Effects of the Finnish Alzheimer Disease Exercise Trial (FINALEX)

A Randomized Controlled Trial

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Importance: Few rigorous clinical trials have investigated the effectiveness of exercise on the physical functioning of patients with Alzheimer disease (AD).

Objectives: To investigate the effects of intense and long-term exercise on the physical functioning and mobility of home-dwelling patients with AD and to explore its effects on the use and costs of health and social services.

Design: A randomized controlled trial.

Setting and Participants: A total of 210 home-dwelling patients with AD living with their spousal caregiver.

Interventions: The 3 trial arms included (1) group-based exercise (GE; 4-hour sessions with approximately 1-hour training) and (2) tailored home-based exercise (HE; 1-hour training), both twice a week for 1 year, and (3) a control group (CG) receiving the usual community care.

Main Outcome Measures: The Functional Independence Measure (FIM), the Short Physical Performance Battery, and information on the use and costs of social and health care services.

Results: All groups deteriorated in functioning during the year after randomization, but deterioration was significantly faster in the CG than in the HE or GE group at 6 (P=.003) and 12 (P=.015) months. The FIM changes at 12 months were −7.1 (95% CI, −3.7 to −10.5), −10.3 (95% CI, −6.7 to −13.9), and −14.4 (95% CI, −10.9 to −18.0) in the HE group, GE group, and CG, respectively. The HE and GE groups had significantly fewer falls than the CG during the follow-up year. The total costs of health and social services for the HE patient-caregiver dyads (in US dollars per dyad per year) were $25,112 (95% CI, $17,642 to $32,581) (P=.13 for comparison with the CG), $22,066 in the GE group ($15,931 to $28,199; P=.03 vs CG), and $34,121 ($24,559 to $43,681) in the CG.

Conclusions and Relevance: An intensive and long-term exercise program had beneficial effects on the physical functioning of patients with AD without increasing the total costs of health and social services or causing any significant adverse effects.

Trial Registration: anzctr.org.au Identifier: ACTRN12608000037303


Cognitive decline and functional deterioration are core features of Alzheimer disease (AD), the most common disease leading to dementia. As dementia progresses, functional deficits lead to disabilities and ultimately in many cases to permanent institutional care.1 Rigidity increases with advancement of disease, and walking speed decreases. This process is heightened by progressive weight loss and sarcopenia.2 Dementia is also a significant risk factor for falls.3

During the past decades, pharmacological research has been active, but no major breakthroughs seem to be on the horizon. Research on nonpharmacological therapies has produced promising effective treatments to improve the quality of life for families of patients with dementia and postpone the need for institutional care.4 More nonpharmacological treatments are urgently needed.

See Invited Commentary at end of article

Although numerous clinical trials demonstrate the beneficial effects of exercise in older persons,5 surprisingly few rigorous studies have investigated its effects in patients with dementia.6 Some high-quality studies demonstrating beneficial effects7,8 have used exercise as part of a comprehen-

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sive intervention, thus not considering the effects of exercise alone on the physical functioning of patients with dementia. Intense and long-term exercise may help physical functioning in institutionalized patients with AD. A recent study also showed that intense exercise may improve motor performance in home-dwelling patients with mild to moderate dementia. However, to our knowledge, no studies have investigated whether exercise can delay the progression of disability in these patients or how it affects the use and costs of health and social services.

The aim of our randomized controlled clinical trial was to investigate the effects of intense and long-term exercise on the physical functioning and mobility of home-dwelling patients with AD. We also explored its effects on the use and costs of health and social services.

The design and end points of this multicenter, prospective, randomized controlled trial in dyads of home-dwelling patients with AD and their spousal caregivers have been presented elsewhere. Briefly, our aim was to study the effects of 2 types of exercise interventions in patients with AD, one administered by a physiotherapist at the participants’ homes for 1 hour twice a week (home-based exercise [HE]) and the other administered at adult rehabilitation day care centers in groups of 10 patients with AD (group-based exercise [GE]) by 2 physiotherapists during 4-hour day care sessions, with approximately 1 hour of training twice a week. Both interventions lasted for 1 year, and results are compared with those from a control group (CG) receiving community care.

