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.

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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 effects[7,8] 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.[9] A recent study also showed that intense exercise may improve motor performance in home-dwelling patients with mild to moderate dementia.[10] 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.

METHODS

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.[11] 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.[12] Further information about the recruitment of participants can be found in the eAppendix (http://www.jamainternalmed.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 participating couples 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[13-19] used are described in detail in the eAppendix.

The primary outcome measures[11] were patients' physical functioning, evaluated with the FIM,[17] and mobility, assessed with the Short Physical Performance Battery (SPPB).[18] These measures were assessed at each study nurse's visit until 12 months or until the patient's institutionalization or death. Complications 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[20] 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[21,22] 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.[23] 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 dementia administered 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-

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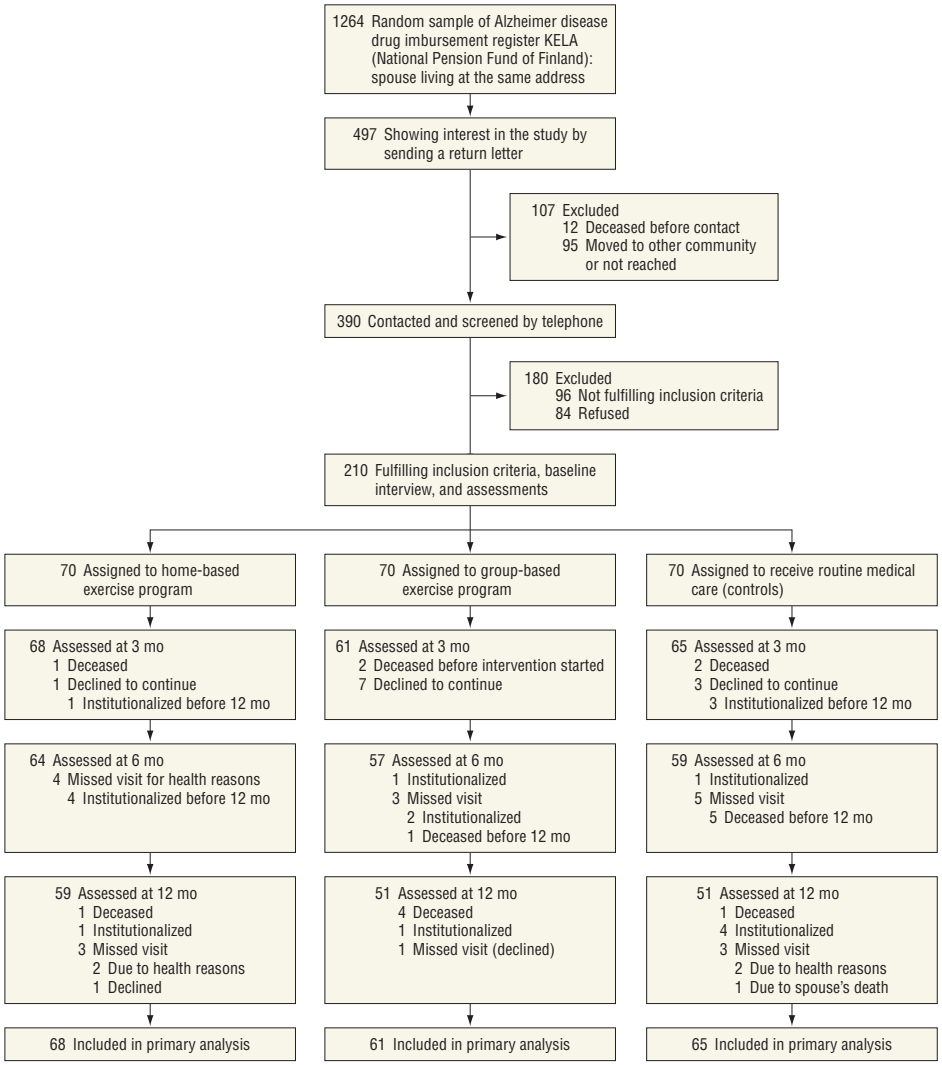

Figure 1. Flowchart of the study. Participants were recruited and baseline assessments were performed from March 25, 2008, through August 8, 2009. The follow-up lasted until October 4, 2011.

