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Exercise Training for Persons with Alzheimer's Disease and Caregivers: A Review of Dyadic Exercise Interventions

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Abstract

Alzheimer's disease (AD) is the most common form of dementia and the prevalence will increase dramatically in the next decades. Although exercise has shown benefits for people with dementia due to AD as well as their caregivers, the impact of a dyadic exercise intervention including both groups as study participants remains to be determined. The authors review the current clinical evidence for dyadic exercise interventions, which are exercise regimens applied to both the person with dementia and the caregiver. A total of 4 controlled trials were reviewed. This review shows that dyadic exercise interventions are feasible and may produce a positive effect on functional independence and caregiver burden. However, there was insufficient evidence to support a benefit of dyadic exercise intervention on cognitive performance and on behavioral and neuropsychiatric symptoms in participants with dementia due to AD. A dyadic exercise intervention improves functional independence and caregiver burden. However, there is a need for well-designed randomized controlled clinical trials to confirm these benefits and to investigate several important points such as the effects of a dyadic exercise intervention on cognitive and noncognitive outcomes of AD, the optimal intensity of exercise training, and the cost effectiveness of such a program.

Keywords

Alzheimer's disease; caregivers; clinical trial; exercise

Alzheimer's disease (AD) is the most common form of dementia. The prevalence of AD in Americans of all ages was estimated to be 5.4 million in 2016 and this number will increase dramatically in the next decades (Alzheimer's Association, 2016). Individuals with AD

present with impaired short- and long-term memory as well as impairment of abstract thinking and judgment, disturbances of higher cortical function (e.g., aphasia, apraxia), changes in personality, and behavioral abnormalities. Both cognitive and noncognitive features of the disease impact the quality of life of people living with AD as well as their caregivers (Alzheimer's Association, 2016). A caregiver is defined as an individual who provides support and care to a person living with AD. Unpaid caregivers are usually immediate family members and the number is estimated to be more than 15 million in the US (three caregivers per person with AD; Alzheimer's Association, 2016). They play a central role in the management of AD and other dementias and the physical and psychological effort required to provide ongoing care grows as the patient's cognitive impairment worsens. Caregivers have been shown to be at increased risk of stress and depression, experience sleep problems more often, and have poor physical health (Adelman, Tmanova, Delgado, Dion, & Lachs, 2014).

There is no known cure for AD. Currently available medications offer, at best, symptomatic relief and are associated with potential side effects (Alzheimer's Association, 2016). Therefore, alternative effective approaches are essential. Exercise training has been shown to be feasible for persons with dementia due to AD and their caregivers with potential benefits in cognitive and noncognitive outcomes for persons with dementia due to AD (Forbes, Forbes, Blake, Thiessen, & Forbes, 2015). It is important to gauge the value of exercise for individuals with dementia due to AD and their caregivers in studies that provide the exercise intervention to (a) persons with dementia due to AD, (b) caregivers, and (c) both persons with AD and their caregivers.

In this article, we review the current clinical evidence for dyadic exercise interventions including both the persons with dementia due to AD and their caregivers. For the purpose of this review, a study was included if the caregivers and the persons with dementia due to AD were actively following the exercise protocol (individual with dementia and caregivers exercising together or individually). We focus on four types of outcomes: cognitive performance, neuropsychiatric and behavioral symptoms, functional outcomes, and caregivers' outcomes. We will then discuss the current clinical evidence for exercise-induced changes in individuals with dementia due to AD and their caregivers. Finally, we discuss the role of the caregivers in a dyadic intervention, the cost effectiveness of such programs and the potential challenges associated with implementing an exercise trial with this dyad.

Methods

Search Strategy

To identify controlled clinical trials using dyadic exercise interventions, the following electronic databases were searched: PubMed (1990 to April 1, 2016), Cochrane Library (1990 to April 1, 2016), Embase (1990 to April 1, 2016), and Google Scholar (1990 to April 1, 2016). Searches were performed utilizing the following terms: *exercise*, *dyad*, *Alzheimer's disease*, *physical activity*, *caregiver*, *dementia*. In addition, citation tracking was used to identify reference lists from included studies.

A study was included in the present review if it met the following criteria: (a) the target population was patients with dementia due to AD according to international diagnostic criteria (if patients with other forms of dementia were studied, the proportion of patient with a clinical diagnosis of dementia due to AD should be > 70% of the total sample for a study to be included in the review); (b) exercise training was the intervention evaluated for both the individual with dementia and the caregiver; (c) the effects of treatment intervention were tested as the primary outcome; (d) the effects of exercise training were compared with control or comparison groups, including other forms of physical activity or exercise; (e) the article was available in English; (f) the study was a controlled clinical trial restricting the review to class I, II, and III studies according to the classification of level of evidence of the American Academy of Neurology (Gross & Johnston, 2009).

Results

The search strategy led to four controlled trials investigating the effect of a dyadic exercise intervention including both the persons with dementia due to AD and the caregivers (Canonici et al., 2012; Lowery et al., 2014; Pitkala et al., 2013; Prick, de Lange, Twisk, & Pot, 2015). We also included secondary analyses of the Pitkala et al. study (Öhman et al., 2016). The main characteristics and results of each study are summarized in Table 1.

Intervention—All the studies evaluated a dyadic exercise intervention against a no-exercise control group (usual care; Canonici et al., 2012; Lowery et al., 2014; Öhman et al., 2016; Pitkala et al., 2013; Prick et al., 2015). One study also compared two different types of intervention: customized home-based exercise and group-based exercise (Pitkala et al., 2013). In one study, the control group also received monthly information bulletins and monthly phone calls for the duration of the study (Prick et al., 2015). Across all of the studies, the interventions were clinically heterogeneous with regard to the frequency and duration of exercise being undertaken and duration of intervention: between 20 and 45 min of exercise per session, between two and five times per week for 3–12 months. The studies also were heterogeneous with regard to the exercise interventions: one study used a combination of aerobic (e.g., Nordic walking), strength, dual-task (e.g., talking while walking), and balance training (Pitkala et al., 2013). One study used a combination of flexibility, strengthening, balance, and endurance exercises as well as psychoeducation, communication training, skills training, and pleasant activities training (Prick et al., 2015). Walking with progressively increasing intensity was used in one study (Lowery et al., 2014), whereas a combination of flexibility, strength, agility and balance exercises as well as walking and dancing were used in another study (Canonici et al., 2012). Three studies reported supervision for the exercise intervention (Lowery et al., 2014; Pitkala et al., 2013; Prick et al., 2015). Patients trained under direct supervision of exercise physiologists for each exercise session in one study (Pitkala et al., 2013). In one study, exercise training was supervised by an exercise trainer weekly for the first four weeks and biweekly for the next eight weeks (Prick et al., 2015), whereas in another study the exercise therapist supervised the exercise program for the first six weeks and the dyad was expected to perform the exercise regimen regularly and independently at least five times per week for the next six weeks (Lowery et al., 2014). Only one study reported the expected exercise intensity

(Lowery et al., 2014). All studies included in this review examined the exercise-induced changes in individuals with dementia in the on-medicated state.

