	No between group differences were found.
Rapp (2002)	2 groups: **1** Multifaceted intervention group	Consortium of the registry of Alzheimer's Disease, Mini-Mental State Examination	Memory Functioning Questionnaire, Memory controllability Inventory, Profile of Mood States	At follow-up, multifaceted intervention group demonstrated better perceived

Author (Year)	Intervention	Primary Outcomes	Secondary Outcomes	Statistically Significant Between Group Findings
	2 No treatment control group			memory ability and mnemonic use relative to control.
Rozzini (2007)	3 groups: **1** Neuropsychological Training with Cholinesterase Inhibitors intervention group **2** Cholinesterase inhibitors intervention group **3** No treatment control group	Short Story, Letter Verbal Fluency, Semantic Verbal Fluency, Raven's Colored Matrices, Rey's Figure Copy, Rey's Figure Recall	Neuropsychiatric Inventory, Geriatric Depression Scale	No between group differences were found.
Scherder (2005)	3 groups: **1** Walking intervention group **2** Hand and face exercise intervention group **3** Social control group	Category Naming, Trail Making A and B, Digit Span, Visual memory Span, Verbal learning and Memory Test, Rivermead Behavioral Memory Test	None listed	When combining the 2 treatment groups, the treatment group demonstrated medium effect sizes for improvement in category naming relative to control.
Stanley (2013)	2 groups: **1** Peaceful Mind intervention group **2** No treatment control group	Neuropsychiatric inventory anxiety subscale, Rating Anxiety in Dementia Scale	Penn State Worry Questionnaire, Geriatric Anxiety Inventory, Geriatric Depression Scale, Quality of life in Alzheimer's Disease	At 3 months (not 6 months), Peaceful mind demonstrated a large effect on Rating Anxiety in Dementia Scale and quality of life relative to control.
Suzuki (2012)	2 groups: **1** Multicomponent exercise intervention group **2** Education class control group	Mini-Mental State examination, WMS-LM I and II, Digit Symbol-Coding, Letter Verbal Fluency Test, Category Verbal Fluency Test, Stroop Tests	None listed	Multicomponent exercise demonstrated modestly larger improvements for Mini- Mental State Examination, immediate recall, and Letter Verbal Fluency Test relative to control.
Tappen (2014)	2 groups: **1** Cognitive training intervention group **2** Life story interview control group	Fuld Object Memory Evaluation, Direct Assessment of Functional Status, Face-Name Association Task, Phonemic Fluency and Controlled Oral Word Association, Picture Description Test, prospective memory tasks	None listed	Cognitive training demonstrated modestly larger improvements for Face-Name Association Task and financial management relative to control.
Troyer (2008)	2 groups: **1** Cognitive training intervention group **2** Lifestyle information control group	Memory Toolbox, Multifactorial Metamemory Questionnaire, Impact Rating Scale, Lifestyle Importance, Objective Memory Ability tests	None listed	Cognitive training showed modestly larger improvements for Mini-Mental State Examination, immediate and delayed recall, and Digit Span Total relative to control.
Tsolaki (2011)	2 groups: **1** Cognitive training intervention group	Rivermead Behavioral Memory Test, Rey Auditory Verbal Learning Test, Rey-Osterrieth Complex Figure	None reported.	Cognitive training demonstrated modestly larger improvements for executive function, verbal memory,

Author (Year)	Intervention	Primary Outcomes	Secondary Outcomes	Statistically Significant Between Group Findings
	2 No treatment control group	Test-Delayed Recall, Montreal Cognitive Assessment, Test of Everyday Attention, Digit Symbol, Functional Cognitive Assessment Scale, Trail Making B, Verbal Fluency Test, Boston Naming Test, Boston Diagnostic Aphasia Examination, Functional Rating Scale of Symptoms of Dementia		praxis, daily function, and general cognition relative to control.
van Paasschen (2013)	3 groups: **1** Cognitive rehabilitation intervention group **2** Relaxation therapy control group **3** No treatment control group	Canadian Occupation Performance Measure (COPM), Hospital Anxiety and Depression Scale	fMRI	With the two control groups combined, cognitive rehabilitation demonstrated modestly large improvements for COPM ratings for satisfaction and performance and fMRI (e.g., superior frontal gyrus and medial front gyrus) relative to control.
van Uffelen (2008)	4 groups: **1** Walking program + vitamin B intervention group **2** Walking program + placebo pill intervention group **3** Low intensity activity + vitamin B intervention group **4** Low intensity activity + placebo pill control group	Memory by the Auditory Verbal Learning Test, Verbal Fluency Test, Digit Symbol Substitute Test, and Stroop Color Word Test	None listed	Women in the walking program + vitamin B group demonstrated modestly large improvements on the Digit Symbol Substitute Test compared to those in the control group.
Wells (2013a, b)	2 groups: **1** Mindfulness based stress reduction intervention group **2** No treatment control group	Safety and feasibility (a), seed-based functional connectivity, volumetric (b)	Alzheimer's Disease Assessment Scale-cognitive subscale	No between group changes were shown for behavioral measures. Mindfulness based stress reduction group demonstrated modestly larger improvements for functional connectivity between the posterior cingulate cortex, bilateral medial prefrontal cortex, and left hippocampus compared to control.
Wesson (2013)	**1** Home hazard reduction and exercise intervention program **2** No treatment control group	Interview for Deterioration of Daily Activities, Cornell Scale for Depression in Dementia, Incidental and Planned Exercise Questionnaire	None listed	No between group differences were found.
Zhuang (2013)	2 groups: **1** Human-computer interaction-based cognitive training intervention group	Addenbrooke's Cognitive Examination -Revised	None listed	No between group differences were found.

Author (Year)	Intervention	Primary Outcomes	Secondary Outcomes	Statistically Significant Between Group Findings
	2 No treatment control group			