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 χ^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

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Table 1. Baseline Characteristics of Patients With Alzheimer Disease and Their Spousal Caregivers

Characteristic	Home-Based Exercise (70 Dyads)	Group-Based Exercise (70 Dyads)	Control Group (70 Dyads)
Patients with AD			
Age, mean (SD), y	77.7 (5.4)	78.3 (5.1)	78.1 (5.3)
Male sex, No. (%)	40 (57.1)	45 (64.3)	44 (62.9)
Years of education, No. (%)			
<8	28 (40.0)	23 (32.9)	29 (41.4)
8-12	25 (35.7)	31 (44.3)	30 (42.9)
>12	17 (24.3)	16 (22.9)	11 (15.7)
Charlson comorbidity index, mean (SD)	2.6 (1.8)	2.5 (1.8)	3.0 (1.7)
Patients receiving AD medications, No. (%)			
Cholinesterase inhibitor only	40 (57.1)	43 (61.4)	44 (62.9)
Memantine only	6 (8.6)	4 (5.7)	3 (4.3)
Both cholinesterase inhibitor and memantine	21 (30.0)	21 (30.0)	20 (28.6)
None	3 (4.3)	2 (2.9)	3 (4.3)
No. of medications, mean (SD)	6.4 (3.6)	6.4 (3.4)	6.6 (3.1)
Malnourished or at risk for malnutrition, No. (%)[a]	53 (75.7)	49 (70.0)	53 (75.7)
CDR, No. (%)			
0.5 or 1	24 (34.3)	23 (32.9)	22 (31.4)
2	30 (42.9)	37 (52.9)	37 (52.9)
3	16 (22.9)	10 (14.3)	11 (15.7)
MMSE, mean (SD)	17.8 (6.6)	18.5 (6.3)	17.7 (6.2)
FIM, mean (SD)			
Total score	87.3 (19.1)	88.5 (19.0)	86.8 (17.9)
Motor score	69.7 (15.3)	70.6 (15.3)	69.7 (13.7)
Cognitive score	17.7 (5.9)	18.1 (5.7)	17.1 (5.6)
SPPB total score, mean (SD)	9.8 (2.2)	9.3 (2.4)	9.7 (2.1)
Use of mobility device, %	15.7	24.3	8.6
Spousal caregivers			
Age, mean (SD), y	75.8 (6.3)	76.4 (7.0)	75.1 (6.4)
Male sex, No. (%)	30 (42.9)	25 (35.7)	26 (37.1)
Years of education, No. (%)			
<8	21 (30.0)	12 (17.1)	22 (31.4)
8-12	32 (45.7)	43 (61.4)	39 (55.7)
>12	17 (24.3)	15 (21.4)	9 (12.9)
Charlson comorbidity index, mean (SD)	1.4 (1.7)	1.4 (1.5)	1.8 (2.1)
No. of medications, mean (SD)	3.6 (2.5)	4.3 (3.0)	4.7 (3.5)

Abbreviations: AD, Alzheimer disease; CDR, Clinical Dementia Rating; FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

[a] Patients were considered malnourished or at risk for malnutrition if their score on the Mini-Nutritional Assessment was ≤23.5.

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 function 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-