Participants—A total of 484 dyads were included in the four studies reported in this review and 391 dyads completed their allocated intervention protocol and were included in the primary analysis. The number of screened patients was reported in three studies (Lowery et al., 2014; Pitkala et al., 2013; Prick et al., 2015). Prick et al. assessed 146 dyads for eligibility to randomize 111 dyads. Lowery et al. screened 474 dyads to select 131 dyads for participation in the study. 1,264 dyads received a letter from the Social Insurance Institution of Finland offering the possibility to participate in the exercise trial, and of these 390 were screened by phone to select 210 dyads in another study (Pitkala et al., 2013). Regarding the inclusion criteria, two studies included only participants diagnosed with AD who fulfilled the criteria for probable dementia due to AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's criteria (Canonica et al., 2012; Pitkala et al., 2013). The two other studies included participants with a clinical diagnosis of dementia made by a physician (Lowery et al. also used ICD-10 Diagnostic Criteria for Research to confirm the diagnosis; Lowery et al., 2014; Prick et al., 2015). AD was the clinical diagnosis for 124 of the 131 participants in one study (other $n = 7$ of 131; Lowery et al., 2014), whereas 78 of the 111 care receivers had a clinical diagnosis of dementia due to AD in the other study (vascular dementia $n = 17$ of 111, other $n = 16$ of 111; Prick et al., 2015). Studies were heterogeneous with respect to the severity of dementia. The Clinical Dementia Rating (CDR) was used to assess the severity of dementia in two studies (Canonica et al., 2012; Pitkala et al., 2013). One study included individuals with mild to moderate dementia due to AD (CDR 1–2; Canonici et al., 2012), whereas another included individuals with mild to severe dementia due to AD (CDR 0.5–3; Pitkala et al., 2013). The two other studies used the Mini-Mental State Examination (MMSE) to assess the severity of dementia (Lowery et al., 2014; Prick et al., 2015). The mean MMSE was 14.9 ± 8.7 in controls and 16.3 ± 7.4 in the intervention group in one study (Lowery et al., 2014), whereas the mean MMSE was 21 ± 5.56 in controls and 21 ± 4.86 in the intervention group in the other study (Prick et al., 2015). Caregivers were a partner or spouse in two studies (Lowery et al., 2014; Pitkala et al., 2013). The demographic characteristics of the caregivers were not reported in one study, whereas there were 39 female controls (60.9%) and 50 women (74.6%) in the intervention group in the other study (Lowery et al., 2014). In one study, 30 of the 32 caregivers were women (93.7%) but the relationship between caregiver and care receiver was not characterized (Canonica et al., 2012). Prick et al. included spouses (100 of 111 dyads) and child or other caregivers (11 of 111) and caregivers were predominantly women (72.1% in the total sample). The adherence was reported as good in the intervention group in two studies (Canonica et al., 2012; Pitkala et al., 2013), whereas the adherence to the full exercise regimen was poor in two studies (Lowery et al., 2014; Prick et al., 2015).

Outcomes

Cognition—One study investigated the effect of exercise training on cognition in individuals with dementia across several outcome measures including the Clock Drawing Test (CDT), verbal fluency (VF), and the MMSE (Öhman et al., 2016). Executive function,

measured using CDT, improved in the home-based exercise group, and changes in the score were significantly better than those of the control group at 12 months. All groups deteriorated in VF and MMSE score during the intervention, and no significant differences between the groups were detected at 12 months (Öhman et al., 2016). In this study, 67% of individuals with AD had moderate or severe AD (CDR 2–3), and 96% were taking AD medication (Öhman et al., 2016). The three other studies did not report cognitive assessment after the intervention in individuals with AD or other types of dementia (Canonici et al., 2012; Lowery et al., 2014; Prick et al., 2015).

Neuropsychiatric and Behavioral Symptoms—Three studies investigated the effect of exercise training on neuropsychiatric and behavioral symptoms (Canonici et al., 2012; Lowery et al., 2014; Prick et al., 2015). In a controlled, single-blind, parallel-group trial of a walking regimen with incremental intensity, the intervention group was 41% more likely to experience a clinically important reduction of the Neuropsychiatric Inventory (NPI) score (Lowery et al., 2014). However, the difference was not statistically significant at week 12 between the intervention and control groups ($p = .6$; Lowery et al., 2014). The authors also did not find any significant effect of exercise training on mental well being assessed with the General Health Questionnaire in individuals with dementia (Lowery et al., 2014). A smaller controlled study found that individuals with mild to moderate AD randomized to the exercise group showed a significant decrease in the NPI score relative to the controls (40.3 ± 34.0 to 16.9 ± 17.6 at six months vs. 39.6 ± 25.0 to 43.3 ± 18.4 at six months; Canonici et al., 2012). The third study did not find any significant effect of exercise training on behavioral symptoms in individuals with AD when assessed with the Revised Memory and Behavior Checklist, a 24-item caregiver-report measure of observable behavioral problems in the care receiver with dementia (Prick et al., 2015).

Functional Performances and General Health—Two studies investigated the effect of exercise training on functional performances in individuals with AD across several outcomes including the Functional Independence Measure (FIM; Canonici et al., 2012; Pitkala et al., 2013), the Short Physical Performance Battery and the 10-m walking test (Pitkala et al., 2013), the Berg Functional Balance Scale and instrumental daily activities assessed with the Pfeffer Questionnaire (Canonici et al., 2012). One study also assessed general health with the Standard single-item scale for self-rated general health (Prick et al., 2015). The FIM was preserved following a six-month multicomponent motor intervention program focusing on stretching, flexibility, strength, agility, and balance, whereas the controls showed a significant decline ($p = .01$; Canonici et al., 2012). This study also reported better scores in functional balance (Berg scale) in the exercise group compared to the control group (Canonici et al., 2012). In another study, the decline in functional independence was slower for the home-based and the group-based exercise groups compared to controls (Pitkala et al., 2013). Even though there was no statistically significant difference regarding the walking speed between the three groups, participants in the exercise groups had significantly fewer falls than the controls during follow-up (Pitkala et al., 2013). Prick et al. did not find any significant difference between the exercise group and the control group regarding general health (Prick et al., 2015).

Caregiver Burden—Caregiver burden was assessed in three studies (Canonici et al., 2012; Lowery et al., 2014; Prick et al., 2015). Caregiver burden as measured by the Zarit Caregiver Burden Interview doubled from 16% at baseline to 32% by week 12 for the control group participants (usual care) but decreased from 23% to 17% for those in the intervention group ($p = .01$) in one study (Lowery et al., 2014). Another study using the same scale found that caregiver's burden decreased in the intervention group while it remained stable in the controls ($p < .5$; Canonici et al., 2012). Conversely, one study did not find any significant effect of the dyadic exercise intervention on caregiver's burden, caregiver's mood or salivary cortisol used as a noninvasive assessment of stress in caregivers (Prick et al., 2015).

