Research paper

Effects of frequent and long-term exercise on neuropsychiatric symptoms in patients with Alzheimer's disease – Secondary analyses of a randomized, controlled trial (FINALEX)☆

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A B S T R A C T

Background: Neuropsychiatric symptoms (NPS) are common in Alzheimer's disease (AD) and are associated with admission to institutional care. Current guidelines recommend non-pharmacological interventions as the first-line treatment for NPS. However, high-quality randomized studies focused on NPS are scarce. The objective here was to examine whether a regular and long-term exercise programme either at home or as a group-based exercise at an adult day care centre has beneficial effects on AD patients' NPS or permanent institutionalizations.
Design, setting, and participants: A randomized, controlled trial with 210 community-dwelling AD patients.
Intervention: Two types of intervention comprising (1) group-based exercise in day care centres (GE) and (2) tailored home-based exercise (HE), both twice a week for 12 months, were compared with (3) a control group (CG) receiving usual community care.
Measurements: NPS were measured with the Neuropsychiatric Inventory (NPI) at baseline and 6 months, and depression with the Cornell Scale for Depression in Dementia (CSDD) at baseline and 12 months. Data on institutionalizations were retrieved from central registers.
Results: No significant differences between the groups were detected in NPI at 6 months or in CSDD at 12 months when analyses were adjusted for age, sex, baseline Clinical Dementia Rating, and Functional Independence Measure. There was no difference in admissions to permanent institutional care between the groups.
Conclusions: Regular, long-term exercise intervention did not decrease NPS in patients with AD.

1. Introduction

Neuropsychiatric symptoms (NPS), such as agitation, anxiety, depression, and delusions, are common in patients with Alzheimer's disease (AD) and are considered clinically as significant as the other core symptoms; cognitive and functional decline. NPS are often associated with a lower quality of life, higher caregiver distress, poor prognosis, earlier institutionalization, and increasing health care costs [1,2]. Of patients with dementia, 80–90% suffer from these symptoms at some point during disease progression [3,4]. In the MAASBED longitudinal study, 65% of dementia patients with NPS at baseline continued to have at least one symptom during the two-year follow-up [3]. Occurrence of the NPS may be persistent or intermittent, complicating their prevention and treatment.

Researchers have suggested that NPS in dementia can be divided into clusters of symptoms or subsyndromes that may differ

in prevalence, course over time, or pathophysiology [5,6]. Although minor differences in the studies exist, definitions of the subsyndromes of hyperactivity, mood, and psychosis are in general agreement and supported by clinical evidence [4–6]. Treatment interventions may be more beneficial when targeting subsyndromes rather than individual symptoms [5].

Traditionally, psychotropic medication, especially antipsychotic drugs, has been used to alleviate NPS. However, the benefits are often modest and must be carefully weighed against the risk of adverse effects [7,8]. Current guidelines recommend non-pharmacological methods as the first-line treatment approach for NPS (Nice guideline 2016). The non-pharmacological treatments comprise various behavioural, environmental, and care giver supportive interventions. Evidence supporting beneficial treatment effects of these therapies has been accumulating during recent years. Still, high-quality randomized studies on non-pharmacological treatments strategies for NPS in AD are few [9].

Over the last decades a considerable amount of evidence has accumulated of the effects of exercise as preventive or even disease-modifying treatment of age-related dementia. The positive effects are thought to be mediated through improvement of cerebrovascular circulation, stimulation of angiogenesis and neurogenesis, and controlling the inflammation processes [10].

It is also possible that such mechanisms as improved well-being and self-esteem, as well as increased social contacts may generate symptomatic relief as a result of exercise in dementia patients [11].

Physical exercise may improve mood and sleep and reduce depressive symptoms in healthy older adults [12,13]. Moreover, a physically active lifestyle in dementia patients has been shown to be associated with a lower frequency of NPS [14]. However, findings of the effects of exercise intervention on NPS in dementia patients from clinical studies and meta-analyses have so far been inconsistent [15,16]. Positive effects of exercise have been found to be more pronounced in some symptoms (depression, agitation, wandering, sleep) than in others (anxiety and apathy) [17]. According to a recent meta-analysis, depression and aberrant motor behaviour appear to be the NPS most positively affected by exercise. However, the effects on global NPI scores have been insignificant [15]. A substantial heterogeneity has been found in the types of exercise used in the intervention studies; aerobic, resistance training and mixed exercise being the most widely used. Recent Cochrane review was not able to give a recommendation of what type of exercise, or at what frequency or duration would the most beneficial for patients with dementia [16].

