Physical exercise and dementia

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CHAPTER 5

A nine-week-long aerobic and strength training program improves cognitive and motor function in patients with dementia: A randomized, controlled trial.[1]

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ABSTRACT

Objectives
1) To compare training and follow-up effects of combined aerobic and strength training versus aerobic-only training on cognitive and motor function in institutionalized patients with dementia and 2) to explore whether improved motor function mediates improved cognitive function.

Design
A nine-week, parallel, three-group, single-blind, randomized, controlled trial with a follow-up assessment at week eighteen.

Setting
A psycho-geriatric nursing home.

Participants
Patients with dementia (N = 109, age = 85.5 ± 5.1 years).

Intervention
Each nine-week-long intervention consisted of 36, 30-minute-long sessions. A Combined group (N = 37) received and completed two strength and two walking sessions per week. An Aerobic group (N = 36) completed four walking sessions and a Social group (N = 36) completed four social visits per week.

Measurements
Cognitive and motor functions were assessed at baseline, after the nine-week-long intervention, and after a consecutive nine weeks of usual care.

Results
Baseline corrected posttest scores in the Combined versus Social group were higher for global cognition, visual memory, verbal memory, executive function, walking endurance, leg muscle strength, and balance. Aerobic versus Social group scores were higher for executive function. Follow-up effects reversed towards baseline values. Changes in motor function did not significantly mediate changes in cognitive function.

Conclusions
Compared to a non-exercise control group, a combination of aerobic and strength versus aerobic-only training is superior in slowing cognitive and motor decline in patients with dementia. No mediating effects between improvements in cognitive function via improved motor function were found, and future research into the underlying mechanistic associations is needed.

INTRODUCTION

Dementia is associated with a decline in cognitive and motor function, which in turn necessitates increasing daily assistance and care. As a care-intensive condition, dementia is expected to exact a severe social and financial impact, making it a ‘public health priority’.[1]

To date there is no cure for dementia. Pharmacological treatments attempt to slow the decline in key elements of cognitive functions, including memory and executive function. However, the clinical and cost-effectiveness of these pharmacological treatments are controversial, and the medications may cause side effects.[2] Moreover, current medications fail to counteract the motor decline associated with dementia, as illustrated by the continued loss of endurance, muscle strength, mobility, and balance.[3] Therefore, there is an urgent need for affordable alternative treatments to combat both the cognitive and motor decline of patients with dementia, preferably with fewer or no side effects.

In light of the recent recognition by the American College of Sports Medicine (ACSM) that ‘exercise is medicine’, exercise is suggested to be a potential treatment for slowing a dementia patient’s decline in cognitive and motor function.[4, 5] However, potential cognitive benefits of exercise treatment should be interpreted with caution because the results have been inconsistent.[4] Small to moderate improvements in mixed cognitive domains (e.g., communication, global cognition, executive function, memory) were found after mainly aerobic exercise (i.e., walking, cycling)[6-9], whereas similar aerobic exercise studies in patients with dementia found no effects.[10, 11] In studies consisting of healthy older people, a combination of aerobic and strength training showed the strongest effects in improving cognitive function compared to single-component aerobic or strength interventions.[12] Therefore, we suggest that after combined training these beneficial effects might also apply to patients with dementia. However, the effects of combined exercise training on cognition have not yet been studied in patients with dementia.

Based on previous evidence in healthy older people[12], we hypothesized that combining aerobic and strength training in patients with dementia will result in stronger effects on cognitive function than aerobic-only training. Leg muscle strength training (e.g., m. quadriceps femoris, m. gastrocnemius, m. biceps femoris) has the potential to improve motor function, such as balance and mobility.[13, 14] These motor improvements may promote higher aerobic training ability, thereby eliciting higher metabolic and cardiovascular responses. With these higher exercise responses, a mediating cascade of neuro-motor events may be initiated.[14-18]

A pilot study we previously conducted showed that alternating aerobic and strength training sessions is safe and feasible for patients with dementia.[19] The potentially favorable motor and cognitive responses in the pilot study prompted us to launch a large-scale randomized controlled trial. The objectives of the present study compare the training and follow-up effects of a combined aerobic and strength versus a aerobic-only intervention on cognitive and motor function in patients with dementia. Furthermore, they examine whether cognitive change is mediated by a change in motor function.

METHODS

The Medical Ethics Committee of the University Medical Center Groningen approved the research protocol. Patients orally agreed to participate and in conjunction their legal representative gave written consent.

Design overview

We compared the effects of three nine-week-long interventions on cognitive and motor function in a parallel, three-group, single-blind, randomized, controlled trial. Institutionalized patients with dementia were assigned to one of the three intervention groups: combined aerobic and strength exercise (Combined group), aerobic-only exercise (Aerobic group), and social visits (Social group). Posttests were conducted after the nine-week-long intervention (time 9-weeks, T1) and follow-up tests nine weeks thereafter (time 18-weeks, F1).

Setting and participants

A three group study design, alpha = 0.05, power = 0.80, and a medium-large effect size determined that approximately 35 participants per group were required.[19] Between January 2011 and May 2013, patients with mild to severe dementia[20], who lived in seven Dutch psychogeriatric nursing homes were recruited. First, a geriatrician checked the following initial eligibility criteria: age over 70, diagnosis of dementia reported in the patient's medical file by Team 290 (i.e., Dutch dementia diagnosis team) or a medical specialist, and absence of serious health problems that could preclude safe participation. Next, a trained Human Movement Sciences (HMS) research assistant tested the patients for the following additional inclusion criteria: Mini Mental State Examination score (MMSE) ≥ 9 to ≤ 23 and the ability to perform the timed up & go test.[21] Those who passed these five criteria completed a neuropsychological and physical test battery in the nursing home at baseline (time zero, T0) administered by an experienced and trained HMS research assistant.