Discussion

Potential Benefits of Exercise Training on the Symptoms of Dementia:

Cognitive Performances, Neuropsychiatric and Behavioral Symptoms—Given the current review, a dyadic exercise intervention may improve executive function in individuals with dementia when compared to a control group. However, change in cognitive performance was only assessed in one study (Öhman et al., 2016) and there is a need for a well-designed controlled clinical trial that is powered to detect differences in cognitive outcomes in individuals with AD and that includes both on and off anticholinergic medication testing to truly assess cognitive changes without any confounding effect of medication. It is important to note that, even though the study by Öhman et al. had a rigorous methodology with a large sample size ($n = 210$ dyads at baseline, $n = 161$ assessed at 12 months), the findings presented were secondary outcomes and the effects were mild and limited to executive functioning. Based on the present review, it is also unclear if a dyadic exercise intervention provides benefit for neuropsychiatric and behavioral symptoms in individuals with dementia. A recent Cochrane review on the effect of exercise on people with dementia included 17 trials with a total of 1,067 participants, most of whom were older individuals with a clinical diagnosis of AD (Forbes et al., 2015). This review suggested that exercise training may improve the ability to perform activities of daily living in people with dementia but found no significant effect of exercise on cognition, behavior disorders, and depression (Forbes et al., 2015). The studies included in this review were heterogeneous with regard to the type of intervention program, the duration of the intervention, or the severity of the disease preventing us from making any clear conclusion in patients with dementia. Other clinical trials have shown that exercise training has positive effects on global cognition and executive function in individuals at risk for AD (Lautenschlager et al., 2008; van Uffelen, Chinapaw, van Mechelen, & Hopman-Rock, 2008). Therefore, individuals with dementia may have less cognitive benefit from exercise than those at risk of AD (i.e., mild cognitive impairment). Further study is needed to investigate the effect of exercise training on different domains of cognition, and to understand central mechanisms that may be responsible for changes in cognitive performances in individuals with AD and its risk of AD.

Potential Benefits of Exercise Training for Physical Functioning and General Health in Individuals with AD

—This review supports the fact that a dyadic exercise training intervention can improve functional outcome and balance in individuals with AD. Balance and mobility impairments in older people have been shown to be a strong

independent risk factor for falling (Deandrea et al., 2010). Falls lead to a fear of falling and loss of confidence, which may result in a decline in activity and ultimately a decrease in strength, balance, and mobility, leading to decreased functional ability and a loss of independence (Rasinaho, Hirvensalo, Leinonen, Lintunen, & Rantanen, 2007). Falls are also often a trigger for emergency department or hospital admission for older people with dementia or admission to residential care (Rowe & Fehrenbach, 2004). In line with the results of the present review, a systematic review and meta-analysis of four randomized controlled studies found that strength, balance, and endurance or mobility training can assist in the reduction of falls in individuals with dementia (Burton et al., 2015).

Going beyond the outcomes reported in the four studies included in this review, another point to consider is the potential impact of exercise training on several aspects of health in persons with AD. The benefits of exercise training for cardiovascular function are well established for several diseases including heart diseases, diabetes and obesity (Ades et al., 2011; Church et al., 2011; Khan et al., 2012). Because of the possible inverse relationship between cardiovascular fitness and cognitive impairment in the elderly and the fact that atherosclerosis and vascular pathology within the brain may play an important role in the pathophysiology of AD and other dementias, we suggest that exercise training (especially endurance exercise training) not only may be a therapy of choice in this population, but may have an even greater benefit for people with dementia with comorbid complications (Buratti et al., 2015; Hillman, Erickson, & Kramer, 2008; Prins & Scheltens, 2015). Moreover, beside the potential benefits for the brain and the cardiovascular system, exercise training has been shown to be beneficial for depression, fatigue, sleep-disorders, autonomic dysfunction and constipation in older adults (Billman & Kukielka, 2006; Kelley & McClellan, 1994; King, Oman, Brassington, Bliwise, & Haskell, 1997; Peters, De Vries, Vanberge-Henegouwen, & Akkermans, 2001). These symptoms are very common in AD and exercise training may have the same beneficial effects in those with AD as in healthy people.

Potential Benefits of Exercise Training for the Caregivers

Direct Benefit of Exercise Training on Caregiver's Burden—Studies have shown that caregivers often do not have the time to engage in preventive health behaviors such as regular exercise training, and studies have found that caregivers participate in less formal exercise compared to noncaregivers (Fredman, Bertrand, Martire, Hochberg, & Harris, 2006; Hirano et al., 2011). Two of the studies included in this present review reported positive effects of exercise training on caregiver burden (Canonici et al., 2012; Lowery et al., 2014) whereas one study did not find any significant benefit (Prick et al., 2015). The negative results in this study may partially be explained by the low compliance during the intervention (Prick et al., 2015). Indeed, only nine dyads (15.8%) were fully compliant with the exercise program and 43 dyads (75.4%) were characterized as moderately compliant (Prick et al., 2015). Therefore, there is evidence that a dyadic exercise training intervention may improve caregiver's burden. A systematic review including four randomized clinical trials comparing physical activity in caregivers of people with dementia with a control group found that physical activity may have direct psychological benefits for the caregivers and may reduce subjective caregiver burden (Orgeta & Miranda-Castillo, 2014). For instance,

King and Brassington (1997) showed that brisk walking was associated with a significant improvement in anger expression in comparison to controls (usual activity). In another study, brisk walking was associated with a significant improvement in caregivers' subjective burden assessed by the Screen for Caregiver Burden scale, depression assessed by the Beck Depression Inventory scale and stress assessed by the Total Manifest Anxiety Scale (TMAS; King et al., 2002). However, there was no significant difference regarding depression and stress between the exercise group and a group following a nutrition education program (King, 2002). A recent 36-week crossover pilot clinical trial investigated the effect of exercise in both individuals with AD and caregivers but was not included in Table 1 (Barnes et al., 2015). Even though participants and caregivers were enrolled as dyads, caregivers were not actively following the exercise protocol and caregiver measures included questionnaires about the participants' functional status, quality of life, and dementia-related behaviors as well as their own level of distress with behaviors and overall burden (Barnes et al., 2015). With respect to caregiver burden, the results were not statistically significant but suggested potentially clinically meaningful improvement (Barnes et al., 2015). The positive effect of an exercise-training program on caregiver burden could be secondary to several potential benefits for the caregivers. First, exercise can decrease levels of stress and has been shown to have a positive effect on depression (Loi et al., 2014). Second, exercise can improve motor and nonmotor functioning of the individual with dementia leading to a reduced burden of care. Third, fostering a bonding experience and establishing mutual purpose with the individual with dementia may reduce caregiver burden. Last, there are likely personal health benefits for the caregiver following an exercise regimen and it may increase their capacity to care for individuals with dementia. Therefore, exercise training may improve psychological outcomes in caregivers of patients with dementia. The heterogeneity between the type of intervention, the inclusion and exclusion criteria, and the small sample sizes restrict the generalizability of results and more research is needed to assess the potential benefit of exercise training in caregivers on psychological and nonpsychological outcomes.