The objective of this study was to examine whether regular, long-term exercise has beneficial effects on depression and other NPS in patients with AD. We also examined the impact of exercise on admissions to permanent institutional care.

2. Methods

2.1. Study design

This paper reports secondary findings of a randomized controlled study, FINALEX, which examined the effects of exercise intervention on AD patients' physical performance, cognition, and NPS [18]. Community-dwelling older adults with AD were randomly allocated into two intervention groups or a control group. The exercise sessions were administered by a physiotherapist either at participants' homes (home-exercise group, HE) or at day care centres (group-exercise group, GE) for 60 minutes twice a week for 12 months. The controls (CG) continued with normal community care. The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital. A detailed description of the design and endpoints of the FINALEX study has been provided earlier [18].

This article evaluates the effects of exercise on NPS, depression, and institutionalizations in AD patients.

2.2. Participants

Patients over 65 years of age living with a spouse in the Helsinki area and who were listed on the AD drug reimbursement register of the Social Insurance Institution of Finland were invited to participate in this trial. Patients in this register are diagnosed with AD according to the NINCD-ADRDA criteria [19] evaluated by a geriatrician/neurologist.

Individuals showing an interest in participating were assessed for additional inclusion criteria: ability to walk independently with or without a mobility aid, no terminal illness, and at least one sign of frailty (one or more falls during the last year, decreased walking speed, or unintentional weight loss). Altogether 210 patient-carer dyads fulfilled all inclusion criteria and were enrolled in the study. Each participant and spousal care giver gave informed, written consent. If the patient's judgement capacity was reduced, the spouse provided consent on behalf of the patient. All patients randomized into one of the exercise groups underwent a thorough medical examination by a geriatrician to ensure safety of the intervention.

2.3. Measures

We used the Neuropsychiatric Inventory (NPI) to assess NPS. The NPI evaluates 12 neuropsychiatric disturbances frequently seen in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities. For each symptom, the severity is multiplied by the frequency, with the summed score providing the total NPI score. The score ranges from 0 (no NPS) to 144 (the highest number and most severe symptoms). The validity and reliability of NPI have been established, and it has also been found to be fairly sensitive [20]. A trained nurse administered the NPI to the spousal informant at baseline and 6 months.

In addition to NPI scores, we investigated the effects of intervention on behavioural subsyndromes. We categorized the individual symptoms into subgroups of "Hyperactivity" (agitation, aggressiveness, disinhibition, irritability, aberrant motor behaviour), "Mood and apathy" (depression, anxiety, euphoria, apathy, sleeping problems, eating problems), and "Psychosis" (hallucinations, delusions) according to Aalten and co-workers [5].

We evaluated depressive symptoms with the Cornell Scale of Depression in Dementia (CSDD) [21] at baseline and 12 months. In CSDD, the information is obtained by interviewing the caregiver and by observing and interviewing the patient. The scale contains 19 items with a maximum score of 38 and a score > 10 indicating depression. This scale has good sensitivity and specificity and has been validated in populations of dementia patients [22].

The stage of dementia was assessed with Clinical Dementia Rating [23], and the Charlson Comorbidity Index [24] was calculated to measure the overall disease burden. At baseline, the demographic data and medical history were collected.

Evaluations of physical functioning were done with Functional Independence Measure (FIM), and cognition with Mini Mental Stage Examination. The participants were followed for two years for use of nursing homes. Data on admissions to permanent institutional care were retrieved from central registers.

2.4. Randomization

The participants were randomized after the baseline visit. A separate randomization centre was used to assign the patient-spouse dyads ($n = 210$) into three groups of equal size ($n = 70$):

- tailored home-based exercise (HE);
- group-based exercise (GE);
- and a control group (CG).