Randomization and interventions

After T0, stratification took place according to gender (male/female), MMSE score (low subgroup, high subgroup), and location (allocation ratio 1:1:1). A researcher, unrelated to the study, performed the randomization procedure.

Patients in each group participated in 36 individualized sessions. Each thirty-minute-long session consisted of one patient being guided by one of the 18 assigned HMS research assistants. The Combined group participated in two strength sessions (s) and two walking sessions (w) per week. In accordance with ACSM guidelines, strength and walking sessions were alternated (w–s–w–s).[22] The Aerobic group participated in four walking sessions (w–w–w–w) and the Social group participated in four social visits each week. An intervention diary was used to monitor fidelity. A trainer used a rate of perceived exertion (RPE) score (range 6-20) to monitor exercise intensity after each session. Furthermore, pre-post session differences in manually measured heart rate in seated position were measured. Trainer monitored RPE scores were used because patient self-reported RPE feedback is insufficient for monitoring exercise intensity.[23] Our aim was to offer a moderate to high intensity exercise program at a rate of perceived exertion 12-15 (e.g. 'somewhat hard' - 'hard')[22], and at 50-85% of maximum heart rate (American Heart Association, AHA).

Strength exercises

Strength exercises for the Combined group focused on lower-limb strengthening because such large muscle group exercises are assumed to lead to enhanced positive responses in gait speed, balance, and mobility.[24-26] The exercises were as follows: seated knee extension, plantar flexion through toe raises while holding both hands of the trainer, hip abduction by moving the straight leg sideways while standing behind and holding on to a chair, and hip extension by moving the straight leg backwards while standing behind and holding on to a chair. Exercise intensity increased gradually by increasing the number of repetitions and by affixing weights around the ankles. To minimize the chance for injury, overload, and drop-out, all participants started with three sets of eight repetitions for each leg without weights. When a participant performed an exercise with ease and according to protocol, the number of repetitions was increased to ten in the next session, and twelve in the session thereafter. When a participant was able to correctly perform twelve repetitions without weights, at a RPE <12, a weight of 0.5 kg was attached to the ankles. After the weight was attached, participants performed eight repetitions and progressed as prescribed above. The trainer increased weights from 0 kg to a maximum of 1.5 kg in 0.5 kg increments. For plantar flexion the number of repetitions increased in increments of 2 per session, to a maximum of 30 repetitions.

Aerobic training

The Combined group and Aerobic group performed moderate to high intensity walking sessions.[22] Walking sessions usually took place indoors. However, if the weather permitted and the nurse gave permission walking took place outdoors. If rest was requested, an appropriate rest period was included in the 30-minute-long session. The training intensity was adjusted by varying the distances the participants walked per session.

Social Program
To control for social and intellectual engagement[27], each participant in the Social group received thirty-minute-long one-on-one social visits (N=36) at the same frequency as the exercise groups. The same HMS research assistants that provided the exercise interventions assessed these sessions.

Outcomes and follow-up
Assessment of cognitive function
A previously described neuropsychological test battery with the corresponding references[19] was used to assess cognitive function. A HMS research assistant, who was blinded to the treatment conditions, administered the tests. Global cognition was measured with the mini mental state examination (MMSE). Both short- and long-term verbal memory were measured with the eight-words test direct recall, eight-words test recognition, and digit span forward test (from the Wechsler Memory Scale Revised [WMS-R]). Short- and long-term visual memory were measured with the visual memory span forward test (WMS-R), face recognition test (Rivermead Behavioral Memory Test [RBMT]), and picture recognition test (RBMT). Executive function was measured using the visual memory span backward test (WMS-R), digit span backward test (WMS-R), the stroop test, verbal fluency test (animals and professions), picture completion test (Groningen Intelligence Test), and trail making test-A.[19]

Assessment of motor function
A previously described physical test battery with corresponding references[19] was used to assess motor function. A HMS research assistant, who was blinded to the treatment conditions, administered the tests. Walking endurance was measured with the 6-minute walk test. Leg strength was measured with the 30-second sit-to-stand test and the maximal knee extension strength was measured with a dynamometer. Mobility was measured with the 6-meter walk test and the timed up & go test. Balance was measured with the frailty and injuries cooperative studies of intervention techniques-subtest 4 (FICSIT-4), the figure of eight test, and the Groningen meander walking test.[19, 28]

Statistical analysis
SPSS 20 was used for data management with two-tailed significance set at $p < .05$. We corrected the p-values for multiple hypotheses testing by multiplying the obtained p-value by four (i.e., four cognitive and motor domains, respectively).

Group characteristics, adherence to the exercise program and the intensity measures of the programs were compared between the three groups with One-way Analyses of Variance, independent samples t-tests, and Chi-square tests.

Multiple imputation was used to account for missing values (8.9% of the values missing; 5.2% at T0, 6.4% at T1, and 14.6% at F1). Characteristic variables of the sample, cognitive and physical test scores set at T0, T1, and F1 were included in the imputation model. The following imputation settings were used: automatic model setting, 100 iterations, and 70 imputations to preserve 99.5% of the relative estimation of the imputed dataset.