Indirect Benefits of Exercise Training on Caregiver's Burden—Exercise training in persons with AD has potential indirect benefits for the caregivers. In a Cochrane review, none of the 17 studies included caregivers as actual exercise participants and no studies reported data on caregivers' quality of life (Forbes et al., 2015). However, two clinical trials have investigated caregiver burden as a secondary outcome (Steinberg, Leoutsakos, Podewils, & Lyketsos, 2009; Vreugdenhil, Cannell, Davies, & Razay, 2012). In one study, a community-based exercise program for participants with AD consisting of 10 simple exercises in addition to brisk walking revealed a significant improvement in caregiver burden evaluated with the Zarit Burden Interview (Vreugdenhil et al., 2012). This study provides evidence that challenging and potentially improving motor function of the individual with AD can lead to a reduced burden of care. However, in the second study, an exercise intervention delivered by caregivers to home-dwelling participants with AD was not associated with a reduction of the caregiver burden evaluated with the Screen for Caregiver Burden (Steinberg et al., 2009). In this study, the role of the caregiver was to supervise the exercise regimen consisting of three components: aerobic fitness, strength training and balance and flexibility training. This supervising role may have been a confounding factor

when analyzing caregiver burden. In another study, 26 individuals with mild to moderate AD performed a six-month cycling program and caregiver burden was assessed using the NPI Caregiver scale (Yu et al., 2015). Caregiver distress decreased by 40% between baseline and the final assessment at six months (30% reduction in baseline score is considered to be clinically meaningful). According to the authors, this finding goes beyond the 8–10 hr of respite per week for the caregivers and they reported improved attitudes and confidence in individuals with AD, which made it easier for them to provide care (Yu & Swartwood, 2012; Yu et al., 2015). More research is needed to investigate the indirect impact of exercise training in persons with dementia on caregivers' psychological outcomes.

Potential Benefits of a Dyadic Exercise Intervention—Using a dyadic intervention could be seen as effective because of the mutual influence between the person with dementia and the informal caregiver. A systematic review including 50 studies between 1992 and 2005 showed that dyadic psychosocial interventions are effective in improving various outcomes in individuals with AD and their caregivers including behavioral problems, quality of life, and mood. However, the outcomes for the person with dementia and the caregiver varied between studies using different interventions, designs, or methodologies (Van't Leven et al., 2013). The authors concluded that studies should carefully match the targeted functional domains, intervention components, and delivery characteristics of a program with the needs of the person with dementia and the family caregiver (Van't Leven et al., 2013). This present review demonstrates that including both persons with AD and their caregivers in exercise clinical trials is feasible and may produce a positive effect on the tested outcomes, especially when programs target caregiver burden and functional independence. However, further study is needed to investigate the effect of a dyadic exercise intervention on cognitive performances, behavioral and neuropsychiatric symptoms, quality of life, and other common symptoms in people with dementia (e.g., sleep disturbances, fatigue).

What Should be the Role of the Caregiver in a Dyadic Exercise Intervention?—

A dyadic exercise intervention provides new information on the effects of exercise training in individuals with dementia and their caregivers. Involving caregivers has been evaluated in other nonpharmacological interventions, such as cognitive stimulation interventions, and it has shown positive benefits for both caregivers and people with dementia (Onder et al., 2005; Quayhagen et al., 2000). To maintain any potential benefit after the end of a trial for the individual with dementia, the caregiver should continue to implement the skills he or she gained during the study. Initial readiness and therapeutic engagement were two factors associated with caregiver readiness to use nonpharmacological strategies to manage behavioral symptoms of dementia in one study (Gitlin & Rose, 2014). There is also evidence that the dynamic and multidimensional relationship between the caregivers and the person with AD is extremely important, and is a key factor in maintaining a sense of self and personhood for the patient (Whitlatch, 2001). Whitlatch argued that the integration of persons with dementia in family caregiving research could provide new insight into caregivers' burden while promoting autonomy of the individual with dementia. We agree with Whitlatch's point of view and we suggest that exercise research is an excellent approach to conducting randomized controlled trials including both populations.

The treatment success of nonpharmacological interventions such as exercise training in persons with dementia depends on the skills and motivation of the medical staff, hospital and primary care environment, and motivation of the persons with dementia to complete the exercise program (Teodorczuk, Welfare, Corbett, & Mukaetova-Ladinska, 2010). However, because of impaired memory, thinking, and judgment, the motivation of the demented persons is directly influenced by caregivers' implementation. This is a very important point to consider in designing an exercise clinical trial for persons with dementia as well as in generalizing and applying the results in routine practice settings. Optimal rehabilitation training should involve the active participation of the patient as opposed to passive manipulation (Katalinic, Harvey, & Herbert, 2011; Nielsen, Willersley-Olsen, Christiansen, Lundbye-Jensen, & Lorentzen, 2015). The other key components of an optimal rehabilitation program include challenging the skill of the person training, motivating and rewarding, intensive training for as long a period of time that is feasible, and carefully organizing the training in the setting of other activities (Nielsen et al., 2015). Importantly, the patients and caregivers need to understand that consistent training several times a week will be part of the rest of their lives if they want to maintain any potential benefits. Ideally, a therapist would be available during all training sessions, however this is not practically possible for the majority of patients outside of a clinical trial setting due to cost, accessibility issues, and other prohibitive factors. Therefore, trained caregivers could play a central role by continuing regular and challenging training with the persons with AD in the absence of a therapist. Periodic reinforcement with a therapist will be a component of the rehabilitation training regimen to adapt the level of difficulty of training with the goals of improving the performance of a given task and achieving new skills to promote brain plasticity (Burke & Barnes, 2006; Nielsen et al., 2015). Thus, we propose that the caregivers would also play a significant role in the training of persons with AD and the promotion of short- and long-term brain plasticity by increasing adherence to the exercise program.

Cost Effectiveness and Health Care Implications—Including both the persons with AD and the caregivers in exercise training clinical trials would also allow more precise cost effectiveness analyses. Lowery et al. (2014) found that a dyadic exercise intervention was more cost effective than usual treatment from both societal as well as health and social care perspectives with respect to behavioral and psychological symptoms as an outcome measure. However, it did not appear to be cost effective in terms of cost per quality-adjusted life-year gain (Lowery et al., 2014). The costs of dementia include direct medical costs for the persons with dementia, informal (family) care and social care costs (World Alzheimer Report, 2010). In a review, Knapp, Iemmi, & Romeo, (2013) found no evidence that physical exercise programs were cost-effective, whereas cognitive stimulation therapy, tailored activity programs and occupational therapy were more cost-effective than usual care for people with AD. The results regarding exercise programs should be interpreted with caution due to low methodological quality of available studies, the difficulty of generalizing from available evidence, and the narrowness of cost measures (Knapp et al., 2013). For these reasons, there is a need for large trials with cost effectiveness analyses that evaluate medical, informal and social costs. With regard to direct medical care, nonpharmacological intervention has been evaluated and occupational therapy was found to be highly cost effective as financial expenditures were reduced for general practitioner and hospital visits

for patients with caregivers who received therapeutic interventions (Graff et al., 2008). By improving caregiver health and well-being, exercise training has the potential to reduce informal care. Cost of institutionalization is the major component of the social care cost in dementia (World Alzheimer Report, 2010). In a hospital setting, a randomized controlled study found that structured caregiver training prolonged the time to nursing home admission and accordingly increased survival of dementia patients over an observation period of eight years (Brodaty, Gresham, & Luscombe, 1997). We expect that including caregivers in exercise training clinical trials will not only improve caregiver burden, but also lead to better training and a more beneficial role for the caregivers, in turn extending the time to nursing home admission. A combined exercise intervention for both persons with AD and their caregivers benefits the health of both groups, and for this reason demonstrates the potential to be cost-effective.