PARTICIPANTS

A letter offering the possibility of participating in the exercise trial was mailed to all patients (aged ≥65 years) on the AD drug reimbursement register of the Social Insurance Institution of Finland who were living at the same address with a spouse in the neighboring cities of Helsinki, Espoo, or Vantaa (N = 1264). To receive AD drug reimbursement in Finland, patients are required to have undergone a detailed diagnostic workup by a geriatrician or neurologist and to fulfill the NINCDS-ADRDA criteria for diagnosis of probable AD.

Further information about the recruitment of participants can be found in the eAppendix (http://www.jamaïnternalmed.com).

A telephone interview with the spousal caregiver of patients interested in the trial was performed to ensure that all inclusion criteria were fulfilled: an established AD diagnosis, a spouse living at the same address, age 65 years or older, no diagnosed terminal disease, and the ability to walk independently with or without a mobility aid. The participant had to fulfill at least 1 of the following signs: at least 1 fall during the past year, decreased walking speed, or unintentional weight loss. Our study was approved by the Ethics Committee of the Helsinki University Central Hospital. Informed consent was obtained from each patient and spousal caregiver. In cases in which a patient’s judgment capacity was reduced, the spouse gave consent for both.

CLINICAL MEASURES

A registered nurse and a physiotherapist assessed the participants at 4 meetings: at baseline and at 3, 6, and 12 months. The research staff was independent from the staff delivering the intervention, and the assessors were not coinvestigators and therefore did not know what was happening in the interventions. The Functional Independence Measure (FIM) assessment was based on caregivers’ evaluation of patients’ performance at home; caregivers did not know about the study hypothesis. All measures used are described in detail in the eAppendix.

The primary outcome measures were patients’ physical functioning, evaluated with the FIM, and mobility, assessed with the Short Physical Performance Battery (SPPB) measured during the 12-month intervention period included falls, fractures, and the number of hospitalizations per patient. All falls were documented by spousal caregivers on calendars returned to the study nurses at each visit.

The information on the use of health and social services by each patient-caregiver dyad was retrieved from central registers and medical records for 2 years after randomization or until the patient’s death. In Finland, all community care services are recorded in central registers and medical records, which were requested according to participants’ permission. Service costs were determined at their mean unit costs according to the national cost registers in 2006 with an appropriate correction for inflation rate. Use and costs were summed together for both patient and caregiver because health problems and care needs are highly intertwined in these families owing to the burden experienced by the caregiver. Costs are presented in our study as total costs of the randomized groups and as the mean cost per couple per year. Costs were initially calculated in Euros but were changed to US dollars (exchange rate, 1.3319 in April 2012) for this article.

RANDOMIZATION

After the baseline visit, the patient-caregiver dyads fulfilling all 3 inclusion criteria (n = 210) were randomized in blocks of 30 from April 28, 2008, through August 8, 2009. The randomization was performed by using computer-generated randomly allocated numbers received by telephone from a randomization center. A study nurse called a person at a randomization center who did not know the identities of the potential participants. The study nurse read the names from a printed list in the order in which they had been assessed. A total of 210 dyads were randomized into 3 groups of 70 dyads: the GE group, the HE group, and the CG receiving routine medical care.

INTERVENTIONS

Participants randomized into the GE or HE group were assessed by a geriatrician to ensure patient safety during the exercise intervention.

The HE group performed physical exercise for 1 hour twice a week for 12 months (2008-2009 and 2009-2010). Physiotherapists who specialized in demen económico goal-oriented, individually tailored training during the home visits, addressing the patient’s individual needs and problems in daily functioning or mobility. Physical exercise for the GE group was provided during 4-hour visits to day care centers twice a week for 12 months. The sessions were organized in groups of 10 participants and supervised by 2 physiotherapists who specialized in dementia. The predetermined exercise program consisted of endurance, balance, and strength training, as well as exercises for improving executive functioning. The mean active exercise time per person was approximately 1 h/d because of breaks and waiting times. The interventions are described in detail in the eAppendix.

Patients in the CG received the usual care provided by the Finnish health care system but were also given oral and writ-
ten advice on nutrition and exercise methods by the study nurses. They also had the right to physiotherapy provided by the community health system.