Mean z-scores of composite factors for cognitive domains (i.e., global cognitive function, verbal memory, visual memory, and executive function) and motor domains (i.e., walking endurance, leg strength, balance, and mobility) were calculated. Analyses of covariance were performed to determine group effects in each domain after the nine-week-long intervention and after the eighteen-week-long total observation. Baseline domain scores were used as covariates. To specify significant group effects, Bonferroni corrected post-hoc tests were done.

For each cognitive and motor domain, mean Cohen's *d* effect sizes were calculated by using a reference group (i.e., Combined versus Social; Aerobic versus Social; Combined versus Aerobic). The following formula was used: $d = [(post_{exp.} - pre_{exp.}) - (post_{ref.} - pre_{ref.})] / \sqrt{[([s^2pre_{exp.} (n_{exp.}) + s^2pre_{ref.} (n_{ref.})] / [n_{exp.} + n_{ref.}]) + ([s^2post_{exp.} (n_{exp.}) + s^2post_{ref.} (n_{ref.})] / [n_{exp.} + n_{ref.}]) / 2]}$.[29] Note: post= mean posttest; pre= mean pretest; s=standard deviation; exp.=experimental group; ref.=reference group. Cohen's benchmarks were used to indicate small (d=0.20), moderate (d=0.50), and large (d=0.80) effect sizes.[29]

To explore mediation of motor effects on cognitive effects, the Hayes & Preacher mediation analysis was completed.[30] The difference scores in global cognition, visual memory, verbal memory, and executive function were the outcome variables. Difference scores in walking endurance, leg muscle strength, balance, and mobility were the mediators in motor domain. Dummy coding was used to test the direct and indirect (i.e., via mediators) effects of the Combined and Aerobic group, using the Social group as a reference. A bootstrapping method with 5000 resamples was used.[30]

RESULTS

Participant characteristics and adherence to the intervention

Figure 5.1 shows the study design and patient flow. In total, 495 patients were screened for eligibility, 132 enrolled in the study. There were no significant between group differences for the descriptive characteristics and the severity of dementia ranged between mild to severe dementia (Table 5.1).[20] Table 5.2 presents the training characteristics for each group. After exercise the mean heart rate increased more in the Combined and Aerobic group than in the Social group (Table 5.2).

Intervention effects

Results on the individual neuropsychological tests per group and time point are presented in Appendix 1. On the cognitive domain level, Table 5.3 shows a significant intervention effect for global cognitive function, visual memory, verbal memory, and executive function. Post-hoc tests using the Bonferroni correction revealed that the Combined group improved compared to the Social group on global cognitive function (mean T1-T0 difference (I-J) = 0.430, 95% confidence interval (CI) = 0.176 to 0.685, $p<.001$), visual memory (mean T1-T0 difference (I-J) = 0.527, 95% CI = 0.231 to 0.823, $p<.001$), verbal memory (mean difference (I-J) = 0.353, 95% CI = 0.078 to 0.628, $p = .007$), and executive function (mean T1-T0 difference (I-J) = 0.305, 95% CI = 0.129 to 0.482, $p<.001$). Furthermore, post-hoc comparisons revealed that the Aerobic versus Social group only differed in favor of the Aerobic group in executive function (mean T1-T0 difference (I-J) = 0.183, 95% CI = 0.005 to 0.360, $p = .042$). After the nine-week delayed posttest, no significant effects of the intervention group in any of the cognitive domains remained (Table 5.3).

Results on the individual motor tests per group and time point are presented in Appendix 2. On the motor domain level, Table 5.4 shows a significant intervention effect for walking endurance, leg muscle strength, and balance. Post-hoc tests using the Bonferroni correction revealed that the Combined group improved compared to the Social group on walking endurance (mean T1-T0 difference (I-J) = 0.578, 95% CI = 0.211 to 0.935, $p<.001$), leg muscle strength (mean T1-T0 difference (I-J) = 0.358, 95% CI = 0.067 to 0.649, $p = .010$), and balance (mean T1-T0 difference (I-J) = 0.329, 95% CI = 0.100 to 0.558, $p = .002$). Furthermore, post-hoc comparisons revealed that the Combined scored higher than the Aerobic group in walking endurance (mean T1-T0 difference (I-J) = 0.363, 95% CI = 0.006 to 0.719, $p = .045$) and leg muscle strength (mean T1-T0 difference (I-J) = 0.359, 95% CI = 0.068 to 0.650, $p = .010$). After the nine-week delayed posttest, no significant intervention effects in any of the motor domains remained (Table 5.4).

