Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial

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OBJECTIVES: To examine whether a regular, long-term exercise program performed by individuals with Alzheimer’s disease (AD) at home or as group-based exercise at an adult daycare center has beneficial effects on cognition; to examine secondary outcomes of a trial that has been published earlier.

DESIGN: Randomized, controlled trial.

SETTING: Community.

PARTICIPANTS: Community-dwelling dyads (N = 210) of individuals with AD and their spousal caregivers randomized into three groups.

INTERVENTION: Two types of intervention comprising customized home-based exercise (HE) and group-based exercise (GE), each twice a week for 1 year, were compared with a control group (CG) receiving usual community care.

MEASUREMENTS: Cognitive function was measured using the Clock Drawing Test (CDT), Verbal Fluency (VF), Clinical Dementia Rating (CDR), and Mini-Mental State Examination (MMSE) at baseline and 3, 6, and 12 months of follow-up.

RESULTS: Executive function, measured using CDT, improved in the HE group, and changes in the score were significantly better than those of the CG at 12 months (adjusted for age, sex, and CDR, \( P = .03 \)). All groups deteriorated in VF and MMSE score during the intervention, and no significant differences between the groups were detected at 12-month follow-up when analyses were adjusted for age, sex, and CDR.

CONCLUSION: Regular, long-term, customized HE improved the executive function of community-dwelling older people with memory disorders, but the effects were mild and were not observed in other domains of cognition.


Key words: physical exercise; cognition; Alzheimer’s disease; randomized controlled trial

The relationship between physical exercise and cognitive function was initially suggested in epidemiological cohort studies examining whether exercise habits of middle-aged persons predict cognitive decline in older age over the long term.1 A number of longitudinal cohort studies have showed that physical exercise protects against cognitive decline and dementia.1,2

A Cochrane review of 11 randomized, controlled trials (RCTs) performed in healthy older adults without known cognitive impairment suggested that aerobic exercise has positive effects on motor function, auditory attention, cognitive speed, and visual attention.3 Two other reviews concluded that physical exercise positively affects executive function but not working memory.4,5

Less is known about the effects of physical activity on cognition in older people with cognitive decline or dementia. Some high-quality trials have suggested that physical exercise has positive effects on executive functioning or global cognition in individuals with mild cognitive impairment,6,7 but several critical reviews have concluded that these associations are unclear in older people with dementia.8–10 Researchers have noted that studies included in reviews have often had methodological weaknesses and that more-rigorous RCTs with larger samples, longer follow-up, and evaluation of adherence are needed.8,9 A recent review found 14 RCTs performed in individuals with dementia that examined the relationship between physical exercise and cognition,10 but none of these were of good methodological quality. Of the six trials of
moderate quality, one suggested effects on global cognition and one on executive function. According to the review, the cognition of individuals with mild cognitive impairment (MCI) appeared to improve with exercise. Effects on global cognition, executive function, or attention were seen in several good-quality studies.

Thus, the aim of the current study was to examine whether a regular, long-term exercise program performed by home-dwelling individuals with Alzheimer’s disease (AD) at home or as a group-based exercise program at adult daycare center has beneficial effects on cognition. This research examined secondary outcomes of a trial whose primary outcomes (physical functioning and mobility) have been previously published. This trial showed that a long-term supervised exercise intervention slowed deterioration of physical functioning in individuals with AD and decreased the risk of falls.

METHODS

The design and endpoints of this multicenter, prospective, randomized, controlled trial of dyads home-dwelling individuals with AD and their spousal caregivers have been previously presented. Briefly, effects of two types of interventions (customized home-based exercise (HE) (1 hour at home) and GE (4 hours at daycare center, effective exercise time 1 hour)) were examined and compared with a control group (CG) receiving normal community care. Both interventions occurred twice a week and lasted for 1 year.

Participants

The Social Insurance Institution of Finland mailed a letter offering the possibility to participate in the exercise trial to all older adults (≥65 years) on The Social Insurance Institution of Finland’s AD drug reimbursement register living at the same address with a spouse in the cities of Helsinki, Espoo, and Vantaa (n = 1,264). To receive AD drug reimbursement in Finland, an individual must fulfill the criteria for probable AD diagnosis according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association Alzheimer’s criteria as evaluated by a geriatrician or neurologist.

Those expressing interest in participating (n = 497) received a postal questionnaire inquiring about demographic factors and confirming inclusion criteria (established AD diagnosis, spouse living at the same address, aged ≥65, no diagnosed terminal disease, ability to walk independently with or without a mobility aid). Participants also had to fulfill at least one of the following signs of frailty: one or more falls during the past year, decrease in walking speed, or unintentional weight loss. After receiving the completed questionnaire, the study nurse conducted a telephone interview with the spousal caregiver to ensure that all inclusion criteria were met. Dyads fulfilling all inclusion criteria (N = 210) were further randomized into three arms. Figure 1 presents the flowchart of the study.