2.5. Interventions

Both intervention groups exercised under supervision of a physiotherapist for 60 minutes twice a week for 12 months. The exercise sessions consisted of aerobic exercise, strength training, balance training, and dual-tasking. Fifteen minutes was allocated to each exercise domain. The intensity of the training was gradually increased, and the balance and dual-task exercises were made more demanding during the intervention phase [25].

In the HE group, the training was individually tailored to meet the needs of the participant and the sessions took place at the participant's home. Aerobic exercises included Nordic walking and training with a restorator bike. Wrist and ankle weights were used to assist the strength training. Balance exercises consisted of stair climbing, picking up items from the floor, and getting up from the floor. Talking while walking, singing while training, and performing two different functions with the left and right hands while counting numbers forward or backward are examples of the dual-task exercises.

The GE group exercised in groups of 10 supervised by two physiotherapists in day care centres. The visits to day care centres lasted 4 hours and included door-to-door taxi service, lunch, and coffee breaks. Actual training time was 60 minutes and consisted of components similar to those described for the HE group. The strength training was, however, assisted with gym equipment.

The control group continued in usual care, but was entitled to physiotherapy provided by the communal health care system if needed. All participants and care givers were also given oral and written information on exercise and nutrition.

2.6. Statistical analyses

Statistical comparison between groups was conducted using analysis of variance (ANOVA), Kruskal-Wallis test, and Chi^2 test, as appropriate. When adjusting for confounding factors (age, sex, baseline CDR and FIM), analysis of covariance or logistic regression model was applied. In the case of violation of assumptions (e.g. non-normality), a bootstrap-type test was used. Effect size ("d")

was calculated by using the method of Cohen for paired samples (mean follow-up scores minus baseline scores, divided by the pooled standard deviation). Effect size of 0.20 was considered small, 0.50 medium, and 0.80 large. Confidence intervals for the effect sizes were obtained by bias-corrected bootstrapping (5000 replications). STATA 14.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

3. Results

The study groups were similar in baseline characteristics. (Table 1). Patients' mean age was 77.8 years, and 61.5% were men. Two in three suffered from advanced dementia (CDR 2–3), and 97.8% were on AD medication. Participants also had several other medical conditions, the mean Charlson comorbidity index being 2.5.

At baseline, 38% of the participants were on psychotropic medication. One in four was on an antidepressive (ATC code N06), and one in ten on an antipsychotic medication (ATC code N05A). The proportion using benzodiazepines regularly or intermittently was 16% (Table 1).

3.1. Effects of exercise intervention on neuropsychiatric symptoms

The NPI was administered at baseline and 6 months. Of the 210 participants, 179 had complete NPI data from baseline and 6 months, and thus, were included in the analyses. Almost 100% of the participants had one or several NPS throughout the study. The most frequently occurring single NPS was apathy, with 96% of the participants suffering from at least some degree of this symptom during the study.

At baseline, the mean NPI scores were fairly low: in HE, the mean NPI was 13.5, in GE 12.1, and in CG 16.6. At 6 months, no significant changes in total NPI or individual symptom scores were detected (Table 2). In GE, a minor decrease in irritability scores was seen, −0.49 (95% CI: −0.99 to −0.54, $P = 0.03$). When examining the effects of exercise on symptom subgroups, the effect sizes remained below statistical or clinical significance (Fig. 1).

3.2. Effects of exercise intervention on depression

The Cornell Scale of Depression in Dementia (CSDD) was utilized for 149 participants at baseline and 12 months. The changes over 12 months were modest: In GE 1.35 (95% CI: 0.14 to

Table 1
Baseline characteristics of Alzheimer's disease patients.