**STATISTICAL ANALYSIS**

Sample size was calculated based on the primary outcome measure FIM.\(^{16}\) A target sample size of about 210 (70 per group) was calculated to ensure 80% power to detect a 10-point difference in FIM between 2 groups (2-sided \(\alpha = .05\)). We estimated a dropout rate of 10%.

All patients assessed at baseline and at 3 months were included in the data analyses of the changes in physical functioning or mobility (modified intention to treat). All randomized patients were included in the use and costs of services analyses (intention to treat). Data are presented as means with standard deviations or numbers with percentages, and 95% CIs are given for the most important outcomes. Statistical comparison between the groups was performed using analysis of variance, Kruskal-Wallis, Mann-Whitney, or the \(\chi^2\) test when appropriate. Repeated measures were analyzed using mixed-effect models with the appropriate contrast. Because the data for costs were highly skewed, bias-corrected and accelerated bootstrap estimation was used to derive 95% CIs. Differences between the means were tested by analysis of covariance with appropriate contrast. Incidence rates of complications were estimated and compared between the groups using the Poisson regression models with robust standard error. No adjustment was made for multiple testing. The Stata 12.0 statistical package (StataCorp) was used for the analyses.

**RESULTS**

Figure 1 is a flowchart of the study. Study attrition was low, with 16 dyads (7.6%) unavailable for follow-up at 3 months. The total study attrition at 12 months was 49 dyads (23.3%). This included 17 deaths (2 in the HE group, 7 in the GE group, and 8 in the CG) and 18 admissions to nursing homes (6 in the HE group, 4 in the GE group, and 8 in the CG). The other reasons for missed visits were the patient’s impaired health or the spousal caregiver’s death. Seven
patients in the GE group refused entirely to participate in the intervention.

Table 1 shows the characteristics of patient-caregiver dyads. All participants were white and married. Of the patients, 67.1% suffered from moderate or severe AD according to the Clinical Dementia Rating (CDR), and 96% were receiving AD medication.

**EFFECT OF INTERVENTION ON PHYSICAL FUNCTIONING AND MOBILITY**

Figure 2 presents the changes in patients’ physical functioning and mobility during a 12-month period. According to the FIM scores, the functioning in each group deteriorated over time. However, the deterioration was significantly slower in the intervention groups than in the CG. The significant mean difference between the groups was apparent at 6 months (FIM change, 6.5 [95% CI, 4.4 to 8.6] in the HE group, 8.9 [6.7 to 11.2] in the GE group, and 11.8 [9.7 to 14.0] in the CG; mixed-effect model, P = .003). This beneficial effect was sustained until 12 months (FIM change, 7.1 [95% CI, 3.7 to 10.5] in the HE group, 10.3 [6.7 to 13.9] in the GE group, and 14.4 [10.9 to 18.0] in the CG; P = .015) (Figure 2A). The difference between the HE group and the CG was significant at 6 (P = .001) and 12 (mixed-effect model, P = .004) months, but the difference between the GE group and the CG was not (6 months, P = .07; 12 months, P = .12). The changes in the FIM motor function scores differed significantly between the groups, but no differences in the FIM cognitive scores were observed. According to the SPPB scores, the interventions did not significantly affect mobility (Figure 2B).

**USE AND COSTS OF HEALTH AND SOCIAL SERVICES**

Table 2 shows the use and costs of health and social services by the 3 groups during the 2-year follow-up. The total health and social service costs were more than $3 759 803 for the CG dyads, and the respective figures for the HE and GE dyads were $3 254 724 and $2 841 788. When costs were calculated with follow-up times and intervention costs taken into consideration and with ad-
adjustments for age, sex, and CDR, the mean cost in the CG dyads (per dyad per year) was $34,121 (95% CI, $24,559 to $43,681). The respective figures for the HE and GE groups were $25,112 ($17,642 to $32,581; bootstrap-type analysis of covariance, $P = .13$ for comparison with the CG) and $22,066 ($15,931 to $28,199; $P = .03$ for comparison with the CG).

The respective figures for patients with AD alone were $29,745 per person per year (95% CI, $20,985 to $39,986) in the CG, $22,646 ($16,115 to $30,792) in the HE group ($P = .22$ for comparison with the CG), and $19,274 ($13,440 to $25,941) in the GE group ($P = .049$ for comparison with the CG). The mean intervention costs were $7838 and $9407 per person in the HE and GE groups, respectively.