Figure 1. Flowchart of the study.
The ethics committee of Helsinki University Central Hospital approved the study protocol. Informed consent was obtained from each person with AD and spousal caregiver. In cases in which an individual’s judgment capacity was lacking, the spouse gave consent for both.

**Measures**

A registered nurse and a physiotherapist assessed participating couples at four meetings (baseline; 3, 6, 12 months). At baseline, demographic data were collected and medical diagnoses confirmed from medical records for individuals with AD and their spouses. A Charlson Comorbidity Index score was calculated to assess severity of disease burden. Cognition was evaluated using the Clock Drawing Test (CDT), Verbal Fluency (VF; animal category fluency), Mini-Mental State Examination (MMSE), and Clinical Dementia Rating Scale (CDR). Results of the primary outcome measures (physical function measured using the Functional Independence Measure, mobility measured using the Short Physical Performance Battery, the interventions’ effects on the use and costs of health and social services, adherence and complications) have been reported previously. The findings of the 10-m walking test of the Short Physical Performance Battery were used to determine changes in physical fitness.

The CDT was used to measure executive function, and VF was used to measure executive function and semantic memory. These tests were assessed at baseline and 3, 6, and 12 months and were both used as outcome measures.

**Randomization**

Dyads fulfilling all inclusion criteria (N = 210) were randomized after the baseline visit into three equal-sized (n = 70) groups (customized HE, GE, and a CG continuing in community care) using computer-generated numbers received by a randomization center.

**Interventions**

A detailed description of the interventions has been published previously. A geriatrician assessed participants randomized to either intervention group to ensure participant safety during exercise.

The HE group performed physical exercise at home for 1 hour twice a week for 12 months. A physiotherapist with a specialty in dementia supervised customized training sessions during the home visits, addressing the individual’s needs and problems with daily functioning. Although the exercises were planned according to the individual’s requirements, they always included elements of executive function training; dual-task exercises; and strength, balance, endurance, and aerobic training (Table 1).

Physical exercise for the GE group was based on 4-hour sessions in adult daycare centers twice a week for 12 months. Door-to-door taxi service and lunches were provided. The sessions were organized in groups of 10 participants and supervised by two physiotherapists with a specialty in dementia. The predetermined exercise program consisted of aerobic, endurance, balance, and strength training, and dual tasking to improve executive functioning (Table 1). Peer support was used to aid in training. The average active exercise time per person was approximately 1 hour per day because of lunch and coffee breaks and waiting times for gym equipment.

Aerobic training was included in both groups (e.g., Nordic walking). Strength training was aided with wrist and ankle weights in home exercise sessions, whereas the group exercise program used gym equipment. The training also included various balance exercises. Dual-task exercises were simple, such as talking while walking (Table 1). Both intervention group participants continued regular exercise even in the case of hospitalization or respite care, but if a participant was admitted to permanent institutional care, the intervention and further study assessments were discontinued.

CG participants received the usual care that the Finnish healthcare system provides but the study nurses also gave them oral and written advice on nutrition and exercise methods. They also access to physiotherapy provided by the community health system.

**Statistical Analyses**

Sample size was calculated based on the primary outcome measure: the Functional Independence Measure. A target sample size of approximately 210 (70 per group) was calculated to ensure 80% power to detect a 10-point
difference between the treatment groups at a two-sided $\alpha$ of 0.05. A dropout rate of 10% was estimated.

The data are presented as means with standard deviations or numbers with percentages. Statistical comparison between the groups at baseline was performed using analysis of variance, Kruskall-Wallis tests, or the chi-square test when appropriate. Differences in adherence between the HE and GE groups was tested using the Mann-Whitney U-test. All participants assessed at baseline and 3 months were included in the data analyses of changes in cognitive function (modified intention to treat). There were no differences in dropouts between the groups with regard to age, sex, comorbidities, CDR, MMSE, or baseline VF or CDT scores. Repeated measures were analyzed using generalized estimating equation (GEE) models with the unstructured correlation structure. GEEs were developed as an extension of the general linear model (e.g., ordinary least-squares regression analysis) to analyze longitudinal and other correlated data. GEE models take into account the correlation between repeated measurements in the same subject; models do not require complete data and can be fitted even when individuals do not have observations at all time-points. The 95% confidence intervals (CIs) and statistical models were obtained using bootstrapping in cases of violation of assumptions. Effect size ($d$) was calculated using the method of variance, Kruskall-Wallis tests, or the chi-square test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous, nonnormally distributed variables.