	Group exercise, $n = 57$	Home exercise, $n = 63$	Control, $n = 59$	P-value[a]
Age, mean (SD)	77.9 (5.2)	77.4 (5.3)	78.1 (5.3)	0.72
Men, n (%)	37 (64.9)	39 (61.9)	34 (57.6)	0.72
Education < 8 years, n (%)	18 (31.6)	25 (40.3)	25 (42.4)	0.45
CDR, n (%)				0.46
0.5	6 (10.5)	4 (6.3)	1 (1.7)	
1	15 (26.3)	18 (28.6)	20 (33.9)	
2	30 (52.6)	30 (47.6)	31 (52.5)	
3	6 (10.5)	11 (17.5)	7 (11.9)	
MMSE, mean (SD)	18.9 (6.5)	18.6 (6.2)	17.8 (6.0)	0.60
On AD medication, n (%)	57 (100)	61 (96.8)	57 (96.6)	0.38
On psychotropic medication, n (%)	20 (35)	27 (43)	21 (36)	0.61
FIMtot, mean (SD)	90.1 (17.6)	88.9 (18.4)	89.1 (18)	0.92
Cornell, mean (SD)	3.9 (3.5)	4.8 (4.7)	5.9 (5.7)	0.23
NPI tot, mean (SD)	12.1 (9.8)	13.5 (12.6)	16.6 (15.2)	0.33
Hyper	4.3 (6.3)	5.1 (7.4)	6.1 (7.5)	0.28
Psych	1.3 (2.3)	1.6 (2.9)	2.8 (5.2)	0.36
Mood	8.1 (5.7)	8.3 (6.2)	9.6 (7.6)	0.56
Charlson comorbidity index, mean (SD)	2.4 (1.6)	2.4 (1.6)	2.7 (1.6)	0.42

SD: standard deviation; CDR: Clinical Dementia Rating; AD: Alzheimer's disease; AChEI: acetylcholinesterase inhibitor; Mem: memantine; FIM: Functional Independence Measure (tot: total score); Cornell: Cornell Scale for Depression; NPI: Neuropsychiatric Inventory (Hyper: Hyperactivity subsyndrome; Psych: Psychosis subsyndrome; Mood: Mood and Anxiety subsyndrome); Psychotropic medication (ATC codes N05A, N05B, N05C, N06).
[a] Differences between the groups were tested by χ^2 test for categorical variables and Kruskal-Wallis test for continuous, non-normally distributed variables.

Table 2

Changes in the Neuropsychiatric Inventory (NPI) [18] scores relative to baseline in the intervention and control groups. Negative points in changes indicate less neuropsychiatric symptoms at 6 months.

	Baseline, mean (SD)			Change from baseline, mean (95% CI)			P-value[*]
	Group exercise	Home exercise	Control	Group exercise	Home exercise	Control	
Hyperactivity	4.33 (6.34)	5.05 (7.41)	6.12 (7.45)	−0.23 (−1.69 to 0.97)	1.42 (0.25 to 2.78)	0.14 (−1.45 to 1.7)	0.13
Agitation, aggression	1.18 (2.16)	1.27 (1.97)	1.58 (2.39)	−0.19 (−0.72 to 0.29)	0.21 (−0.23 to 0.66)	0.02 (−0.70 to0.68)	0.27
Disinhibition	0.81 (2.44)	0.89 (2.67)	0.69 (1.85)	−0.49 (−1.24 to 0.15)	0.03 (−0.57 to 0.65)	−0.25 (−0.55 to0.18)	0.24
Irritability	1.28 (2.43)	1.35 (2.57)	1.39 (2.24)	−0.46 (−0.99 to −0.54)	0.13 (−0.25 to 0.69)	0.34 (−0.18 to 0.83)	0.03
Aberrant motor behaviour	1.07 (2.03)	1.53 (2.62)	2.46 (3.51)	0.91 (0.22 to 1.59)	1.05 (0.29 to 1.86)	0.03 (−0.88 to 0.96)	0.65
Psychosis	1.33 (2.28)	1.61 (2.88)	2.75 (5.15)	0.46 (−0.67 to 1.09)	0.74 (0.34 to 1.66)	0.27 (−1.00 to 1.39)	0.81
Delusions	0.89 (1.96)	1.02 (2.24)	1.49 (2.84)	0.18 (−0.40 to 0.63)	0.52 (0.19 to1.03)	0.51 (−0.24 to 1.26)	0.31
Hallucinations	0.44 (1.05)	0.60 (1.41)	1.25 (2.55)	0.28 (−0.03 to 0.67)	0.23 (−0.24 to 0.73)	−0.24 (−0.85 to0.35)	0.97
Mood and apathy	8.07 (5.71)	8.27 (6.23)	9.63 (7.61)	1.25 (−0.55 to 3.21)	0.40 (−1.16 to 2.03)	0.31 (−1.38 to 2.12)	0.76
Depression	0.89 (1.45)	1.15 (1.92)	1.59 (2.55)	0.11 (−0.23 to 0.48)	−0.05 (−0.71 to 0.54)	−0.07 (−0.69 to0.55)	0.90
Anxiety	0.96 (2.18)	1.06 (2.39)	1.51 (2.34)	−0.05 (−0.72 to 0.55)	0.03 (−0.53 to 0.53)	−0.49 (−1.24 to 0.20)	0.79
Euphoria	0.18 (0.57)	0.35 (1.60)	0.31 (1.64)	0.11 (−0.07 to 0.34)	−0.08 (−0.36 to 0.14)	−0.10 (−0.33 to0.67)	0.33
Apathy	4.12 (2.3)	4.24 (2.19)	4.32 (2.51)	0.40 (−0.19 to 0.97)	0.69 (0.11 to 1.34)	0.83 (0.13 to 1.71)	0.33
Sleeping problems	0.96 (2.38)	0.66 (1.70)	0.97 (2.50)	0.37 (−0.26 to 1.05)	0.29 (−0.34 to 1.03)	0.51 (−0.88 to 1.05)	0.84
Eating problems	0.84 (2.46)	0.81 (2.15)	0.93 (2.34)	0.03 (−0.53 to 1.24)	−0.48 (−0.98 to −0.10)	0.08 (−0.79 to 0.98)	0.04
NPI total	12.05 (9.77)	13.45 (12.61)	16.56 (15.20)	0.88 (−1.30 to 2.84)	2.73 (1.08 to 5.05)	0.64 (−2.23 to 3.46)	0.41