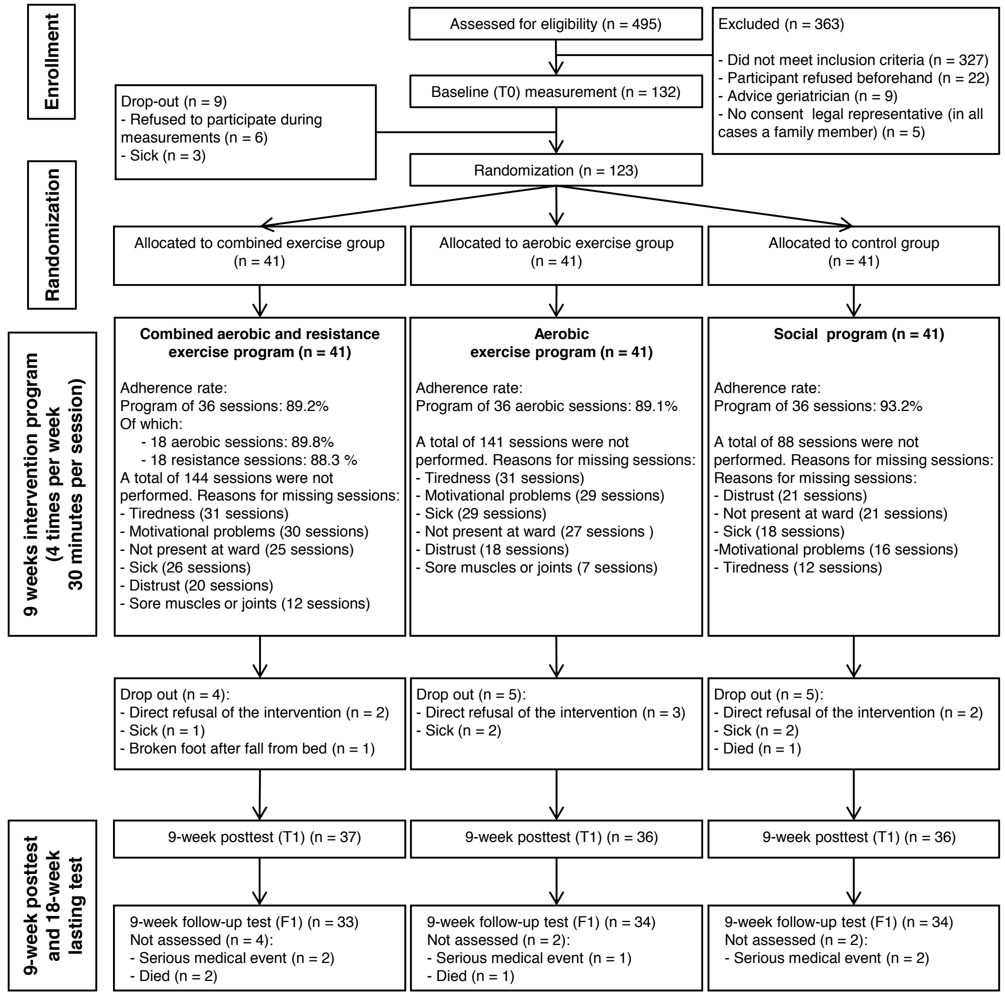

Figure 5.1. *CONSORT flowchart of the study design and patient flow.*

Table 5.1. Baseline characteristics of the Combined group (N = 37), Aerobic group (N = 36) and Social group (N = 36).

Characteristic	Combined group	Aerobic group	Social group	F / Chi^2 test-value, (df), p-value
Mean age, (SD)	85.7 (5.1)	85.4 (5.4)	85.4 (5.0)	F = 0.03, (2,106), p = .973 [a]
Males, %	21.6%	22.2%	30.6%	Chi^2 = 0.97, (2), p = .616 [b]
Dutch education level, %				Chi^2 = 5.87, (10), p = .826 [b]
Finished primary school or lower	16.7%	24.3%	18.5%	
Lower than finished higher education	48.6%	45.9%	56.8%	
Finished higher education	34.7%	29.8%	24.7%	
Use of walking aid (%)	43.2%	63.9%	61.1%	Chi^2 = 3.73, (2), p =.155 [b]
Mean Mini Mental State Examination (SD), Range [c]	15.8 (4.3), 9 - 23	15.2 (4.8), 9 - 23	15.9 (4.2), 9 - 23	F = 0.24, (2, 106), p = .784 [a]
Mild dementia (score 20-23), %	27.0%	22.2%	22.2%	
Moderate dementia (score 11-20), %	59.5%	44.5%	61.1%	
Severe Dementia (score 9-11), %	13.5%	33.3%	16.7%	
Mean number of medication used (SD)	6.0 (2.4)	6.9 (2.6)	7.4 (2.9)	F = 2.45, (2, 106), p = .091 [a]
Mean Functional Comorbidity Index (SD) [d]	3.6 (1.8)	3.2 (1.8)	3.6 (1.8)	F = 2.23, (2, 106), p = .112 [a]
Mean Katz index (SD) [e]	10.5 (1.8)	11.0 (2.6)	10.9 (2.8)	F = 0.55, (2, 106), p =.580 [a]
Cause of dementia, %				Chi^2 = 0.97, (6), p =.360 [b]
Alzheimer's Disease	54.1%	58.3%	47.2%	
Vascular Dementia	13.5%	22.2%	13.9%	
Alzh. Disease / Vasc. Dementia	13.5%	16.7%	19.4%	
Type not reported	18.9%	2.8%	19.5%	

[a], Differences between the groups were tested with One-way Analysis of Variance.
[b], Differences between the groups were tested with Chi-Square Test.
[c], theoretical range 0 – 30 and a higher score indicates better performance.
[d], theoretical range 0 – 18 and a higher score indicates more comorbidities.
[e], theoretical range 6 – 18 and a higher score indicates higher ADL dependency.

Table 5.2. Training characteristics of the nine-week-long interventions for the Combined group (N = 37), Aerobic group (N = 36), and Social group (N = 36) as mean (SD).