Results

Participants at Baseline

The baseline findings and main outcomes of the intervention have been reported previously.13,26 At baseline, the mean age of the participants with dementia was 78.1 ± 5.3, 39% were female, and 39% had less than 8 years of education. Mean MMSE score was 18, according to the CDR, 67% had moderate or severe AD, and 96% were taking AD medication. Mean CDT score was 2.3, and participants were able to name a mean 7.9 animals in 1 minute. At baseline, the groups were similar in demographic factors and cognitive test results (Table 2).

Effect of Intervention on Cognition

Table 3 presents the baseline values and mean changes over 12 months on the CDT and VF. Figure 2 shows changes in cognition according to various tests over 12 months. Mean change in executive functioning at 12 months according to the CDT was $-0.21$ (95% CI = $-0.67$ to $-0.25$) in the CG (effect size $=0.10$, 95% CI = $-0.27$ to $-0.16$), $0.01$ (95% CI = $-0.44$ to $-0.46$) in the GE (effect size 0.30, 95% CI = $-0.20$ to $-0.25$), and 0.48 (95% CI = $0.06$ to $0.91$) in the HE (effect size 0.25, 95% CI = $0.06$ to $0.48$). There were no significant differences between the three groups at 12 months (degrees of freedom ($df$) = 2, chi-square $=5.3$, $P = .07$, adjusted for age, sex, and CDR baseline); the difference between the HE group and the CG was significant at 12 months ($P = .03$, adjusted for age, sex, and CDR baseline); the difference between the GE and the CG was not significant (Figure 2A). Effect sizes for completed cases were $-0.07$ for the CG, 0.07 for the GE, and 0.31 for the HE.

All groups deteriorated in VF during the intervention, and differences in change between the groups were not statistically significant when adjusted for age, sex, and CDR. The change from baseline to 12 months was $-1.14$ (95% CI = $-1.86$ to $-0.41$) in the CG (effect size $-0.21$, 95% CI = $-0.39$ to $-0.05$), $-0.95$ (95% CI = $0.00$ to $-0.23$) in the GE (effect size $-0.16$, 95% CI = $-0.33$ to $-0.03$), and $-0.99$ (95% CI = $-1.67$ to $-0.32$) in the HE (effect size $-0.18$, 95% CI = $-0.38$ to $-0.04$) ($df$ = 2, chi-square $=15.15$; $P = .93$, adjusted for age, sex, and CDR) (Figure 2B). Effect sizes for completed cases were $-0.30$ for the CG, $-0.19$ for the GE, and $-0.15$ for the HE.

Table 2. Baseline Characteristics of Participants with Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Home-Based Exercise, n = 70</th>
<th>Group Exercise, n = 70</th>
<th>Control, n = 70</th>
<th>P-Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>77.7 ± 5.4</td>
<td>78.3 ± 5.1</td>
<td>78.1 ± 5.3</td>
<td>.82</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>30 (42.9)</td>
<td>25 (35.7)</td>
<td>26 (37.1)</td>
<td>.66</td>
</tr>
<tr>
<td>Education &lt;8 years, n (%)</td>
<td>28 (40.6)</td>
<td>23 (32.9)</td>
<td>29 (41.4)</td>
<td>.53</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean ± SD</td>
<td>2.6 ± 1.8</td>
<td>2.5 ± 1.8</td>
<td>3.0 ± 1.7</td>
<td>.13</td>
</tr>
<tr>
<td>Clinical Dementia Rating, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 or 1</td>
<td>24 (34.3)</td>
<td>23 (32.9)</td>
<td>22 (31.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30 (42.9)</td>
<td>37 (52.9)</td>
<td>37 (52.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16 (22.9)</td>
<td>10 (14.3)</td>
<td>11 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination score, mean ± SD (range 0–30)</td>
<td>17.8 ± 6.6</td>
<td>18.5 ± 6.3</td>
<td>17.7 ± 6.2</td>
<td>.64</td>
</tr>
<tr>
<td>Clock Drawing Test score, mean ± SD (range 0–6)</td>
<td>2.3 ± 2.0</td>
<td>2.3 ± 2.0</td>
<td>2.4 ± 2.1</td>
<td>.99</td>
</tr>
<tr>
<td>Verbal Fluency score, mean ± SD</td>
<td>8.2 ± 4.7</td>
<td>7.9 ± 4.2</td>
<td>7.5 ± 4.4</td>
<td>.60</td>
</tr>
<tr>
<td>Taking Alzheimer medication, n (%)</td>
<td>67 (95.7)</td>
<td>68 (97.1)</td>
<td>67 (95.7)</td>
<td>.88</td>
</tr>
<tr>
<td>10-m walking speed, m/s, mean ± SD</td>
<td>0.77 ± 0.26</td>
<td>0.81 ± 0.27</td>
<td>0.82 ± 0.23</td>
<td>.55</td>
</tr>
</tbody>
</table>

aDifferences between the groups were tested using the chi-square test for categorical variables and analysis of variance or Kruskall-Wallis test for continuous, nonnormally distributed variables.