Potential Challenges of Implementing a Dyadic Exercise Intervention—

Interventional studies provide social engagement and interaction in individuals with dementia and their caregivers. However, many caregivers still carry professional and familial responsibilities and one can imagine a potential burden for caregivers with an exercise program repeated several times a week with the same type of exercise for several weeks. This could influence recruitment of dyads and outcomes such as quality of life or caregiver burden as well as compliance to the exercise regimen. On the other hand, elderly spouses or partners may have physical limitation or mental illness themselves and may not be able to provide support and follow an exercise regimen. By using a dyadic intervention design, one may predict that caregivers would spend more time with the care recipients. Even though the benefit of respite care for caregivers is unclear (Maayan, Soares-Weiser, & Lee, 2014) it has been shown to have potential beneficial effects for the care recipients and possibly delay nursing home admission (Health Quality Ontario, 2008). The issue of low compliance with exercise interventions is an important point to consider and adherence rates to an exercise regimen are difficult to measure accurately. Several assessment methods are used including self-report inventories and exercise logs, objective measurements such as heart rate monitors, and observational measurements such as research assistants recording the amount of exercise participants completed. Each of these methods has relative strengths and weaknesses in terms of accuracy, cost, and feasibility (Linke, Gallo, & Norman, 2011). Therefore, we recommend using a combination of subjective and objective measurements to assess adherence to the exercise intervention. In this review, adherence to the exercise regimen for individuals with dementia ranged greatly between studies and explicit reasons why exercise adherence was low were not always reported. Suttanon et al. (2012) and Suttanon et al. (2013) conducted a detailed analysis, interviewing the persons with dementia and caregivers included in a randomized clinical trial investigating the effect of a home-based exercise programme for older people with AD. They found that preexisting or acute health conditions, a dislike of structured exercise, and caregiver causes (health and unavailable) were reasons for lower levels of adherence and concluded that regular support from a physiotherapist and caregiver were key elements facilitating program adherence in people with AD (Suttanon et al., 2012). Behavioral and cognitive strategies have been reported to increase the adherence to exercise (Woodard & Berry, 2001) and cognitive behavioral therapy has also been shown to be effective in reducing symptoms of depression

and anxiety for people with dementia (Orgeta, Qazi, Spector, & Orrell, 2015). Therefore, we recommend including the caregiver as an active participant and using a multicomponent intervention with exercise, cognitive behavioral therapy, skills training, or coping strategies for the caregivers as a way to improve adherence to the exercise regimen and decrease drop out. As exercise awareness increases, it will also be more difficult to include patients and caregivers in a control group as motivated patients with mild dementia or caregivers in the control group may recognize potential exercise benefits and engage on their own. Maintaining persistent adequate levels of exercise for several months may also be a challenge in clinical trials. Furthermore, to maintain any potential benefit, people will likely need to exercise on their own with the risk of developing poor exercise habits without supervision. Another gap in our knowledge is whether exercise is still beneficial to patients in the later stages of dementia. Indeed, with the progression of the disease, individuals with dementia often have increased fall risk, dysautonomia, hallucinations, depression, and psychosis. Therefore, patients in a later stage of their disease may not be able to follow an exercise protocol safely. Future studies of longer duration and with appropriate follow-up are necessary to consider the impact of the stage of disease progression as the goal of the intervention may be different at different stages of the disease.

Limitations

There were several limitations to this review. We limited our search strategy and subsequent review to evidence ranked as level I, II, or III in articles that were published in English-language, peer-reviewed publications. Therefore, studies with positive results and lower level of evidence were not analyzed. Most of the studies that have investigated the effects of exercise training in dementia and their caregivers included a limited number of participants with mild to moderate disease severity and were highly supervised with a short duration. Therefore, the results of the study are not fully generalizable to the population with dementia and their caregivers at large. Finally, two of the studies in this review used a diagnosis-related sample (AD; Canonici et al., 2012; Pitkala et al., 2013), whereas the other two studies included participants with other types of dementia (Lowery et al., 2014; Prick et al., 2015). Given the differing etiology, pathology, symptoms, and progression of disease between the various types of dementia, future researchers should focus on a specific diagnosis.

Conclusion

Including both persons with AD and their caregivers in exercise clinical trials is feasible and may produce a positive effect on caregiver burden and functional independence. However, there is not yet a proven effect of a dyadic exercise intervention on cognitive performances, behavioral and neuropsychiatric symptoms, quality of life, and other common symptoms in people with dementia (e.g., sleep disturbances, fatigue). In conclusion, there is a need for more studies that include both persons with AD and their caregivers to assess several important points: (a) the feasibility of a combined AD person-caregiver exercise program; (b) the effects of a combined AD person-caregiver intervention on the mood and burden of caregivers and cognitive and noncognitive outcomes of persons with AD; (c) the optimal intensity of exercise training; (d) the impact of exercise training on the dynamic relationship

between the persons with AD and their caregivers; (e) determination of which people benefit most from exercise training; and (f) the cost effectiveness of such a program.

References

- Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS. Caregiver burden: a clinical review. *JAMA*. 2014; 311:1052–1060. <http://dx.doi.org/10.1001/jama.2014.304>. [PubMed: 24618967]
- Ades PA, Savage PD, Lischke S, Toth MJ, Harvey-Berino J, Bunn JY, Schneider DJ. The effect of weight loss and exercise training on flow-mediated dilatation in coronary heart disease: a randomized trial. *Chest*. 2011; 140:1420–1427. <http://dx.doi.org/10.1378/chest.10-3289>. [PubMed: 21778256]
- Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2016; 12:459–509. <http://dx.doi.org/10.1016/j.jalz.2016.03.001>.
- Barnes DE, Mehling W, Wu E, Beristianos M, Yaffe K, Skultety K, Chesney MA. Preventing loss of independence through exercise (PLIE): a pilot clinical trial in older adults with dementia. *PLoS One*. 2015; 10:e0113367. <http://dx.doi.org/10.1371/journal.pone.0113367>. [PubMed: 25671576]
- Billman GE, Kukiela M. Effects of endurance exercise training on heart rate variability and susceptibility to sudden cardiac death: protection is not due to enhanced cardiac vagal regulation. *Journal of Applied Physiology*. 2006; 100:896–906. <http://dx.doi.org/10.1152/japplphysiol.01328.2005>. [PubMed: 16322370]
- Brodsky H, Gresham M, Luscombe G. The Prince Henry Hospital dementia caregivers' training programme. *International Journal of Geriatric Psychiatry*. 1997; 12:183–192. [PubMed: 9097211]
- Buratti L, Balestrini S, Altamura C, Viticchi G, Falsetti L, Luzzi S, Silvestrini M. Markers for the risk of progression from mild cognitive impairment to Alzheimer's disease. *Journal of Alzheimer's Disease*. 2015; 45:883–890. <http://dx.doi.org/10.3233/jad-143135>.
- Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*. 2006; 7:30–40. <http://dx.doi.org/10.1038/nrn1809>. [PubMed: 16371948]
- Burton E, Cavalheri V, Adams R, Browne CO, Boverly-Spencer P, Fenton AM, Hill KD. Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: a systematic review and meta-analysis. *Clinical Interventions in Aging*. 2015; 10:421–434. <http://dx.doi.org/10.2147/cia.s71691>. [PubMed: 25709416]
- Canonici AP, Andrade LP, Gobbi S, Santos-Galduroz RF, Gobbi LT, Stella F. Functional dependence and caregiver burden in Alzheimer's disease: a controlled trial on the benefits of motor intervention. *Psychogeriatrics*. 2012; 12:186–192. <http://dx.doi.org/10.1111/j.1479-8301.2012.00407.x>. [PubMed: 22994617]
- Church TS, Thomas DM, Tudor-Locke C, Katzmarzyk PT, Earnest CP, Rodarte RQ, Bouchard C. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. *PLoS One*. 2011; 6:e19657. <http://dx.doi.org/10.1371/journal.pone.0019657>. [PubMed: 21647427]
- Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology*. 2010; 21:658–668. <http://dx.doi.org/10.1097/EDE.0b013e3181e89905>. [PubMed: 20585256]
- Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews*. 2015; 4:CD006489. <http://dx.doi.org/10.1002/14651858.CD006489.pub4>.
- Fredman L, Bertrand RM, Martire LM, Hochberg M, Harris EL. Leisure-time exercise and overall physical activity in older women caregivers and non-caregivers from the Caregiver-SOF Study. *Preventive Medicine*. 2006; 43:226–229. <http://dx.doi.org/10.1016/j.ypmed.2006.04.009>. [PubMed: 16737731]
- Gitlin LN, Rose K. Factors associated with caregiver readiness to use nonpharmacologic strategies to manage dementia-related behavioral symptoms. *International Journal of Geriatric Psychiatry*. 2014; 29:93–102. <http://dx.doi.org/10.1002/gps.3979>. [PubMed: 23653143]
- Graff MJ, Adang EM, Vernooij-Dassen MJ, Dekker J, Jonsson L, Thijssen M, Rikkert MG. Community occupational therapy for older patients with dementia and their care givers: cost