Training characteristic	Combined group	Aerobic group	Social group	F / t test-value, (df), p-value
Mean % adherence rate (SD)	89.2 (9.8)	89.1 (10.6)	93.2 (6.7)	F = 2.34, (2,106), p =.101 [a]
Mean duration per session, min (SD)	30.9 (1.9)	30.9 (2.9)	29.9 (2.0)	F = 2.31, (2,106), p =.104 [a]
Mean resting heart rate, beats/min^{-1} (SD)	73.1 (7.9)	74.3 (7.2)	73.4 (8.0)	F = 2.26, (2,106), p =.775 [a]
Mean heart rate after exercise, beats/min^{-1} (SD)	83.4 (10.4)	86.7 (10.3)	74.2 (8.3)	F = 16.22, (2,106), p = <.001 [a] t = 4.22, (71), p < .001 [b] t = 5.73, (70), p < .001 [c]
Mean heart rate difference, beats/min^{-1} (SD)	10.3 (4.7)	12.3 (6.5)	0.8 (2.0)	F = 59.98, (2,106), p = <.001 [a] t = 11.15, (71), p < .001 [b] t = 10.19, (70), p < .001 [c]
Mean Rate of perceived exertion after session, (SD) [d]	13.2 (2.9)	13.8 (1.7)	Not collected	t = -1.11 (71), p =.272

[a], Differences between groups were tested with One-way Analysis of Covariance tests.
[b], For post-hoc comparison between the Combined and Social group, independent-sample t-test was done.
[c], For post-hoc comparison between the Aerobic and Social group, independent-samples t-test was done.
[d], Theoretical range 6 – 20 where score 6 indicates lowest intensity level and score 20 indicates highest intensity level.

Mediating effect of motor domain difference scores on cognitive domain difference scores

A mediation effect equals the multiplication of the direct effect of each intervention group on motor function (i.e., 'path a') by the direct effect of each motor function on cognitive function (i.e., 'path b') represented as 'ab'.[30] In line with results presented in Table 5.4, the Aerobic group showed no significant direct effects on 'path a'. However, in the Combined group, significant 'path a' effects on walking endurance (B = 0.69, t(36) = 2.13, p = .040), leg strength (B = 0.50, t(36) = 2.18, p = .036), and balance (B = 0.43, t(36) = 2.40, p = .021) were found. Despite this result, no significant 'path b' effects were found. Subsequently, mediating effects 'path ab' in both intervention groups were non-significant.

Table 5.3. Cognitive data representing group effects and effect size for the 9-week intervention period (T0-T1) and for the total 18 week period (T0-F1), including post-hoc group comparisons.

	9-week intervention period (T0-T1)				**9-week lasting (T0-F1)**			
Cognitive domains	**F-value, (df), p-value** [b]	**Mean effect size** Combined vs. Social (range)	**Mean effect size** Aerobic vs. Social (range)	**Mean effect size** Combined vs. Aerobic (range)	**F-value, (df), p-value** [c]	**Mean ffect size** Combined vs. Social (range)	**Mean effect size** Aerobic vs. Social (range)	**Mean effect size** Combined vs. Aerobic (range)
Global cognition [a]	F = 8.46, (2,105), p < .001 [d]	0.48 (-)	0.21 (-)	0.23 (-)	F = 3.96, (2,105), p = .088	0.45 (-)	0.28 (-)	0.15 (-)
Visual memory [a]	F = 6.72, (2,105), p = .008 [d]	0.46 (0.35-0.61)	0.26 (0.05 - 0.62)	0.20 (-0.40 - 0.32)	F = 1.83, (2,105), p = .660	0.26 (0.17 - 0.32)	0.14 (-0.06 - 0.27)	0.12 (-0.05 - 0.39)
Verbal memory [a]	F =5.10, (2,105), p = .032 [d]	0.37 (0.32-0.43)	0.29 (0.15 - 0.39)	0.06 (0.00 - 0.15)	F = 3.23, (2,105), p = .176	0.34 (0.17 - 0.56)	0.28 (-0.04 - 0.52)	0.28 (-0.05 - 0.22)
Executive function [a]	F = 9.26, (2,105), p<.001 [d, e]	0.37 (0.13-0.51)	0.17 (-0.04 - 0.33)	0.18 (0.05 - 0.30)	F = 3.31, (2,105), p = .160	0.23 (0.12 - 0.31)	0.04 (-0.08 - 0.11)	0.17 (0.06 - 0.38)

*, p < .05 (Bonferroni corrected for multiple hypothesis testing).
[a], Composite factors for cognitive function domains global cognition, visual memory, verbal memory, and executive function were calculated by averaging z-values of test scores that measured these domains (see Appendix 1 for separate test values).
[b], Model used for data analysis: ANCOVA with T0 as covariate, T1 as dependent variable, and Group as a fixed factor.
[c], Model used for data analysis: ANCOVA with T0 as covariate, T2 as dependent variable, and Group as a fixed factor.
[d], Significant Bonferroni corrected post-hoc effect between the Combined and Social group (see text for statistics).
[e], Significant Bonferroni corrected post-hoc effect between the Aerobic and Social group (see text for statistics).

Table 5.4. Motor data representing group effects and effect size for the 9-week intervention period (T0-T1) and for the total 18 week period (T0-F1), including post-hoc group comparisons.