**TREATMENT COMPLIANCE AND COMPLICATIONS**

Adherence to the exercise intervention was high. The median numbers of session participations were 81 (range, 7-89) in the HE group and 75 (range, 7-89) in the GE group (Mann-Whitney test, $P = .16$). Of patients in the HE group, 92.9% participated in at least half the sessions compared with 78.6% of patients in the GE group.

Participants in the CG suffered the most falls per person-year ($P < .001$). The incidences of fractures or hospitalizations did not differ between groups (Table 3).

**COMMENT**

To our knowledge, this is the first randomized clinical trial exploring the effects of intensive and long-term exercise on the physical functioning of home-dwelling patients with AD and their use of health and social services. The expected deterioration in these patients’ physical functioning was delayed with home-delivered, individually tailored exercise without causing any harm or risks. The intervention was administered without increasing the total health and social service costs. Our study suggests that group exercise may even decrease the use and costs of other health and social services.

There was a mean 7-point difference in the FIM ratings between the HE group and the CG. Although this did not reach the predetermined level, we believe this 6% difference is clinically meaningful because it indicates less need for help in several daily activity categories. Very few prior clinical intervention trials have demonstrated beneficial effects in the physical functioning of patients with AD. Successful exercise interventions have usually positively affected functional limitations, such as walking speed, balance, and muscle strength, which may or may not translate into improved functioning in everyday life. Prior interventions successful in improving physi-
cal functioning have usually been multicomponent and tailored to participants’ needs.8,27 There are probably several reasons why the HE intervention was successful in our study. First, it was tailored to individual patients and performed at home, which is pleasant for older persons. Second, the exercise was intense and sufficient in duration. Third, the physiotherapists delivering the intervention were specially trained to treat patients with dementia. Exercises were versatile and included “brain training” exercises, such as executive function and dual-tasking exercises. Fourth, adherence to the intervention was exceptionally high among HE participants, thus ensuring high levels of training activity. In previous exercise trials, adherence to schedules has been low.7,9

It is somewhat surprising that the GE participants did not show significant changes in functioning or mobility scores. The mean strength increase with use of gym training machines was remarkable (56%-81% during the year), which suggests that participant fitness improved during the

Table 2. Total Use and Costs of Health and Social Services for Dyads and Patients’ Intervention Costs During 24-Month Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit Cost, US Dollars</th>
<th>Services Used, No.</th>
<th>Total Costs, US Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Home-Based Exercise (70 Dyads)</td>
<td>Group-Based Exercise (70 Dyads)</td>
</tr>
<tr>
<td>Days in primary care hospitalsa</td>
<td>294</td>
<td>1349</td>
<td>807</td>
</tr>
<tr>
<td>Days in specialized care hospitalsa</td>
<td>1371</td>
<td>776</td>
<td>732</td>
</tr>
<tr>
<td>Days of “hospital-at-home” servicesa</td>
<td>269</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Primary care physician visitsa</td>
<td>176</td>
<td>505</td>
<td>604</td>
</tr>
<tr>
<td>Home visits by primary care physiciana</td>
<td>176</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>Ambulatory visits in hospitalsa</td>
<td>294</td>
<td>180</td>
<td>171</td>
</tr>
<tr>
<td>Primary care nurse visitsa</td>
<td>107</td>
<td>388</td>
<td>458</td>
</tr>
<tr>
<td>Physiotherapist visits from community carea</td>
<td>139</td>
<td>350</td>
<td>165</td>
</tr>
<tr>
<td>Other professionals’ visits (occupational therapist, social worker)4</td>
<td>145</td>
<td>69</td>
<td>62</td>
</tr>
</tbody>
</table>

a Includes use and costs of health and social services in both patients with dementia and spousal caregivers.
b Only patients with dementia used day care, respite care, and nursing home days.