- effectiveness study. *BMJ (Clinical Research Edition)*. 2008; 336:134–138. <http://dx.doi.org/10.1136/bmj.39408.481898.BE>.
- Gross RA, Johnston KC. Levels of evidence: Taking Neurology to the next level. *Neurology*. 2009; 72:8–10. <http://dx.doi.org/10.1212/01.wnl.0000342200.58823.6a>. [PubMed: 19122025]
- Health Quality Ontario. Caregiver- and patient-directed interventions for dementia: An evidence-based analysis. *Ontario Health Technology Assessment Series*. 2008; 8(4):1–98.
- Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews Neuroscience*. 2008; 9:58–65. <http://dx.doi.org/10.1038/nrn2298>. [PubMed: 18094706]
- Hirano A, Suzuki Y, Kuzuya M, Onishi J, Hasegawa J, Ban N, Umegaki H. Association between the caregiver's burden and physical activity in community-dwelling caregivers of dementia patients. *Archives of Gerontology and Geriatrics*. 2011; 52:295–298. <http://dx.doi.org/10.1016/j.archger.2010.04.011>. [PubMed: 20462643]
- Katalinic OM, Harvey LA, Herbert RD. Effectiveness of stretch for the treatment and prevention of contractures in people with neurological conditions: a systematic review. *Physical Therapy*. 2011; 91:11–24. <http://dx.doi.org/10.2522/ptj.20100265>. [PubMed: 21127166]
- Kelley G, McClellan P. Antihypertensive effects of aerobic exercise. A brief meta-analytic review of randomized controlled trials. *American Journal of Hypertension*. 1994; 7:115–119. [PubMed: 8179846]
- Khan KM, Thompson AM, Blair SN, Sallis JF, Powell KE, Bull FC, Bauman AE. Sport and exercise as contributors to the health of nations. *Lancet*. 2012; 380:59–64. [http://dx.doi.org/10.1016/S0140-6736\(12\)60865-4](http://dx.doi.org/10.1016/S0140-6736(12)60865-4). [PubMed: 22770457]
- King AC, Brassington G. Enhancing physical and psychological functioning in older family caregivers: the role of regular physical activity. *Annals of Behavioral Medicine*. 1997; 19:91–100. [PubMed: 9603683]
- King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. *JAMA*. 1997; 277:32–37. [PubMed: 8980207]
- King AC, Baumann K, O'Sullivan P, Wilcox S, Castro C. Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: a randomized controlled trial. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2002; 57(1):M26–36.
- Knapp M, Iemmi V, Romeo R. Dementia care costs and outcomes: a systematic review. *International Journal of Geriatric Psychiatry*. 2013; 28:551–561. <http://dx.doi.org/10.1002/gps.3864>. [PubMed: 22887331]
- Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008; 300:1027–1037. <http://dx.doi.org/10.1001/jama.300.9.1027>. [PubMed: 18768414]
- Linke SE, Gallo LC, Norman GJ. Attrition and adherence rates of sustained vs. intermittent exercise interventions. *Annals of Behavioral Medicine*. 2011; 42:197–209. <http://dx.doi.org/10.1007/s12160-011-9279-8>. [PubMed: 21604068]
- Loi SM, Dow B, Ames D, Moore K, Hill K, Russell M, Lautenschlager N. Physical activity in caregivers: What are the psychological benefits? *Archives of Gerontology and Geriatrics*. 2014; 59:204–210. <http://dx.doi.org/10.1016/j.archger.2014.04.001>. [PubMed: 24798641]
- Lowery D, Cerga-Pashoja A, Iliffe S, Thune-Boyle I, Griffin M, Lee J, Warner J. The effect of exercise on behavioural and psychological symptoms of dementia: the EVI-DEM-E randomised controlled clinical trial. *International Journal of Geriatric Psychiatry*. 2014; 29:819–827. <http://dx.doi.org/10.1002/gps.4062>. [PubMed: 24338799]
- Maayan N, Soares-Weiser K, Lee H. Respite care for people with dementia and their carers. *Cochrane Database of Systematic Reviews*. 2014; 1:Cd004396. <http://dx.doi.org/10.1002/14651858.CD004396.pub3>.