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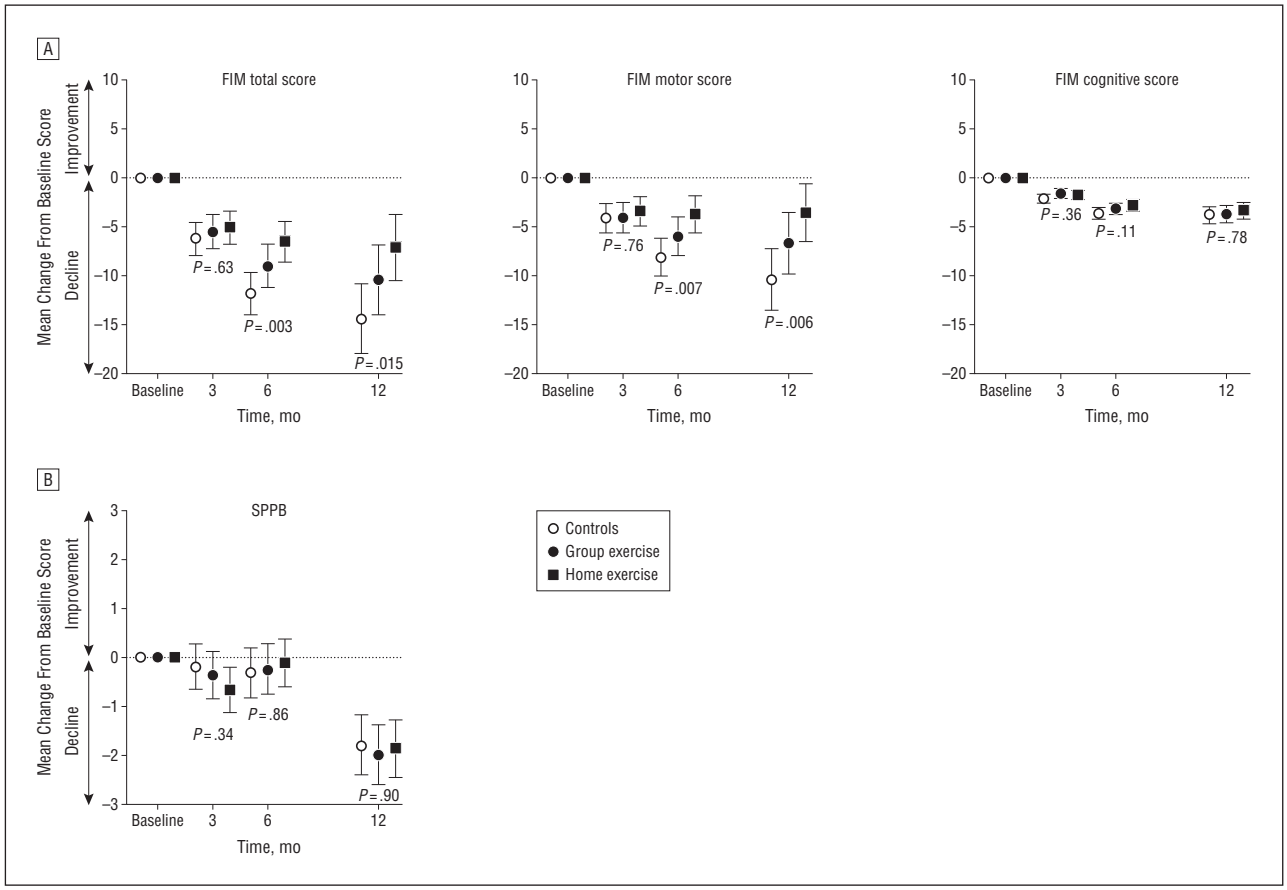

Figure 2. Changes in Functional Independence Measure (FIM) (A) and Short Physical Performance Battery (SPPB) (B) scores relative to baseline (adjusted for age, sex, and use of mobility devices).

justments 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) (all adjusted for age, sex, and CDR). 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, $P = .016$). 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.[9] Successful exercise interventions have usually positively affected functional limitations, such as walking speed, balance, and muscle strength,[24-26] which may or may not translate into improved functioning in everyday life. Prior interventions successful in improving physi-

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

Variable	Unit Cost, US Dollars	Services Used, No.			Total Costs, US Dollars		
		Home-Based Exercise (70 Dyads)	Group-Based Exercise (70 Dyads)	Controls (70 Dyads)	Home-Based Exercise (70 Dyads)	Group-Based Exercise (70 Dyads)	Controls (70 Dyads)
Days in primary care hospitals[a]	294	1349	807	780	397 078	237 540	229 593
Days in specialized care hospitals[a]	1371	776	732	1219	1 063 527	1 003 224	1 670 670
Days of "hospital-at-home" services[a]	269	1	17	33	269	4574	8878
Primary care physician visits[a]	176	505	604	583	88 784	106 190	102 498
Home visits by primary care physician[a]	176	47	37	51	8263	6505	8966
Ambulatory visits in hospitals[a]	294	180	171	174	52 983	50 334	51 217
Primary care nurse visits[a]	107	388	458	443	41 342	48 801	47 203
Physiotherapist visits from community care[a]	139	350	165	464	48 481	22 855	64 272
Other professionals' visits (occupational therapist, social worker)[a]	145	69	62	59	10 017	9001	8565
Days in day care center[b]	236	230	49	53	54 222	11 552	12 495
Days of respite care in institutions	224	2560	2234	2336	572 824	499 878	522 701
Days in nursing homes[b]	224	3675	3354	3490	822 315	750 488	780 920
Domestic help, visits[a]	64	1480	1421	3939	94 618	90 846	251 825
Total cost of services	. . .	. . .	. . .	. . .	3 254 724	2 841 788	3 759 803
Intervention costs	. . .	. . .	. . .	. . .			
Physiotherapist visits	. . .	. . .	. . .	. . .	568 398	548 303	
Transportation	. . .	. . .	. . .	. . .		134 017	
Total cost of services plus intervention	. . .	. . .	. . .	. . .	3 823 122	3 524 108	3 759 803

[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

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

[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.

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

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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.[7,9,29]

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 administrated 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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INVITED COMMENTARY

Exercise in Alzheimer Disease

Alzheimer 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,[1] we have seen little real progress in achieving a cure.[2] 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

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