[*] Adjusted for baseline age, sex, Clinical Dementia Rating (CDR), and Functional Independence Measure (FIM).
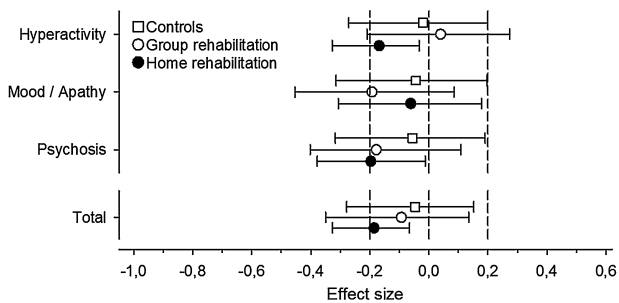

Fig. 1. Effect sizes of changes in neuropsychiatric subsyndromes in persons with Alzheimer's disease. Positive Effect size indicates a decrease in Neuropsychiatric Inventory (NPI) [18] scores (improvement), whereas negative Effect size indicates an increase in NPI scores (worsening). Effect size of 0.20 was considered small, 0.50 medium, and 0.80 large. "Hyperactivity" (agitation, aggressiveness, disinhibition, irritability, aberrant motor behaviour), "Mood and apathy" (depression, anxiety, euphoria, apathy, sleeping problems, eating problems), and "Psychosis" (hallucinations, delusions), "Total" (total score of the NPI) [5].

2.66), in HE 0.5 (95% CI: −0.67 to 1.54), and in CG 0.04 (95% CI: −1.56 to 1.40). The differences between the groups were not significant (P = 0.81, adjusted by age, sex, baseline CDR and FIM).

3.3. Effects of exercise intervention on institutionalizations

Thirteen participants were permanently institutionalized in each of the intervention groups, whereas the respective figure in the control group was 11 (P = 0.79, adjusted by age, sex, baseline CDR and FIM).

4. Discussion

Among patients with AD, an exercise intervention, which had achieved positive results on physical performance and cognition previously [25,26], had no significant effect on NPS, measured by the NPI after 6 months of exercise training, or on depression, measured by the CSDD after 12 months of exercise training. Neither could we show any effect on rate of institutionalizations.