- Nielsen JB, Willerslev-Olsen M, Christiansen L, Lundbye-Jensen J, Lorentzen J. Science-based neurorehabilitation: recommendations for neurorehabilitation from basic science. *Journal of Motor Behavior*. 2015; 47:7–17. <http://dx.doi.org/10.1080/00222895.2014.931273>. [PubMed: 25575219]
- Öhman H, Savikko N, Strandberg TE, Kautiainen H, Raivio MM, Laakkonen ML, Pitkala KH. Effects of exercise on cognition: The Finnish Alzheimer disease exercise trial: A randomized, controlled trial. *Journal of the American Geriatrics Society*. 2016; 64:731–738. <http://dx.doi.org/10.1111/jgs.14059>. [PubMed: 27037872]
- Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, Bernabei R. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. *British Journal of Psychiatry*. 2005; 187:450–455. <http://dx.doi.org/10.1192/bjp.187.5.450>. [PubMed: 16260821]
- Orgeta V, Miranda-Castillo C. Does physical activity reduce burden in carers of people with dementia? A literature review. *International Journal of Geriatric Psychiatry*. 2014; 29:771–783. [PubMed: 25191688]
- Orgeta V, Qazi A, Spector A, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *British Journal of Psychiatry*. 2015; 207:293–298. <http://dx.doi.org/10.1192/bjp.bp.114.148130>. [PubMed: 26429684]
- Peters HP, De Vries WR, Vanberge-Henegouwen GP, Akkermans LM. Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. *Gut*. 2001; 48:435–439. [PubMed: 11171839]
- Pitkala KH, Poysti MM, Laakkonen ML, Tilvis RS, Savikko N, Kautiainen H, Strandberg TE. Effects of the finnish alzheimer disease exercise trial (FINALEX): A randomized controlled trial. *JAMA Internal Medicine*. 2013; 173:894–901. <http://dx.doi.org/10.1001/jamainternmed.2013.359>. [PubMed: 23589097]
- Prick AE, de Lange J, Twisk J, Pot AM. The effects of a multi-component dyadic intervention on the psychological distress of family caregivers providing care to people with dementia: a randomized controlled trial. *International Psychogeriatrics*. 2015; 27:2031–2044. <http://dx.doi.org/10.1017/s104161021500071x>. [PubMed: 26004290]
- Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nature Reviews Neurology*. 2015; 11:157–165. <http://dx.doi.org/10.1038/nrneurol.2015.10>. [PubMed: 25686760]
- Quayhagen MP, Quayhagen M, Corbeil RR, Hendrix RC, Jackson JE, Snyder L, Bower D. Coping with dementia: evaluation of four nonpharmacologic interventions. *International Psychogeriatrics*. 2000; 12:249–265. [PubMed: 10937544]
- Rasinaho M, Hirvensalo M, Leinonen R, Lintunen T, Rantanen T. Motives for and barriers to physical activity among older adults with mobility limitations. *Journal of Aging and Physical Activity*. 2007; 15:90–102. [PubMed: 17387231]
- Rowe MA, Fehrenbach N. Injuries sustained by community-dwelling individuals with dementia. *Clinical Nursing Research*. 2004; 13:98–110. discussion 111–116. <http://dx.doi.org/10.1177/1054773803262520>. [PubMed: 15104853]
- Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. *International Journal of Geriatric Psychiatry*. 2009; 24:680–685. <http://dx.doi.org/10.1002/gps.2175>. [PubMed: 19089875]
- Suttanon P, Hill KD, Said CM, Byrne KN, Dodd KJ. Factors influencing commencement and adherence to a home-based balance exercise program for reducing risk of falls: perceptions of people with Alzheimer's disease and their caregivers. *International Psychogeriatrics*. 2012; 24:1172–1182. <http://dx.doi.org/10.1017/s1041610211002729>. [PubMed: 22265269]
- Suttanon P, Hill KD, Said CM, Williams SB, Byrne KN, LoGiudice D, Dodd KJ. Feasibility, safety and preliminary evidence of the effectiveness of a home-based exercise programme for older people with Alzheimer's disease: a pilot randomized controlled trial. *Clinical Rehabilitation*. 2013; 27:427–438. <http://dx.doi.org/10.1177/0269215512460877>. [PubMed: 23117349]
- Teodorczuk A, Welfare M, Corbett S, Mukaetova-Ladinska E. Developing effective educational approaches for Liaison Old Age Psychiatry teams: a literature review of the learning needs of

- hospital staff in relation to managing the confused older patient. *International Psychogeriatrics*. 2010; 22:874–885. <http://dx.doi.org/10.1017/s1041610209991475>. [PubMed: 20003634]
- van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. *British Journal of Sports Medicine*. 2008; 42:344–351. <http://dx.doi.org/10.1136/bjsm.2007.044735>. [PubMed: 18308888]
- Van't Leven N, Prick AE, Groenewoud JG, Roelofs PD, de Lange J, Pot AM. Dyadic interventions for community-dwelling people with dementia and their family caregivers: a systematic review. *International Psychogeriatrics*. 2013; 25:1581–1603. <http://dx.doi.org/10.1017/s1041610213000860>. [PubMed: 23883489]
- Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomized controlled trial. *Scandinavian Journal of Caring Science*. 2012; 26:12–19. <http://dx.doi.org/10.1111/j.1471-6712.2011.00895.x>.
- Whitlatch CJ. Including the person with dementia in family care-giving research. *Aging & Mental Health*. 2001; 5:S20–22. [PubMed: 11513493]
- Woodard CM, Berry MJ. Enhancing adherence to prescribed exercise: structured behavioral interventions in clinical exercise programs. *Journal of Cardiopulmonary Rehabilitation*. 2001; 21:201–9. [PubMed: 11508179]
- World Alzheimer Report. The Global Economic Impact of Dementia. 2010. <https://www.alz.co.uk/research/files/WorldAlzheimerReport2010.pdf>
- Yu F, Swartwood RM. Feasibility and perception of the impact from aerobic exercise in older adults with Alzheimer's disease. *American Journal of Alzheimer's Disease and Other Dementias*. 2012; 27:397–405. <http://dx.doi.org/10.1177/1533317512453492>.
- Yu F, Thomas W, Nelson NW, Bronas UG, Dysken M, Wyman JF. Impact of 6-month aerobic exercise on Alzheimer's symptoms. *Journal of Applied Gerontology*. 2015; 34:484–500. <http://dx.doi.org/10.1177/0733464813512895>. [PubMed: 24652914]

Clinical Trials Investigating the Effect of a Dyadic Exercise Training Intervention Including Both the Persons with AD and the Caregivers

TABLE 1

Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Pitkala et al. (2013) Özkan et al. (2016)	Randomized controlled trial	(1) HB (2) GB (3) CG Exercise: aerobic, strength and endurance, dual-task, and balance training (15 min for each component) + executive functioning training (15 min), two times/week Intensity: not reported HE: physical exercise at home for 1 h two times/week for 12 months, supervised by a physiotherapist GE: 4-hr sessions (1 h of exercise) in adult daycare centers two times/w for 12 months. Groups of 10 supervised by two physiotherapists. Assessments at baseline, three months, six months, and 12 months	Community-dwelling dyads ($n = 210$) of individuals with AD and their spousal caregivers (1) $n = 70$ (59 at 12 months) (2) $n = 70$ (51 at 12 months) (3) $n = 70$ (51 at 12 months)	(1) Cognition: CDT, VF, CDR, and MMSE (2) Neuropsychiatric and behavioral outcomes: NA (3) Physical functioning (primary outcome): FIM, Short Physical Performance Battery, 10-m walking test (4) Caregivers' outcomes: NA (5) Other: NA	Between-group differences CDT: HB > CG ($p = .07$) VF: NS MMSE: NS 10-m walking speed: NS FIM: HB and GB > CG Falls: HB and GB fewer falls vs. CG ($p < .05$) Within-group differences: change from baseline CDT HB +0.48 (95% CI [0.06, 0.91]) GB +0.01 (95% CI [-0.44, 0.46]) CG -0.21 (95% CI [-0.67, 0.25]) VF HB -0.99 (95% CI [-1.67, -0.32]) GB -0.95 (95% CI = 0.00, -0.23) CG -1.14 (95% CI [-1.86, -0.41]) MMSE HB -1.63 (95% CI [-2.64, -0.61]) GB -1.23 (95% CI [-2.33, -0.14])	- Caregivers were included in the trial but caregiver's burden was not reported as an outcome

Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Prick et al. (2015)	Randomized controlled trial	<p>(1) Ex</p> <p>(2) C (usual care + three written information bulletins and three phone calls)</p> <p>Exercise: four types of physical exercises: flexibility, strengthening, balance and endurance exercises; >30 min per session, three times/week for three months</p> <p>Support component: (a) psychoeducation, (b) communication, skills training, (c) pleasant activities training</p> <p>Intensity: not reported</p> <p>Supervision by a coach weekly the first four weeks, biweekly the next eight weeks</p> <p>Assessments at baseline, three months,</p>	<p>Community-dwelling patients with dementia and their caregivers with a score on the CESD > 5 $n = 111$ dyads randomized</p> <p>(1) $n = 57$ (45 caregivers and 45 persons with dementia at six months)</p> <p>(2) $n = 54$ (43 caregivers and 42 persons with dementia at six months)</p>	<p>(1) Cognition: MMSE (only at baseline)</p> <p>(2) Neuropsychiatric and behavioral outcomes: Dutch version of the RMBPC</p> <p>(3) Physical functioning: Standard single item-scale for self-rated general health</p> <p>(4) Caregivers' outcomes: CES-D (primary outcome), Dutch SPICC</p> <p>(5) Other: salivary cortisol</p>	<p>CG -1.08 (95% CI [-2.17, 0.02])</p> <p>10-m walking test</p> <p>HB -0.09 (95% CI [-0.14, -0.03])</p> <p>GB -0.12 (95% CI [-0.17, -0.06])</p> <p>CG -0.16 (95% CI [-0.22, -0.11])</p> <p>FIM</p> <p>HB -7.1 (95% CI [-3.7, -10.5])</p> <p>GB -10.3 (95% CI [-6.7, -13.9])</p> <p>CG -14.4 (95% CI [-10.9, -18.0])</p>	<ul style="list-style-type: none"> - Inclusion criteria not limited to AD - Compliance: full compliance = nine dyads (15.8%), moderate compliance = 43 dyads (75.4%) - Small sample size according to power calculation - No result for MMSE at follow-up - Short duration of the study

Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Lowery et al. (2013)	Randomized controlled trial	and at six-month follow-up (1) Ex (2) C (usual care) Exercise: walking designed to become progressively more intensive and last between 20 and 30 min. Goal: five times/week for 12 weeks Intensity: RPE 12–14 Supervision with a physical therapist for the first six weeks Assessments at baseline, six weeks, and 12 weeks	Community-dwelling patients with ICD-10 confirmed dementia and significant behavioural and psychological symptoms and their caregivers. $n = 131$ dyads (1) $n = 67$ (59 at 12w) (2) $n = 64$ (57 at 12w)	(1) Cognition: NA (2) Neuropsychiatric and behavioral outcomes: composite NPI score (primary endpoint)*, mean differences in NPI score, GHQ score, GHQ (3) Physical functioning: NA (4) Caregivers' outcomes: DemQOL-Proxy (DemQol), ZCBS (5) Other: NA *Clinically significant reduction (Baseline—Week 12): reduction of the composite NPI score 3 points	Between-group differences NPI composite: NS Ex 41% more likely to reach a clinically significant reduction 3 points of NPI composite score by week 12. However, NS between Ex and C Mean NPI: NS ZCBS: Ex (23% to 17%) > C (16 to 32%; $p = 0.01$) GHQ, DemQOL-Proxy: NS Self-reported walking time: NS Within-group differences No within-group statistical analysis	<ul style="list-style-type: none"> - Adherence: prescribed frequency of walks was achieved by only 30.77% of the Ex group, and prescribed intensity was achieved in only 53.25% of the walks. - Inclusion criteria not limited to AD - Short duration of the study - Weakness of self-report in measuring exercise
Canonici et al. (2012)	Controlled trial	(1) Ex (2) C (usual care) Exercise: (i) initial warm up; (ii) initial stretching; (iii) flexibility, strength, agility and balance; (iv) return to physical calm; and (v) final stretching. Walking and dancing were also part of the program. three times/week for six months Intensity: not reported Supervision: not reported	Community patients with probable mild to moderate AD and their caregivers $n = 32$ dyads (1) $n = 16$ (16 at six months) (2) $n = 16$ (11 at six months)	(1) Cognition: MMSE (only at baseline) (2) Neuropsychiatric and behavioral outcomes: NPI and Cornell Scale for Depression in Dementia (3) Physical functioning: FIM, BFBS, instrumental daily activities assessed with the Pfeiffer Questionnaire	Between-group differences NPI (patient): Ex > C FIM: Ex > C ($p = .01$) BFBS: Ex > C ($p = .001$) Pfeiffer quest: NS NPI-caregiver: Ex > C ($p = .01$) ZCBS: Ex > C ($p = .01$)	<ul style="list-style-type: none"> - Randomization not mentioned - Evaluation not blinded - Small sample size - Primary and secondary endpoint not clearly stated - - No result for MMSE at follow-up

Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
		Assessments at baseline and six months		(4) Caregivers' outcomes: NPI-caregiver, ZCBS (5) Other: NA	Within-group differences; change from baseline NPI (patient): Ex: 40.3 ± 34.0 to 16.9 ± 17.6 vs. C: 39.6 ± 25.0 to 43.3 ± 18.4 FIM (total): Ex: 09.6 ± 12.5 vs. C: 108.4 ± 10.299.5 ± 18.0 to 71.6 ± 31.0 BFBS: Ex: 46.4 ± 7.8 to 51.9 ± 3.4 vs. C: 46.4 ± 8.1 to 26.9 ± 17.7 Pfeiffer quest: Ex: 19.8 ± 7.4 to 22.3 ± 7.4 vs. C: 23.0 ± 5.3 to 28.2 ± 3.0 NPI-Caregivers: Ex: 18.3 ± 13.8 to 3.3 ± 6.5 vs. C: 19.6 ± 14.3 to 20.4 ± 9.6 ZCBS: Ex: 32.3 ± 14.7 to 14.6 ± 8.1 vs. C: 35.6 ± 14.9 to 35.5 ± 13.7	

AD = Alzheimer's disease; BFBS = Berg Functional Balance Scale; CES-D = Centre for Epidemiologic Studies-Depression; DemQol = DemQOL-Proxy; HB = home-based exercise; C = control group; CDT = Clock Drawing Test; CDR = Clinical Dementia Rating; CG = control group; FIM = Functional Independence Measure; GB = group-based exercise; GHQ = General Health Questionnaire; MMSE = Mini-Mental State Examination; NA = not assessed; NPI = Neuropsychiatric Inventory; NS = no significant difference ($p > .05$); RMBPC = Dutch version of the Revised Memory and Behavioral Problem Checklist; RPE = rating of perceived exertion; SPICC = Dutch Self-Perceived from Family Care; VF = Verbal Fluency; ZCBS = Zarit Caregiver Burden Scale.