	9-week intervention period (T0-T1)				**9-week lasting (T0-F1)**			
Motor domain	**F-value, (df), p-value** [b]	**Mean effect size** Combined vs. Social (range)	**Mean effect size** Aerobic vs. Social (range)	**Mean effect size** Combined vs. Aerobic (range)	**F-value, (df), p-value** [c]	**Mean effect size** Combined vs. Social (range)	**Mean effect size** Aerobic vs. Social (range)	**Mean effect size** Combined vs. Aerobic (range)
Walking endurance [a]	F = 4.53, (2,105), p < .049* [d, e]	0.47 (-)	0.08 (-)	0.38 (-)	F = 1.23, (2,105), p = .296	0.19 (-)	-0.06 (-)	0.27 (-)
Leg muscle strength [a]	F = 7.07, (2,105), p = .004* [d, e]	0.38 (0.26-0.49)	0.04 (0.00-0.07)	0.36 (0.15-0.56)	F = 2.86, (2,105), p = .247	0.27 (0.20-0.33)	0.25 (0.14-0.36)	0.01 (-0.15-0.17)
Mobility [a]	F =1.28, (2,105), p = .282	0.28 (0.18-0.39)	0.06 (0.03-0.12)	0.26 (0.17-0.33)	F = 2.36, (2,105), p = .398	0.29 (0.12-0.41)	0.00 (-0.03-0.04)	0.34 (0.20-0.44)
Balance [a]	F = 5.36, (2,105), p = .024* [d, e]	0.30 (0.14-0.65)	0.08 (-0.06-0.16)	0.33 (0.10-0.72)	F = 2.86, (2,105), p = .247	0.24 (0.02-0.54)	-0.19 (-0.43-0.00)	0.48 (0.23-0.67)

*, p < .05 (Bonferroni corrected for multiple hypothesis testing).
[a], Composite factors for motor function domains walking endurance, leg muscle strength, mobility, and balance were calculated by averaging z-values of test scores that measured these domains (see Appendix 2 for separate test values).
[b], Model used for data analysis: ANCOVA with T0 as covariate, T1 as dependent variable, and Group as a fixed factor.
[c], Model used for data analysis: ANCOVA with T0 as covariate, T2 as dependent variable, and Group as a fixed factor.
[d], Significant Bonferroni corrected post-hoc effect between the Combined and Social group (see text for statistics).
[e], Significant Bonferroni corrected post-hoc effect between the Combined and Aerobic group (see text for statistics).

DISCUSSION

This is the first study that provides evidence for the effectiveness of a combined aerobic and strength training program to improve cognitive and motor function in older patients with dementia. Cognitive and motor function improved after nine weeks of training. Moreover, an alternating form of aerobic and strength training sessions were more effective than aerobic-only training.

Patients with dementia suffer from a continuous loss in global cognition.[31] Previous studies show an average twelve-month global-cognitive decline of 2.3 MMSE-points.[31] However, our study results demonstrate that the Combined and Aerobic group improved by 2.1 and 1.0 MMSE-points after the intervention, respectively. These values were computed by adjusting for the natural decline of 0.72 MMSE-points in the Social group. These short-term improvements suggest that the Combined and Aerobic group respectively compensated eleven (1.35 - -0.72 = 2.1 MMSE-points) and five months (0.28 - -0.72 = 1.0 MMSE-points) of the average twelve-month 2.3 MMSE deterioration[31], which is of high clinical relevance. Thus, the current data suggest that a combined aerobic and strength training slows the natural global cognitive decline in patients with dementia and is more effective than aerobic-only training.
In addition to global cognitive benefits, the patients who received the combined exercise program also improved their verbal memory, visual memory, and executive function. This is in line with previous findings in healthy elderly people.[5, 12] In our previous six-week-long pilot study we showed only a moderate non-significant effect size in visual memory[19], whereas the current longer training period resulted in larger significant cognitive effect size in all cognitive domains. These larger significant effects can be explained by the longer training duration and larger sample size, which result in higher statistical power. The improvements in verbal memory, visual memory, and executive function are linked to circuits in the posterior hippocampus, anterior hippocampus, and the frontal lobe.[32] These circuits are vulnerable in normal aging and critically involved in dementia progression.[5, 33] Thus, the nine-week-long combined aerobic and strength training strategy may have induced changes in different brain areas (i.e., frontal, hippocampal). If possible, brain imaging is needed to visualize whether these changes are expressed in differences in brain activity, connectivity, and/or composition.

Our aerobic-only training improved cognitive function, since there were significant increases in executive function. However, aerobic-only training did not significantly improve motor function. Surprisingly, the improved executive function after aerobic-only training contradicts the results as presented in a review by Scherder et al. (2013). They showed that aerobic-only training did not improve executive function in patients with dementia, and had only an effect in cognitively non-impaired older people.[5] A possible explanation could be the high level of participation, combined with the one-on-one training program in the current study. Although aerobic-only training improved executive function, it did not improve memory function. Improvements in both executive and memory function were reached after combining aerobic with strength training, as was done in the Combined group. Furthermore, compared to the non-exercise Social group, the Combined group scored higher than the Aerobic group on walking endurance, leg muscle strength, and balance after the nine-week program. These findings agree with our pilot study, which showed medium to large effect sizes on motor function after a six-week-long combined aerobic and strength training program.[19] Taken together, aerobic-only training may not be sufficient to elicit both improvements in cognitive (i.e., executive and memory function) as well as improvements in motor function. Therefore, we suggest to combine aerobic and strength training.

Although the Combined group improved in motor function, we could not confirm that these improvements mediated the improvement in cognitive function. There may be other possible underlying mechanisms involved that explain how physical exercise is related to cognition in patients with dementia. Previous research suggests that complementary neurobiological and physiological mechanisms may arise from alternating aerobic and strength training sessions, compared with those arising from single training programs. Such a combined exercise program could conceptually be more effective for slowing the dementia-related cognitive deterioration. Both aerobic and strength training can favorably influence brain-derived neurotropic factors and levels of insulin-like growth factor-1, which mediate cell growth, proliferation, survival, and differentiation.[15] Strength training may lower levels of neurotoxic homocysteine, which is related to improved cognition.[16, 18] The improvements in motor function after a combination of aerobic and strength training, as seen in the present study, have the potential to increase angiogenesis via vascular endothelial growth factor, thereby increasing cerebral blood flow which is a key factor related to cognitive function.[14, 18] The current study lacks imaging, blood, and more comprehensive cardiovascular data which could support such a mechanistic understanding as described above. Future studies should include these outcome measures.