SD = standard deviation.
Adherence and Physical Fitness

Adherence was good in both intervention groups. The mean number of sessions attended was 81 (range 7–89) in the HE and 75 (range 7–89) in the GE (P = .02, Mann Whitney U-test). Sixty-five (93%) HE participants and 55 (79%) GE participants attended at least half of the training sessions. No statistically significant correlation was found between the number of sessions attended and change in CDT (baseline adjusted Spearman correlation = −0.15, 95% CI = −0.33 to 0.06), nor was there any statistically significant difference between those attending fewer than half of the sessions and those attending more than half (P = .33).

Mean change from baseline to 12 months in 10-m walking speed was −0.16 (95% CI = −0.22 to −0.11) in the CG (effect size = −0.68 (95% CI = −0.94 to −0.42), −0.12 (95% CI = −0.17 to −0.06) in the GE (effect size = −0.38, 95% CI = −0.60 to −0.19), and −0.09 (95% CI = −0.14 to −0.03) in the HE (effect size = −0.28, 95% CI = −0.48 to −0.08) (df = 2, chi-square = 3.65; P = .16, adjusted for age, sex, and baseline walking speed).

DISCUSSION

Regular long-term, customized HE may have had some positive effects on the executive function of community-dwelling older people with AD, but the effects were mild, and participants had to exercise 12 months until positive results were observed on the CDT. These positive findings were observed only in the HE group. Moreover, the effects were not seen in VF, which measures semantic memory in addition to executive function, or on the MMSE, which measures global cognition.

A strength of this study was its rigorous methodology; it was a randomized, controlled trial with separate study personnel performing assessments and interventions and had a larger sample size than previous trials. The intervention was carefully planned and executed to train all domains of physical exercise (aerobic, strength, balance, endurance), and it was regular and long term. Adherence was good in the exercise arms, which means that the efficacy of exercise on cognition could truly be measured. The cognitive measures have been well validated and are widely used. The intervention was simple and could be easily executed in primary care.
Although the study was designed to avoid the methodological deficits discussed in previous reviews, it nonetheless had some limitations. First, because of the selected participants, generalization to other populations must be done with caution. Participants and their caregivers were motivated volunteers. The primary endpoint was physical functioning; the study was not designed primarily to detect differences in cognition between the groups. The extent of cognitive measures was limited because of the primary focus on physical functioning. Cognitive domains other than semantic memory and executive function were not measured. Furthermore, the interventions included dual-task exercises along with endurance, strength, and balance training. Dual tasking may be considered to be a combination of cognitive and exercise training, so the title “exercise intervention” can be questioned, but the dual-task exercises accounted for only a minority of the training time and were simple and repetitious. A prior trial found significant effects of dual-task training only on attention-related dual-task performance and only under complex and variable dual-task conditions.

The study was not blinded. Physiotherapists performing the intervention knew whom they were treating but were unaware of the study outcome measures. Study nurses who were not part of the intervention staff were not informed about the group allocation of participants, but participants were eager to share their experiences, so study nurses could not be kept entirely blinded. Nevertheless, they did not know what occurred in the interventions, nor were they co-investigators. No restrictions were set for participants on engaging in additional physical exercise or rehabilitation during the study, and information on this was not systematically collected, so it was not possible to measure the total amount of exercise participants performed, although the randomized study design controlled for this possible bias. Finally, a limitation of the study is that no tests were performed to measure whether the intervention improved participants’ cardiorespiratory fitness; muscle strength was shown to improve during the intervention year, but 10-m walking speed did not improve during follow-up in any of the groups. An additional limitation is that, although the cognitive measures were validated, some of them, such as the MMSE, are not sensitive to change.