Table 3. Complications Among Participants During the Intervention Year

<table>
<thead>
<tr>
<th>Variable</th>
<th>Home-Based Exercise (n = 68)a</th>
<th>Group-Based Exercise (n = 61)a</th>
<th>Controls (n = 65)a</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>29</td>
<td>30</td>
<td>37</td>
<td>.63</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>0.47 (0.31-0.68)</td>
<td>0.54 (0.37-0.77)</td>
<td>0.65 (0.46-0.90)</td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>83</td>
<td>101</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>1.35 (1.07-1.67)</td>
<td>1.86 (1.51-2.26)</td>
<td>3.07 (2.63-3.57)</td>
<td>.005</td>
</tr>
<tr>
<td>All fractures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>.05</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>0.06 (0.02-0.17)</td>
<td>0.09 (0.03-0.21)</td>
<td>0.07 (0.02-0.18)</td>
<td>.88</td>
</tr>
<tr>
<td>Hip fractures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>.91</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>0.05 (0.01-0.14)</td>
<td>0.04 (0.00-0.13)</td>
<td>0.05 (0.01-0.15)</td>
<td></td>
</tr>
</tbody>
</table>

a Those patients participating in the intervention and/or attending the first follow-up assessment and returning their calendars for falls are included in these analyses.
b Poisson regression analysis with robust standard error estimates.
intervention year. Although the participation rate in the GE group was high compared with rates in many previous trials, it was significantly lower than in the HE group. It is evident that not all patients with dementia accept group intervention at a day care center, although caregivers preferred it and were very satisfied.28 The GE intervention decreased use of health and social services, probably because of the respite it provided for caregivers.

The SPPB mobility test proved unsatisfactory in our patient population. It was difficult to instruct patients with dementia to perform the test properly. Because the use of mobility devices and neuropsychiatric symptoms were inconsistent from one assessment to another, variability was high for individual patient scores.

Our intervention seemed safe and did not increase the number of falls or fractures. More falls occurred among control participants, although no differences were recorded in the numbers of fractures or hospitalizations. To our knowledge, this is the first study to show that exercise may reduce falls in patients with AD.7,29

Our study has several limitations. First, interventions were tested on selected, motivated volunteers, all of whom were white. Generalizing these findings to other populations thereby warrants caution. Second, the small sample size and the number of dropouts may not provide sufficient power to detect differences between the GE group and the CG. Third, the study was not blinded. The staff performing the intervention naturally knew whom they were treating, but during the study we also realized that it was practically impossible to keep the assessing study nurses blinded. The assessment sessions with long discussions were intimate, and both patients and their spouses wanted to share their experiences with the study nurses. However, study nurses performing the assessments were independent of the staff delivering the intervention. Thus, they did not know what was actually happening in the interventions for participants, nor were they coinvestigators. The FIM assessment was based on the caregiver’s evaluation of the patient’s performance at home, and caregivers did not know about the study hypothesis. The staff did not have access to prior data when assessing participants; this is reflected, for example, in the inconsistent SPPB scores. Finally, the high quality of community care received by the control patients tends to dilute differences between the groups. It was evident from the use of services that control patients also received large amounts of physiotherapy and day care.

The strength of our study is that it relies on a single intervention implementable by a single professional group in primary care. It shows that a patient group especially vulnerable to functional decline can benefit from exercise. Our findings also suggest that tailoring treatment and paying attention to patient adherence might be key to achieving actual effects in functioning in patients with AD. We also suggest that exercise administered at a patient’s home results in better adherence and more favorable effect in respect to functioning. Although home visits by physiotherapists are fairly laborious and expensive, our financial analysis suggests that they do not increase net costs.

In conclusion, this study demonstrates that exercise administered at the patient’s home may attenuate the deleterious effects of AD on physical functioning. This intervention provides new means of helping patients with dementia and their families maintain their way of life longer without increasing the total use or costs of health and social services.

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Exercise in Alzheimer Disease

A lzheimer disease (AD), first described more than a century ago, continues to challenge our generation. If we compare the therapeutic progress that modern science has made in this condition with that achieved in treating bacterial infectious diseases, we are unfortunately still in the preantibiotic era with respect to AD. Despite a huge leap in our understanding of the basic science and pathogenesis of this devastating neurodegenerative disease and the many clinical trials of various drugs with disease-modifying potential, we have seen little real progress in achieving a cure. Alzheimer disease is a frightful malady: early on for the person with failing cognition and loss of self-esteem and function, and later for the caregivers.

INVITED COMMENTARY

REFERENCES