In addition to the mechanistic exercise-cognition discussion above, another possible explanation why the combined intervention produced higher cognitive and motor scores could be related to a stronger neuro-motor stimulus after the strength exercises. These exercises required the patient to perform complex cognitive tasks, such as comprehending the instructions, moving the limbs in the correct order, and mimicking the trainer's movements. In addition, strength exercises incorporate motor-coordination and balance tasks, known to activate specific cerebellar-cortical connections, which can act as a stimulus for concurrent improvements in cognitive function and balance.[34] Such responses were demonstrated after Tai-Chi training in healthy older adults[35], but data in older patients with dementia is lacking. In the current study no data was collected to confirm the cerebellar-cortical hypothesis and future studies in patients with dementia are needed.

Nine weeks after the intervention was ended, follow-up effects reversed towards baseline values. Thus the current data stress that a structural exercise program is essential to maintain the demonstrated positive effects of regular exercise. Long term maintenance of physical exercise and activities could potentially slow disease progression, which is of high clinical relevance (i.e., 'exercise is medicine').

We conclude that, compared to a non-exercise control group, a combination of aerobic and strength training elicits stronger effects than the aerobic-only training in slowing the cognitive and motor function decline in institutionalized patients with dementia. However, we did not confirm that improved motor function mediates improved cognitive function. Future research is needed to study the underlying mechanisms that are involved in the link between exercise and the cognitive and motor deterioration processes in dementia.

Limitations

We were limited in collecting and using data of patients who dropped-out prior to the start of the intervention. Also, only a specific segment of institutionalized patients with dementia participated (e.g., those who were mobile and motivated enough). When generalizing the results both factors should be taken into account.

This is the first study that used trainer monitored RPE to determine exercise intensity in patients with dementia. Indeed, we were confronted with the fact that no clinimetric data on external RPE in patients with dementia is available. However, a significant correlation between RPE and heart rate data in the exercise groups was found (Spearman's $r = 0.314$, $n = 73$, $p = .007$), indicating that sessions that led to a larger difference in heart rate were scored with a higher RPE. More research is needed in measuring exercise intensity in patients with dementia to evaluate the dose-response relationship between exercise and cognition.

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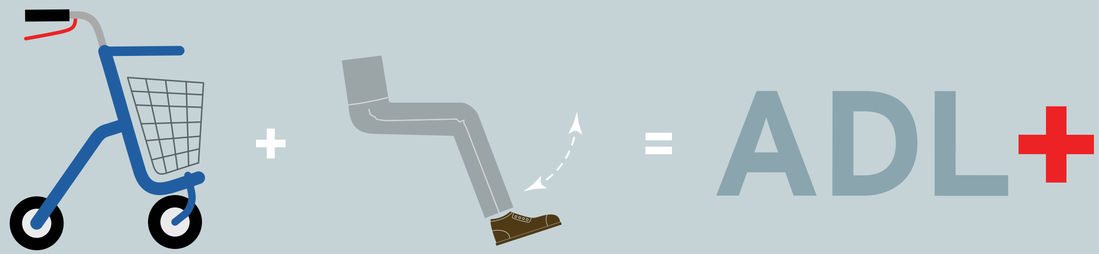
APPENDIX

Appendix 1. Data of cognitive tests for each intervention group as mean (standard deviation).

		T0, pretest	T1, posttest after 9 weeks	F1, follow-up at week 18
Domain global cognition				
Mini Mental State Examination	Combined group	15.81 (4.30)	17.16 (4.33)	15.91 (4.60)
	Aerobic group	15.22 (4.79)	15.50 (5.51)	14.62 (5.61)
	Social group	15.89 (4.20)	15.17 (4.48)	13.88 (5.73)
Domain visual memory				
Faces recognition	Combined group	4.25 (3.39)	5.72 (3.10)	4.68 (3.79)
	Aerobic group	3.94 (3.30)	5.53 (3.87)	4.57 (4.66)
	Social group	4.68 (4.30)	3.89 (4.16)	4.45 (3.70)
Picture recognition	Combined group	8.67 (6.96)	10.68 (5.99)	8.38 (6.70)
	Aerobic group	9.92 (6.52)	9.86 (6.93)	9.58 (7.48)
	Social group	10.06 (7.67)	9.17 (6.76)	7.74 (7.56)
Visual memory span forward	Combined group	4.73 (1.86)	5.22 (2.88)	4.79 (1.87)
	Aerobic group	4.94 (2.34)	4.75 (1.84)	4.20 (2.22)
	Social group	4.69 (2.08)	4.39 (2.25)	4.09 (2.41)
Domain verbal memory				
Digit span forward	Combined group	8.86 (2.99)	9.08 (2.73)	8.84 (3.65)
	Aerobic group	8.67 (2.94)	8.83 (3.13)	8.81 (3.39)
	Social group	9.25 (3.11)	8.42 (3.06)	8.28 (3.28)
8-Words test–direct recall	Combined group	14.35 (7.30)	15.51 (6.04)	14.23 (6.35)
	Aerobic group	11.79 (7.79)	11.82 (8.43)	10.05 (8.28)
	Social group	12.78 (7.82)	11.58 (8.29)	11.40 (8.42)
8-Words test–recognition	Combined group	10.65 (2.19)	11.46 (1.97)	11.15 (2.46)
	Aerobic group	10.25 (2.41)	11.06 (2.68)	10.72 (2.79)
	Social group	10.72 (2.15)	10.61 (2.40)	9.92 (2.60)
Domain executive function				
Word fluency	Combined group	11.92 (6.63)	13.46 (6.73)	11.58 (6.93)
	Aerobic group	10.31 (8.23)	11.50 (8.15)	9.41 (7.12)
	Social group	11.36 (7.30)	10.69 (8.26)	10.22 (7.12)
Digit span backward	Combined group	5.14 (2.65)	5.44 (2.43)	4.81 (2.12)
	Aerobic group	5.20 (3.07)	5.05 (3.22)	4.61 (3.36)
	Social group	4.78 (2.49)	3.97 (2.56)	3.88 (2.69)
Incomplete figures	Combined group	4.96 (2.03)	6.33 (2.90)	5.23 (2.72)
	Aerobic group	5.78 (3.52)	6.25 (3.68)	5.86 (3.66)
	Social group	5.14 (2.89)	5.11 (3.22)	5.04 (2.79)
Stroop test	Combined group	-26.19 (9.35)	-24.79 (11.26)	-24.83 (7.83)
	Aerobic group	-21.95 (12.37)	-22.47 (11.05)	-24.57 (12.62)
	Social group	-22.96 (12.24)	-23.02 (12.74)	-24.57 (11.18)
Trail making test- A (s)	Combined group	198.27 (77.67)	161.85 (38.52)	195.74 (87.22)
	Aerobic group	188.44 (130.40)	179.60 (127.88)	202.17 (121.55)
	Social group	182.33 (108.50)	185.83 (117.03)	209.09 (106.37)
Visual memory span backward	Combined group	3.13 (3.33)	3.48 (3.14)	3.20 (2.02)
	Aerobic group	3.48 (2.33)	3.56 (2.50)	2.92 (2.70)
	Social group	2.92 (1.90)	2.28 (1.96)	2.37 (2.06)