As reported in a previous article, the intervention proved to be effective in improving physical functioning and diminishing falls. Therefore, it was somewhat surprising that the effects of the physical activity intervention on cognition were small and seen only on the CDT. The intervention was regular and long term, and the participation rate was high. Improvement in physical functioning was seen in the HE group, although the intensity of training may have still been too low. In previous trials in which positive effects of exercise on cognition have been found, the exercise rate has been daily or three times a week. The outcomes of cognitive tests did not correlate with the number of sessions attended. The fact that cognition declines at different speeds at different stages of dementia, being faster in moderate and severe stages than in the mild stage may explain this. Participants with better cognition attended fewer sessions than those with more-advanced dementia.

Previous studies have indicated that exercise has a differential effect on various domains of cognitive function. The current study findings are in line with earlier studies suggesting that exercise affects executive function. Cognitive functions are complex and difficult to quantify. The cognitive assessment tools (VF, CDT, MMSE, CDR) used in this study have all been validated and used in many earlier studies. Improvement was not seen in VF scores in the current study. Although VF measures executive function, it is also a measure of semantic memory. Therefore, poor performance on tests of semantic fluency may reflect problems with semantic memory and not executive dysfunction. Previous studies have suggested that exercise may not improve memory function as effectively as executive function. The CDT is widely used to measure executive function. Although a strong association between the CDT and executive function has been established, global cognitive functioning, visuospatial abilities, and semantic knowledge also influence the test results.

More than 95% of participants in all three groups were taking AD medication, and the CG received high-quality community care, which may have diluted the effect of the intervention. It has been suggested that women benefit more from exercise with respect to cognition. Therefore, the large proportion of participants being male may have attenuated the effectiveness of the interventions.

It has been suggested that exercise improves cerebral circulation by increasing blood flow and oxygen supply to the brain and promotes vascular health by lowering blood pressure and lipid levels. Exercise also has positive effects on inflammatory markers and enhances endothelial function. Moreover, physical exercise can stimulate neuronal proliferation in the hippocampal areas. It may be that the effects of exercise on cognition in individuals with AD are modest because the brain is too damaged at the stage of clinical AD, with the protective effects of exercise coming too late. The finding that effects of exercise are more evident in individuals with MCI supports this although not all MCI studies show positive findings.

There may be several reasons why improvement in executive function was seen in the HE group but not the GE group. First, the intervention, especially the HE, included dual-tasking and other exercises performed in participants’ own homes, activated the brain in addition to the body. Thus, exercise also trained the frontal lobe, the region mainly responsible for executive function. Second, although adherence was good in both intervention groups, it was better in the HE group, resulting in more exercise for these participants. In addition, the intermittent or discontinuous nature of the exercise in the adult day-care setting and customizing the exercises in the HE group might be responsible for differing effects. Thus, when planning GEs in day care settings, participant adherence to training should be supported, and the exercise program should be customized to participants’ needs.

The improvement in cognition seen only in executive function is interesting. The HE intervention also improved physical functioning. It may be that the improvement in HE participants’ executive function was responsible for improvement in physical function as well. Future exercise interventions in individuals with AD should include...
dimensions that train the frontal lobe, which is the main mediator of tasks requiring executive function.

CONCLUSIONS

Participation in a long-term, customized home exercise program may have some effects, albeit modest, on executive function in individuals with AD, although individuals with dementia seem to derive less cognitive benefit from exercise than those with MCI. Regardless of cognitive effect, the intervention enhanced participants’ level of physical functioning and independence, so individuals with AD should be encouraged to engage in regular supervised home-based physical activity.

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Conflict of Interest: The authors declare they that have no conflict of interest directly relevant to this report. Prof. Strandberg reports having educational, consultative, and professional cooperation with several companies and societies, a minor amount of stock in Orion Pharma, and grants from foundations and hospitals. Dr. Minna Raivio reports having educational cooperation with several pharmaceutical companies. Prof. Pitkälä reports having professional cooperation with Orion Pharma.

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Author Contributions: Strandberg, Raivio, Laakkonen, Tilvis, Kautiainen, Pitkälä: conception and design. Öhman, Savikko, Strandberg, Kautiainen, Pitkälä: acquisition, analysis, and interpretation of data. Öhman, Savikko, Strandberg, Kautiainen, Raivio, Laakkonen, Tilvis, Pitkälä: drafting or critically revising the manuscript for relevant intellectual content. Öhman, Savikko, Strandberg, Kautiainen, Raivio, Laakkonen, Tilvis, Pitkälä: approval of final manuscript. Kaisu H. Pitkälä had full access to the data used in the study, is responsible for the integrity of the data and the accuracy of data analysis, and is the guarantor.

Sponsor’s Role: The sponsors had no role in study design, data analysis, interpretation of results, writing the report, or in the decision to submit for publication. The authors were independent researchers not associated with the sponsors.

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