The results of this study are in line with earlier studies where exercise as a single intervention was unable to reduce NPS in dementia patients [27,28]. A fairly large study among home-dwelling dementia patients did not find positive effects on behavioural symptoms measured with the NPI after 12 weeks of regular walking sessions [28]. Similar results were obtained in a Chinese study where dementia patients practised Tai Chi three times a week for 12 weeks [27]. The best effects in reducing NPS in dementia patients have thus far been achieved by tailoring multicomponent interventions for the patients combining exercise with, for example, support and educational programmes for the carers [8,29].

A strength of this study is its sound methodology. All participants had an established AD diagnosis, and the intervention was performed twice weekly for a year by well-trained physiotherapists. There was good compliance among AD participants [25], and the outcome measures were valid. The exercise interventions were simple and could be easily implemented in primary care. However, some limitations should be recognized when interpreting the results of this study. The power calculations were based on physical performance measured with the Functional Independence Measure (FIM). Neuropsychiatric measures were only secondary endpoints of the study. The primary focus being on physical performance, the timing and extent of the neuropsychiatric measures may be considered suboptimal. Moreover, the participants were motivated volunteers living in their own homes with a spouse, and thus, generalizing the results to other patient groups should be done with caution.

Several explanations may be offered for the results in neuropsychiatric measures not reaching statistical significance, although a positive trend was seen. The primary outcome of this study was physical performance. Hence, the interventions were not aimed at decreasing NPS in general. In previous studies with positive results, the objective has often been to explore a single NPS and the effects of an intervention targeted to reduce this particular symptom such as depression or apathy [30,31]. It has also been shown that different NPS, e.g. motor hyperactivity and apathy, can occur simultaneously in dementia, perhaps needing a different clinical approach [32]. The participants of our study were volunteers from the community who lived with a carer, and thereby, may reflect a lower probability of NPS. Patients with more severe symptoms and their carers may be less keen to participate in an intervention study. The NPS scores were relatively low at baseline, thus, there was a floor effect in reducing NPS. Furthermore, 99% of the patients were on Alzheimer's medication, which may alleviate the NPS. A large percentage of the participants used psychotropic medication at the beginning of the study, possibly distorting the results. Abundant use of psychotropic medication can also reflect the current need for more safe and effective treatment of NPS in dementia. We did not collect data on use of psychotropic medication post-intervention so we are unable

to determine whether the exercise intervention was effective in decreasing the use of these potentially harmful medications. This aspect has been only marginally explored previously [15], and further studies are needed.

Frequent NPS in dementia are often the leading cause of early institutionalization [2]. In this study, we were unable to show beneficial effects of exercise on NPS, which may, to some degree, explain the non-existent effects on the rate of permanent care placement. Exercise as a single intervention may be insufficient to overcome the wide spectrum of individual medical, psychological, and social factors leading to NPS and permanent institutionalization. Further evaluations are required to determine the best combinations of non-pharmacological interventions for various patient groups and symptom clusters.

5. Conclusions

The 12-month exercise intervention showed no positive effects on neuropsychiatric symptoms in patients with Alzheimer's disease.

Author contributions

Conception and design (T.E.S., M.M.R., M.L.L., R.S.T., H.K., K.H.P.), acquisition of data or analysis and interpretation of data (H.Ö., N.S., T.E.S., H.K., K.H.P.), drafting or critically revising the manuscript for relevant intellectual content (H.Ö., N.S., T.E.S., H.K., M.M.R., M.L.L., R.S.T., K.H.P.), approval of the final manuscript (H.Ö., N.S., T.E.S., H.K., M.M.R., M.L.L., R.S.T., K.H.P.). K.H.P. had full access to the data used in the study and is responsible for the integrity of the data and the accuracy of data analysis. K.H.P. is the guarantor.

Disclosure of interest

The authors declare that they have no competing interest.

However, professional cooperation occurred with various companies. Professor Strandberg reports educational, consultative, and professional cooperation with several companies and societies, a minor amount of stock in Orion Pharma, and grants from the above-mentioned foundations and the hospital. Dr. Raivio reports educational cooperation with several pharmacological companies. Professor Pitkälä reports professional cooperation with Orion Pharma. The other authors have no relevant cooperation to disclose.

Acknowledgements

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