Appendix 2. Data of motor test for each intervention group as mean (standard deviation).

		T0, pretest	T1, posttest after 9 weeks	F1, follow up at week 18
Domain aerobic capacity				
6-minute walk test (m)	Combined group	217.58 (90.25)	267.15 (101.22)	230.63 (76.43)
	Aerobic group	231.47 (136.40)	235.45 (148.69)	217.93 (97.25)
	Social group	229.50 (136.38)	221.84 (159.51)	223.33 (102.21)
Domain leg strength				
Sit to stand test (no.)	Combined group	6.77 (3.43)	8.19 (3.55)	7.32 (3.45)
	Aerobic group	7.07 (4.37)	6.25 (4.79)	6.97 (4.00)
	Social group	6.21 (4.83)	5.40 (6.33)	5.54 (3.13)
Knee extension strength (N)	Combined group	205.92 (90.99)	208.83 (85.57)	203.41 (88.37)
	Aerobic group	196.02 (98.97)	186.07 (84.31)	206.19 (75.93)
	Social group	218.89 (84.06)	203.19 (73.96)	198.87 (85.00)
Domain mobility				
Timed up & go (s)	Combined group	22.98 (12.95)	20.40 (9.20)	21.72 (10.20)
	Aerobic group	24.28 (14.04)	23.84 (15.02)	25.45 (12.61)
	Social group	27.59 (18.75)	27.73 (19.16)	28.10 (15.60)
Walking speed (m/s)	Combined group	0.70 (0.26)	0.75 (0.28)	0.72 (0.24)
	Aerobic group	0.78 (0.32)	0.73 (0.37)	0.68 (0.29)
	Social group	0.70 (0.30)	0.64 (0.29)	0.61 (0.29)
Step length (m)	Combined group	0.40 (0.10)	0.42 (0.10)	0.42 (0.12)
	Aerobic group	0.42 (0.11)	0.41 (0.13)	0.40 (0.11)
	Social group	0.40 (0.12)	0.39 (0.11)	0.38 (0.13)
Domain balance				
FICSIT-4	Combined group	2.28 (1.04)	2.77 (0.89)	2.53 (0.87)
	Aerobic group	2.75 (1.24)	2.48 (1.11)	2.32 (0.94)
	Social group	2.31 (1.40)	2.04 (1.35)	1.96 (1.13)
Figure of 8 (m/s)	Combined group	0.33 (0.22)	0.38 (0.32)	0.35 (0.19)
	Aerobic group	0.41 (0.26)	0.43 (0.40)	0.38 (0.21)
	Social group	0.35 (0.25)	0.32 (0.33)	0.34 (0.21)
Figure of 8 (overstep)	Combined group	7.74 (7.56)	7.33 (7.54)	6.74 (6.51)
	Aerobic group	5.91 (7.44)	7.86 (7.69)	8.23 (7.42)
	Social group	9.03 (8.03)	9.73 (8.23)	8.14 (7.22)
Groningen Meander Walking Test (s)	Combined group	23.30 (12.65)	21.61 (11.37)	21.63 (8.66)
	Aerobic group	18.67 (7.71)	19.02 (8.95)	21.24 (10.88)
	Social group	21.53 (12.72)	23.18 (13.69)	24.05 (12.95)
Groningen Meander Walking Test (overstep)	Combined group	2.08 (2.08)	1.73 (2.36)	1.48 (2.09)
	Aerobic group	0.84 (1.55)	1.05 (1.56)	1.40 (2.03)
	Social group	2.63 (2.88)	2.71 (2.69)	2.36 (2.93)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